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Consensus on nomenclature for clinical staging models in bipolar disorder: A narrative review from the International Society for Bipolar Disorders (ISBD) Staging Task Force.

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Abstract

Objectives: Clinical staging is widely used in medicine to map disease progression, inform prognosis and guide treatment decisions; in psychiatry, however, staging remains a hypothetical construct. To facilitate future research in bipolar disorders (BD), a well-defined nomenclature is needed, especially since diagnosis is often imprecise with blurred boundaries, and a full understanding of pathophysiology is lacking.

Methods: Under the auspices of the International Society of Bipolar Disorders, a Task Force of international experts was convened to review, discuss, and integrate findings from the scientific literature relevant to the development of a consensus staging model and standardize a terminology that could be used to advance future research including staging of BD and related disorders.

Results: Consensus opinion and areas of uncertainty or difference were identified in regard to terms referring to staging as it may apply to BD, to at-risk status and subthresholdhold stages, and to various clinical stages of BD as it is currently diagnosed.

Conclusion: The use of a standardized nomenclature about the clinical stages of BD will facilitate communication about research on clinical and pathological components of this heterogeneous group of disorders. The concepts presented are based on current evidence, but the template provided allows for further refinements as etiological advances come to light.

Key words: bipolar disorders; clinical staging; nomenclature

Introduction

Staging is a widely used approach in medicine to improve early recognition of at risk states, confirm diagnosis, guide effective treatment, and inform prognosis, especially for illnesses with a potentially progressive course. The prototypical example of staging systems in medicine is the TNM system in oncology. This classification scheme was intended to encompass all aspects of cancer in terms of primary tumor (T), regional lymph nodes (N), and distant metastasis (M), and was first introduced by the International Union Against Cancer (UICC) in 1958 for worldwide use and is now in its eighth edition [1]. TNM differentiates between clinical stage (cTNM), based on all available information from history, physical examination, blood tests, radiology, biopsy, and endoscopy, and pathological stage (pTNM), based on microscopic examination of the tumor after surgical removal.

In Psychiatry, there is hope that clinical staging models could improve early recognition, inform diagnosis, and aid treatment decision-making [2]. However, staging systems in Psychiatry are hampered by the fact that the etiology and pathophysiology of the vast majority of psychiatric disorders are still largely unknown, and recognition of structural or neurobiological markers that occur in specific disorders is currently in its infancy [3]. Disorders are defined and classified in DSM-5 [4] and ICD-11 [5] on the basis of current symptomatology and longitudinal course. Current diagnoses do not take into account other relevant information such as developmental or family history. Moreover, there is a considerable overlap in phenomenology between disorders, especially at the early stages of illness development and in acute episodes. Nonetheless, there are distinctive differences between disorders in terms of development, clinical course, response to treatment, and family history of psychiatric illness, improving the ability to differentiate illness trajectories early in the emergent course and being informative for treatment prediction [6, 7].

There is a growing body of knowledge about risk factors and prodromal signs and symptoms in individuals at identified clinical and/or familial high-risk for developing a psychiatric illness, some of which is shared and some of which is specific [8], with substantial overlap in risk factors [9].

Further challenges remain including the timely recognition of mental disorders, understanding the biological, psychological, and social factors that contribute to the risk of onset and progression, selecting effective treatments for acute symptoms and the prevention of recurrences, and developing predictive validity models [10]. A developmental approach including identifying reliable stages in the onset and progression of psychiatric illness may therefore complement traditional diagnostic approaches, and contribute to the advancment of personalized treatment and risk prediction [11,12,13,14,15].

Kraepelin pioneered the use of charting the evolution and clinical course of major mood and psychotic disorders in individual patients, demonstrating the feasability and importance of identifying different illness trajectories for illness classification, treatment response and prognosis [16]. Fava and Kellner [17] made the first attempt to construct staging models for psychiatric illnesses, including schizophrenia, depression, bipolar disorder, and panic disorder. Cosci and Fava [18] reviewed the literature on staging for a range of mental disorders, and derived a general template with the following stages: (1) prodromal phase; (2) acute manifestations; (3) residual phase; and (4) recurrent or

chronic disorder. Critics of this approach argued that the model was more applicable to older adults with an established illness, it also included the phenomenon of 'roll back' into a previous stage (which is not included in any other staging model), and most importantly, it does not incorporate an 'at risk' phase, which is a critical element of all medical models of staging [19,20]. Furthermore, the Cosci and Fava[18] model fails to adequately capture the early development and childhood clinical antecedents predicting onset [12,13,15]. Nevertheless, Fava and Kellner's original publication stimulated discussions that led to the further development of staging models in psychiatry, and the evolution of disorder-specific as well as transdiagnostic models. For example, McGorry et al [21,22] proposed a model for psychosis and severe psychotic spectrum disorders that extended from an asymptomatic at-risk stage (stage 0) to a sub-threshold (stage 1), first episode (stage 2), recurrence (stage 3), leading to a severe, persistent illness (stage 4). More recently, McGorry and Hickie have led discussions about the potential utility of transdiagnostic staging models, noting that the antecedents (e.g. childhood experiences of sleep, anxiety, and mood problems) and the subthreshold stages of most major illnesses have common elements, are diagnostically fluid, and may lack the definitive characteristics of persistent disorders meeting established diagnostic criteria [19,23,24,25]. This transdiagnostic model is in an early phase of development, and has not been adopted universally in research or clinical settings. Critics of a transdiagnostic model express concerns that operationalizations of stages is difficult (e.g. being more reliant on functional level rather than phenomenology) and that it may promote a hierarchical model that is biased toward psychotic disorders over e.g. depressive disorders. Also, trans-diagnostic models have not as yet addressed the differential impact of family history of psychiatric disorders on clinical course of different clinical presentations[7,26,27]. A recent consensus document has detailed the pros and cons of trans-diagnostic models and a discussion of these unresolved issues.[25] Given the availability of that publication, alongside our primary goal to focus on the development of a clinical staging model of BD, we focus primarily on the development of a standardized nomenclature to facilitate communications among BD researchers and clinical experts in the field. However, we acknowledge that several elements may be applied to other disorders. [28,29]

An important goal for developing a clinical staging model for bipolar disorder (BD), would be to enhance the approach to treatment through placing individuals on the illness trajectory and providing more precise stage-appropriate (and developmentally appropriate) treatment [14,19,30]. At present time, there are very few examples of clinical trials showing the clinical utility of staging models in predicting treatment response [31], but there is promise especially if trials include a longitudinal perspective [32]. As an example, in a first episode cohort, superiority of lithium over quetiapine was demonstrated [33], an outcome not seen in a large and rigorous trial in a late stage cohort [34]. In the development of staging systems in psychiatry, different proposals are being put forward, in part reflecting the different populations and research approaches (i.e. high-risk offspring, first episode psychosis, patients with chronic illness). This variation also reflects the heterogeneity inherent in current diagnostic classifications that include various subtypes within each class of disorders, each with a different underlying course, treatment response and likely pathophysiology [35,36]. To move forward with testing and validating alternative staging models in clinical practice, it is essential to improve communication across research teams and fields. As a first step, it is important to

reach a consensus about the terminology used for the operationalization of various stages, transitions, risk factors, and clinical outcomes.

In 2009, the International Society for Bipolar Disorders (ISBD) Task Force report on the nomenclature of course and outcome in BD focused on the terms used in clinical studies of BD (response, remission, recovery, relapse, recurrence, switch, subsyndromal states, predominant polarity, functional outcome) as a first step to provide a standardized system to identify predictors of outcome and effects of treatment [37]. Later, the ISBD Task Force on staging of BD published a paper and a monograph on the current status of staging models in BD [38,39]. To follow-up on these initiatives, a second ISBD Task Force has been created to establish a consensus nomenclature for staging models of BD. It must be stressed that the aim of this Task Force was not to develop or promote one particular staging model for BD, but rather to review the 'state of the art' in this evolving field.
The current report describes the proposed terminology and areas that are still in need of further research and clarification. Since staging starts with at risk states and clinical presentations that do not meet full criteria for a diagnosis of BD, the proposed nomenclature is in line with the terminology as recommended by the ISBD Task Force on precursors and prodromes of BD [30], albeit with some precautions within a staging framework.
Together, these three Task Force reports provide a comprehensive nomenclature for the longitudinal evolution, manifestation, course, progression, and long-term outcome of BD in its various subtypes. It was recognized that nomenclature may need further refinement as the understanding of etiology and related diagnostic constructs advances.

Three clinical staging models in bipolar disorder from different perspectives

Current staging models for BD have been reviewed in detail elsewhere [14, 38, 41, 42, 43]. Here we mention three of these models that together provide a complementary and more comprehensive approach to staging BD; considering observations of familial and clinical at-risk youth and clinical patients over the illness course and life span, and describing illness progression by recurrence of mood episodes, or increasing functional impairment.
These models are summarized in tables 1 and 2.

[table 1 here]

[table 2 here]

These clinical staging models for BD have been described by Berk et al [44], Kapczinski et al [45] (table 1) and Duffy et al [41,43] (table 2). The staging model proposed by Berk et al. [44] is an elaboration of the model describing the development of psychosis first put forward by McGorry et al [46] and based on observations of clinically at-risk help-seeking patients attending first episode psychosis clinics. The model by Berk et al. emphasizes the recurrent clinical course starting with prodromal and first manic episode symptoms. Kapczinski et al [45] proposed a staging model

based on studies from patients with established BD that emphasizes inter-episode cognitive and psychosocial functioning over the course of illness and the lifespan of the patient. The assumption in these models is that recurrence and chronicity, and functional disability and cognitive decline, reflect underlying progressive pathophysiological processes ('neuroprogression'). Although preliminary, there is some evidence to link biomarkers to clinical stages of established BD [47,48,49]. Duffy [41] developed a model of the developmental trajectory of BD based on longitudinal prospective observations of children of parents with well-characterized BD observed up to two decades. This model emphasizes the developmental history, clinical antecedents, and early course of diagnosable mood episodes, both depressive and hypomanic/manic, in children and adolescents at confirmed familial risk. Clinically significant symptoms were also added to the model more recently [43] . The model highlights the stages leading up to a clinical presentation that meets full criteria for a diagnosis of BD and is able to partially account for heterogeneity, by differentiating the trajectory of classical, episodic, lithium-responsive BD from other more heterogeneous presentations such as those characterized by the presence of psychotic spectrum symptoms and non-fully remitting course that predict non-response to lithium prophylaxis (table 2). Since these three models address staging from different perspectives and examine the phenomenon in different populations studied during different phases of illness, they can be viewed as complementary. The highly heterogeneous course of bipolar spectrum disorders suggests that these disorders do not follow the same longitudinal illness course but evolve over time and development following a range of illness trajectories [26].

Method

Under the auspices of the International Society for Bipolar Disorders (ISBD), a task force was formed to examine, standardize, and integrate the current nomenclature as used in the literature on risk factors, subthreshold syndromes, prodromal development, early intervention, illness progression, and staging of BD. The proposed nomenclature should be congruent with nomenclature used in staging models of other psychiatric disorders or even other medical disorders, where that makes sense. However, in some instances different terms have been used interchangeably to indicate a phenomenon from a slightly different perspective. In those cases we make a recommendation which term to use in the context of staging. The task force had several in-person meetings (2016, 2017, 2018, 2019, 2020) and conference calls in-between. During the whole process, and especially in the later phases of writing the manuscript, every proposed change was communicated by email to all task force members by either asking specific questions on a particular topic, or sending the revised draft with proposed changes. In response, task force members, especially with a specific area of expertise, endorsed, suggested proposed changes, added literature references and/or made comments in the margin of the draft. All task force members were regularly asked to comment on all new proposals made, suggest further changes or nuances, add references, and finally consent. In general, all task force members responded to all issues raised and reached consensus on the nomenclature and the final manuscript. All previous drafts with track changes and detailed minutes of meetings

remained available via dropbox shared by all task force members. The whole process, covering all sections of the manuscript, was coordinated by the first author (RK) and a core group of taskforce members (MA, MB, AD, FK, JS). The task force convened four working groups that focused on: general definitions applicable to all stages; definitions applicable to asymptomatic, at risk and subthreshold stages; definitions applicable to the stages associated with BD presentations that meet threshold diagnostic criteria; and definitions applicable to late stage BD. We choose to avoid the terms 'early stage BD' (and therefore also 'middle stage BD'), as used by e.g. Salagre et al [14] , since especially the term 'early' may cause confusion about subthreshold versus early manifest BD; we retained the term 'late(r) stage BD' since this refers always to established BD. An overview of the proposed terminology is given in table 3.

[table 3 here]

Proposed terminology

(1) General definitions

In this section, we operationalize key terms that are relevant for all stages of BD: (clinical) staging; profiling; illness progression; neuroprogression; biomarker; transition (sometimes referred to as 'conversion').

(Clinical) staging. In a medical context, staging can be defined as (1) the determination or classification of distinct phases or periods in the course of a disease or pathological process, or (2) the determination of a specific extent of a disease process in an individual patient. A staging system is a heuristic tool intended to indicate where an individual is located on a continuum from 'at risk' but asymptomatic to 'end-stage' (poor prognosis) illness [19, 38]. In oncology, staging differentiates between clinical stage (cTNM) and pathological stage (pTNM), see introduction. In rehabilitation medicine, functional staging models are used [50]. Since much of the pathophysiology of psychiatric disorders is still unclear, staging models in psychiatry refer to clinical staging. Advances in the search for biomarkers may contribute to refined clinical staging mode and the development of a pathological staging model.

Risk profiling. Although not commonly used in psychiatry, we propose that the term risk profiling refers to the determination of individual characteristics (phenotype, endophenotype, genetic risk factors, family history, treatment response or paradoxical response) that have prognostic significance for individual susceptibility to disease, the course of a specific illness, or the response to a specific treatment [51, 52]. Profiling has overlaps with the construct of formulation, similarly aimed at personalising treatment [53] . Profiling includes elements of 'precision medicine', which is more directed toward disease-related factors, and 'personalized medicine' that has a much wider scope of patient-related factors [54] . E.g., in precision oncology, 'molecular profiling' (or 'tumor genomic profiling') refers to a form of testing that classifies tumors based on this genetic make-up to help diagnose and treat cancer. In BD,

optimal personalized treatment for a given patient could be determined by combining symptomatic phase of the illness (mania, depression, or euthymic interval), clinical stage, and specific individual characteristics (profile).

Illness progression is conceptualized as a unidirectional process, but pace and endpoint show a considerable variations [55]. It typically follows the sequence from subthreshold (subsyndromal) symptoms to a threshold mood disorder (e.g., major depressive disorder), which subsequently may or may not evolve into other, more severe forms of BD. Illness progression shows considerable heterogeneity. Some individuals evolve rapidly from a subthreshold state to a very severe disorder, whilst others may remain with subthreshold symptoms or show episodic symptoms that only progress to full threshold BD after many years. Subsequently, patients may experience repeated episodes over many years, but do not necessarily progress to a chronic ('late') stage. A recent cohort study reported that almost 50% of BD patients followed a progressive course, with signficant impact on their functional outcome [56]. A higher number of mood episodes has been associated with increased duration and symptomatic severity of subsequent episodes, decreased social functioning, cognitive impairment, and reduced treatment response [57,58,59,60,61,62]. In addition, the number of episodes has been associated with decreased threshold for developing further episodes and increased risk of dementia in the long term [54]. There is a considerable variation in cognitive [63,64] and social [65] functioning among patients with BD in various subtypes and stages of the illness, with clusters of intact functioning, mild-moderately impaired, and severely impaired. It remains unclear to what degree deterioration or progression reflects a primary illness process or associated secondary burden of illness effects related to suboptimal treatment, poor quality of remission, substance abuse, and medical comorbidity, and whether it applies to BD in general or only to a distinct BD subtype.

Neuroprogression. This concept was first used in BD [66], and has since expanded to other psychiatric conditions [67,68]. Neuroprogression is defined as the pathophysiological process of illness stage-related progressive structural, functional, and neurochemical brain changes. These are reflected by cognitive and functional decline, poorer treatment response, and an increasing vulnerability to relapse and chronicity. As mentioned before, such illness progression may apply only to a subgroup of BD patients [64]. The underlying molecular mechanisms of neuroprogression are thought to include neurotrophins and regulation of neurogenesis and apoptosis; neurotransmitters; inflammatory, oxidative and nitrosative stress; mitochondrial dysfunction; cortisol and the hypothalamic-pituitaryadrenal axis; and epigenetic influences [69,70] . In BD, the term neuroprogression is used to define the biological basis of clinical progression hypothesized as the pathological brain rewiring that occurs with recurrent mood episodes [71]. Recent studies show that only a proportion of BD patients show evidence of neuroprogression [72]. Individuals with a classical manic depressive or lithium responsive illness, estimated to represent approximately one-third of the BD population, do not show evidence of a deterioration over many years of follow-up [73]. In contrast, some individuals present with a neurobiological signature showing a more pernicious course already at illness onset, particularly those that respond preferentially to antipsychotic long-term treatment, have mostly manic/mixed episodes, and derive from families in which relatives manifest psychotic and/or chronic

illnesses [36]. Therefore, the biological changes described in association with multiple episodes may be a predictor, and not necessarily a consequence, of multiple mood episodes [74]. In a recent review, based on seven cognition studies (322 BD patients; 172 healthy controls), 13 neuroimaging studies (604 BD; 1167 HC), and four pharmacological (lithium) studies (313 BD; 48 HC) Serafini et al [75] concluded that most of the existing neuropsychological, neuroimaging, and molecular evidence demonstrates the existence of neuroprogression, at least in a subgroup of individuals with BD.

Biomarker. In the broadest sense, biomarkers refer to a measureable feature of a patient that is associated with risk, disease onset, course, diagnostic transition or conversion, prognosis, response to treatment, or the current general health status of the patient [76,77]. Biomarkers are specific measurable alterations in brain function or structure, or abnormalities in peripheral systems (e.g., hyperactive inflammatory cascades, endocrine effects) reflecting components of disease pathogenesis which are thought to be intermediate between the aberrant genes and the overt clinical manifestations of disease [70,78]. It is likely to be some time before researchers identify the optimal combination of clinical factors and multimodal biomarkers (e.g., blood omics, neuroimaging, and actigraphy derived-markers) or biosignatures that identify clinico-pathological boundaries between stages in BD [79].

Transition. The term transition reflects progression and may be used either within the framework of staging or within the context of diagnostic classification. *In a clinical staging model* (such as described above) transition indicates the a shift from one stage to a more advanced stage. Transition from at-risk state or subthreshold syndrome to full threshold mood disorder occurs when a person experiences their first major depressive or manic episode that meets full DSM-5 or ICD-11 criteria (hypomania and cyclothymia will be addressed in the section on subsyndromal conditions). Since this is a unidirectional transition, once a person has experienced a fully syndromal manic or major depressive episode, the staging model does not allow for a transition back to a previous stage, even if the person has a complete symptomatic and functional recovery from the index episode. Within each of these stages there may be signs of illness progression, e.g., increasing severity or frequency of episodes, or need for more complex treatment strategies, but transition to a next stage requires not only a quantitative, but also a meaningful qualitative change in clinical status. The unidirectional nature of these clinical staging models can be questioned in the latest stages, when late recovery can occur even after a prolonged period of unremitting illness or severe functional impairment, with or without treatment. Obviously, this also depends on the duration of longitudinal follow-up.

Transition *in a diagnostic model* indicates a change from one established major diagnostic category to another, e.g., from (unipolar) depressive disorder to bipolar disorder after a first (hypo)manic episode in a previously depressive illnes [80], or within a certain major diagnostic category from one subtype to another, more severe, subtype, e.g., from bipolar II to bipolar I disorder after a first full manic episode in a person with previously only depressive and hypomanic episodes [81,82] .

Depending on subsequent mood episodes, a person may experience a transition from MDD to BD-II or BD-I; or from BD-II to BD-I. These are unidirectional transitions: for example, staging models and classification systems as DSM-5 and ICD-11 do not allow a reverse transition from BD-I to BD-II, or from BD-I or BD-II to MDD.

- *Transition from MDD to BD-I or BD-II* occurs occurs when a person diagnosed with MDD experiences a first manic episode and is then classified as BD-I, or a first hypomanic episode and classified as BD-II. Since 45% - 90% of persons with BD experience depression as their first mood episode, this will be a frequently occurring transition [13,15,83,84,85,86].
- *Transition from Other Specified Bipolar and Related Disorder (BD-NOS in DSM-IV-TR) to BD-I or BD-II* occurs when a person with the former diagnosis experiences a manic episode (± depressive episodes) and then is classified as BD-I; or experiences a depressive episode and then is classified as BD-II. About 45% of youths progress from BD-NOS to BD-I or BD-II particuarly if there is family history of BD [81]. Since people with unipolar hypomania are relatively unlikely to present clinically (due to the typically short duration of hypomania, the limited functional impairment associated with it by definition, and the frequent lack of awareness of it as a pathological state), these will be relatively rare diagnostic transitions [87,88].
- *Transition from BD-II to BD-I* occurs when a person diagnosed with BD-II experiences a first manic episode. Approximately 15%-20% of youth initially diagnosed with BD-II subsequently meet criteria for BD-I, making this a relatively common phenomenon [89].

Transition from one diagnostic category to another within the spectrum of BD must be distinguished from reconsidering differential diagnosis and subsequent diagnostic reformulation, such as rediagnosing bipolar (spectrum) disorder as borderline personality disorder (or vice versa) as a cause of mood instability.

Transition as described here has in the literature also been referred to as *'conversion'* [80]. However, especially in an illness with multiple clinical manifestations such as BD, there is a meaningful difference. 'Conversion' suggests that there is a fundamental change in the nature of the illness, while 'transition' more adequately reflects an evolution of clinical manifestations within the mood disorder spectrum or the natural emergent or developmental course of an underlying (singular) form of BD. In the context of staging BD we therefore recommend to use the term 'transition' instead of 'conversion'. From a strict viewpoint of our current classification systems, one could argue that a diagnostic change from MDD to BD, or from BD to schizoaffective disorder, could be considered a 'conversion' since there is a shift from one group of mood disorders to another. However, this reflects an artifact of these classification systems that do not allow for the emergent course of illness, whereas in BD the vast majority of first mood episodes are depressive in polarity that are at that point inevitably classified as MDD. [90,91]. Shah et al [25] introduced the term 'heterotypic progression' to describe what we would conceptualize as 'conversion', in contrast to 'homotypic progression', e.g. to indicate diagnostic shifts to a more severe form of the same illness ('transition').

(2) Nomenclature for clinical presentations that are subthreshold for the diagnosis of BD

There are several terms pertaining to the earliest stages in the development of BD for which clearer definitions would be helpful. The following is a list of commonly used terms and examples to illustrate the intended meaning: at risk; prodrome; antecedents and precursors; positive family history; prevention; and early intervention.

At risk. Individuals 'at risk' for BD have typically been identified through a confirmed family history (i.e., child of an affected parent) and/or based on clinical profile (i.e., a partiular combination of symptoms with or without other risk exposures such as family history, maltreatment, stress, and substance abuse). It should be noted that a risk factor, while associated with illness onset, does not necessarily imply inevitability of illness, or illness causality..

Faedda et al [40] distinguished between *homotypic risk factors* for BD (phenomenological expressions overlapping with the diagnostic criteria for BD: mood lability, mood elation, irritability, mood swings, subsyndromal depression, recurrent or persistent hypomanic symptoms, and cyclothymic temperament) and *heterotypic risk factors* for BD (not overlapping and may be precursor of other psychiatric disorders or no disorder, e.g. anxiety syndromes, sleep disturbances, substance abuse, and behavior disorders). It must be stressed that 'homotypic' does not imply specificity. In case of a positive family history for BD these risk factors become more predictive of BD.

Prospective studies of high-risk offspring of BD parents have reported that mood lability, childhood anxiety and sleep disorders are associated with an increased risk of subsequent mood episodes related to BD [12,13,92, 93,95,96,97,98]. Moreover, clinically significant anxiety and depressive symptoms have also been shown to increase the likelihood of transition to more advanced stages and development of major mood disorders in offspring at confirmed familial risk [15]. The nature of these symptoms and relationship with the emerging mood disorder course (i.e., sequential versus concurrent comorbidity), diffentiate trajectories of classical lithium responsive compared to lithium non-responsive BD [41]. At a symptomatic level, elated mood, decreased need of sleep, racing thoughts, suicidal ideation, and middle insomnia have been significantly associated with the onset of BD in youth at confirmed familial risk [12] . A preliminary study reported an approach to calculate the individualized 5-year risk for BD in offspring of BD parents [11].

Prospective studies of the high-risk children of BD parents provide very strong evidence that BD most often debuts with a depressive episode [12,13,82,86,92,94,99]. There may be a long delay between an index depressive episode and a first (hypo)manic episode, and substantial associated morbidity may accrue before the diagnosis of BD is made [6,15,86,100] . Evidence suggests that depression in offspring of BD parents can be severe, and may include suicidal thoughts and behaviours or mixed subsyndromal manic features [101]. Further, psychotic symptoms in depressive episodes increase the risk of transition to BD [15]. Mitchell et al [102] explored the phenotype of bipolar depression, finding significant differences to unipolar depression that may form the basis of predictive algorithms, the best known being Bechdolf's Bipolar At Risk (BAR) criteria [103,104].

Family studies of adult relatives of BD probands have provided clear evidence that major depression is a part of the BD spectrum segregating in these families [105]. Moreover, prospective studies of children of BD parents have

provided independently replicated evidence that BD typically onsets as major depression in these at-risk children, yet depression is a relatively common diagnosis in the general population and there is a debate around how to include major depression in the staging of BD.
We submit that based on the weight of evidence, major depressive disorder in young people at confirmed familial risk of BD be considered an early at-risk stage of BD, especially if that major depression is characterized by an abrupt early onset, highly recurrent course, mood congruent psychotic or mixed symptoms.
Subthreshold syndromes, such as single or repeated hypomania without depression, and cyclothymia, will be discussed in the following section.

Prodrome. In medicine, 'prodrome' refers to a premonitory sign or symptom of a developing disorder or attack such as an aura warning of an epileptic seizure or an attack of migraine. A prodrome can only be identified as such when the disorder has become manifest. A prodrome of BD would refer to early warning signs or symptoms that had occured prior to the index hypomanic or manic episode [40]. However, this can only be done retrospectively after the person has experienced this first (hypo)manic episode. Given the prospective nature of staging models, defining a prodrome for mania in the context of staging BD is not possible, and it is therefore more accurate to speak prospectively of risk factors or describe an at risk phenotype instead of using the term prodrome.

Antecedents and **precursors.** In general, an antecedent is an event that exists or comes before another event, and may have influenced it. In the progression of BD this term would refer to early clinical presentations that come before the onset of the first major mood episode representing the syndromal onset of BD. As with prodromes, this can only be determined after the onset of BD. Therefore, in a prospective staging model also the term 'antecedent' is only useful in hindsight. The same applies for the term 'precursor'.

Positive family history. Although a positive family history of mood disorders is only one of the risk factors for developing BD, we highlight this given the evidence that BD has a high heritability, the fact that it is easily identifiable in a clinical setting, and has obvious importance for patients and families. The task force consented on the most often used definition of positive family history as the confirmed presence of MDD or BD in at least one first or second degree relative. Still, there is significant phenotypic heterogeneity to consider in which the BD trait manifests as a spectrum of illnesses segregating in families, and which differ somewhat between BD subtypes, i.e., classical manic depressive illness trait includes recurrent major depression, while psychotic spectrum BD trait includes chronic depression, psychosis and schizoaffective disorder [36,106]. In addition, completed suicide is often viewed as part of the BD spectrum [107]. Early (< 21) age of onset of BD in the parent further increases the risk for BD in offspring [93,108,109,110]. Furthermore, while the estimated lifetime risk across family studies of BD is 8-fold given an affected first-degree relative [10], risk to any individual should be adjusted for the loading in that individual's own family, e.g., having two parents with BD further increases the risk [111]. The segregation pattern and penetrance of the

BD trait is highly variable between individual families [96]. *Multigenerational* refers to the observation of an illness trait being present or segregating in multiple generations of the same family or pedigree.

Prevention. In medicine prevention is typically defined as primary, secondary, and tertiary. *Primary prevention* refers to efforts aimed at preventing illness in well individuals by either eliminating risk factors or building resilience, and can be further specified as universal (for an entire population), selective (for a specific subgroup at risk), and indicated (for a specific subgroup with minimal symptoms) [112] . *Secondary prevention* refers to detecting a disease as early as possible in its course and providing targeted treatment to prevent the further progression. *Tertiary prevention* aims to reduce the morbidity and mortality associated with a full-blown or advanced illness. Therefore, in applying these definitions to the BD staging literature, *Selective (primary) prevention* in high-risk offspring of BD parents would refer to the reduction of proven risk factors and building resilience, for example by fostering healthy parental attachments, reducing exposure to lifestyle risk factors such as poor diet, physical inactivity and substance use, trauma or to unstable parental illness [113,114,115,116]. *Indicated (primary) prevention* would in addition aim to reduce transition from an at risk condition in those at familial risk of BD to full bipolar disorders by treatment targeting sleep or anxiety disorders, risk taking and substance misuse, or rumination [117,118,119,120]. These interventions may have the advantage that some of these phenomena are also present in populations at risk of other major mental disorders and so they can represent important transdiagnostic targets for intervention, not just for those at risk of BD [121,122]. *Secondary prevention* would apply to early diagnosis and optimal treatment of manifest BD and interventions to reduce further illness progression, such as managment of comorbidity, psychoeducation and maintenance pharmacotherapy. Finally, *tertiary prevention* would apply to efforts at reducing the associated damage (morbidity and mortality) by providing effective pharmacotherapy, rehabilitation, improving adherence to effective treatment, and reducing medical comorbidity.

Early intervention refers to treatments or interventions that aim to intervene as early as possible in the illness course and thereby reduce progression and associated damage [123]. This term would mostly therefore equate in high-risk offspring populations to secondary prevention as described above, but would also be appropriate to refer to any intervention in those meeting major depressive disorder with confirmed familial risk or BD diagnostic criteria that targets early course intervention, i.e., prevent depressive recurrences or first manic episodes. Note that 'early intervention' is not restricted to youth or young adults.

(3) Nomenclature for clinical presentations that meet diagnostic criteria for BD

The terminology in this section addresses (1) the transition from at-risk states or subthreshold syndromes to a syndromal mood disorder and beyond, (2) in some patients, the transition from an initially-diagnosed mood disorder

(eg. major depressive disorder) to a subsequently-diagnosed mood disorder (eg. BD-I or BD-II); and (3) the illness course following the diagnosis of BD. We further address the definition of age at onset, and of duration of illness, interval, and functional recovery.

Full syndromal bipolar disorder begins with the transition from an at-risk state or subthreshold syndrome to a syndromal mood disorder, or with the onset of a first fullblown manic episode without any of these. The initial syndromal mood episode (sometimes called index episode, although this may also refer to any episode currently under observation [124]) may be depressive, hypomanic, or manic. This stage of the disorder is the most likely to show a good response to mood stabilizing medications and an episodic course with complete remission between mood episodes [125,126].

Depression as the first mood episode. When a person experiences a first spontaneous depressive episode (i.e., not better explained by another medical condition or substance use) meeting diagnostic criteria, without a previous manic or hypomanic episode, he is diagnosed with major depressive disorder (MDD). It is important to note that a person with MDD can be at-risk for BD, especially if risk factors as previously described are present, such as a family history of BD, or subthreshold conditions such as cyclothymia. One could argue that such a person has a ultra-high risk for BD. DSM-5 addresses this in the section on depressive episodes with mixed features, noting that these indicate a risk for (although not a diagnosis of) BD. If a person with one or repeated depressive episodes later develops mania or hypomania, the first depression can only retrospectively be regarded as the first manifestation of BD (see also: age at onset).

Mania as the first mood episode. When a person experiences a first spontaneous manic episode, she/he is diagnosed with BD-I, even in the absense of previous depressive episodes. Although there is some evidence that recurrent unipolar mania should be regarded as a separate subtype [127], this is not relevant in this early stage of ilnness.

Hypomania as the first mood episode. When a person experiences a first spontaneous hypomanic episode, without previous depressive or manic episodes, we reach the point where a categorical and a dimensional conceptualisation of psychopathology are potentially conflicting. Is hypomania (defined as a mood episode in DSM-5) a subthreshold syndrome (i.e., subthreshold mania), and in the absense of full depressive or manic episodes thus a manifestation of a subthreshold mood disorder, especially if recurrent? People will rarely seek help for hypomania only, since this condition by definition does not lead to marked impairment in social or occupational functioning. Still, according to DSM-5 criteria, such person would be diagnosed with Other Specified Bipolar and Related Disorder (hypomanic episode without prior major depressive episode), although that category 'applies to presentations in which symptoms characteristic of bipolar disorder cause clinically significant distress or impairment in social, occupational, or other important areas of functioning' [4], which in itself is conflicting with the definition of hypomania. It is even more complicated if this occurs in an individual with an established diagnosis of dysthymia, in which case both diagnoses are given. Something similar applies to cyclothymia, a subthreshold bipolar disorder not even meeting criteria for hypomania, but in DSM-5 and in ICD-11 still classified as a mood disorder. Moreover, in ICD-11

cyclothymia 'the hypomanic symptomatology *may or may not* be sufficiently severe or prolonged to meet the full definitional requirements of a hypomanic episode', while in DSM-5 'hypomanic symptoms *do not meet* criteria for a hypomanic episode' [128]. Prospective studies suggest that these subthreshold conditions warrant attention [81,129]. Also on the continuum from normality to psychopathology are the 'affective temperaments' (depressive, anxious, irritable, hyperthymic, and cyclothymic), not included in DSM-5 or ICD-11, but defined as subclinical, sub-affective, trait-like manifestations that may or may not be associated with mood disorders [130], and are somewhat more prevalent among patients with mood disorders than among those with another psychiatric illness or the general population [131]. Of these, cyclothymic and hyperthymic temperaments have the strongest association with BD [132,133,134]. The above once again reveals the unclear boundaries between normality, hypomania, and mania, and the ambiguous ways how these are defined [135], as well as the limitations of the notions of 'subthreshold/subsyndromal' and 'threshold/syndromal' disorders [25].

Transition to a next stage in established BD would go from first episode to recurrent episodes, and from recurrent episodes to chronic unremitting illness in the Berk et al model [44], and over increasing levels of interepisodic functional impairment in the Kapczinski et al model [45]. As stated earlier, not all patients will proceed to a next, let alone an end stage, although obviously this also will depend on the length of follow-up.

Age at onset (AaO) is optimally estimated as the age at which the individual experiences a first mood episode that meets internationally recognized diagnostic criteria (depression, hypomania, or mania). We recommend that age at onset be defined as the age at first mood episode of any type, and to specify AaO of a first depressive episode (in MDD or BD), as well as first hypomanic episode (in BD II), and first manic episode (in BD I). This approach minimizes confusions regarding the evolution of a mood disorder over time: e.g., if an individual experiences a depressive episode at age 17 (making the AaO for MDD 17 years), and at age 21 experiences a manic episode (and then meeting diagnostic criteria for BD-I), the AaO of BD then would be recorded as 17, specifying AaO for depression at 17 and AaO for mania at 21.

Duration of Bipolar Disorder is estimated as the individual's current age minus the age at onset of BD as defined above.

Duration of Untreated BD is the time elapsing between the onset of first depressive or manic episode that meets internationally recognized diagnostic criteria and the administration of the first adequate guideline concordant treatment for BD.

Duration of Illness is estimated as the individual's current age minus the age at onset of any recognized clinical syndrome that may have preceded threshold BD. This thus defines the time that a person has experienced any psychiatric disorder at a syndromal level.

Duration of Untreated Illness likewise is the time elapsing between the onset of any psychiatric disorder according to internationally recognized diagnostic criteria and the administration of the first adequate guideline concordant treatment for that disorder.

Inter-episode period. Time period between mood episodes of any polarity, in which syndromal criteria for mania/hypomania/depression are no longer met (i.e., syndromal recovery). It is also denominated as 'interval'. There may be residual subsyndromal mood symptoms (i.e., incomplete symptomatic remission) during the interval, and/or functional impairment (i.e., incomplete functional recovery). Also, in the interval of BD, persons may suffer from comorbid psychiatric at a syndromal level, or from medical disorders.

Remission and **recovery** were defined by the ISBD Task Force on the Nomenclature of Course and Outcome in BD [37]. Remission implies that the signs and symptoms of mania or depression are absent or nearly absent. In *syndromal remission* DSM-5 criteria are no longer met; in *symptomatic remission*, symptom levels fall below a certain threshold of an appropriate rating scale and predict recovery over a predetermined period. *Symptomatic recovery* can be ascribed after a period of eight consecutive weeks of symptomatic remission, such that the recovered state is likely to persist for a reasonalble period of time [37].

Here we make the addition of ***functional recovery*** since incomplete functional recovery, i.e., persistent functional impairment, is especially relevant for the staging model as described by Kapczinski et al [45]. The combination of illness severity and cognitive impairment were the two empiricall-driven dimensions underlying a staging model based on functioning [136]. Wingo et al [137] defined functional recovery as regaining individual premorbid psychosocial, residential, and occupational status. Even when criteria for symptomatic recovery are met, a substantial number of patients do not return to their premorbid level of psychosocial functioning. Apart from persistent cognitive impairment, as discussed earlier, this can be due to multiple factors, such as shame or fear regarding the illness; social stigma; untreated comorbid conditions; subthreshold depressive symptoms; medication side effects; weight gain; and life goal, marital, and occupational disruption [138,139,140,141]. We suggest that *functional recovery* refers to a return to an individual's highest previous level of work, school, and relationship functioning. This may differ from the level of functioning immediately preceding the index mood episode, which, depending on the person's illness course, might be lower than their prior best functioning. The proposed definition thus emphasizes the importance of a full return to premorbid health.

(4) Late stages of established bipolar disorder

Although the course BD is heterogeneous, in a substantial group of patients the risk of recurrence increases with the number of previous episodes [54,142]. Overall, the model of staging has helped clinicians to appreciate the importance of early identification and treatment in BD [143]. Models of staging do not imply a uniform or inevitable progression from less severe to more complicated presentations. This is reflected by the heterogeneity in clinical course, suggesting various illness trajectories. Rather, staging aims to create more homogeneous categories to predict prognosis and guide clinical intervention.

Late-Stage Bipolar Disorder should not be confused with BD of long duration per se, BD in elderly patients, or late-onset BD. Later stages are characterized by less symptomatic recovery and increased functional impairment; only having had multiple recurrences is not sufficient. Late-stage BD may present relatively early in the life of a patient with BD, reflecting rapid illness progression. Still, in the clinical setting patients with late-stage BD tend to be older and present with a history of multiple mood episodes, particularly mania [38]. Patients at a late stage may experience persistent symptoms between episodes [144], work disability, and in some cases have major difficulty to live autonomously [38]. At any point of the trajectory of BD, patients may present impairments in cognition, functioning [46] and more pronounced volumetric changes in brain [145,146]. The number and frequency of pretreatment episodes and the duration of untreated illness is not necessarily associated with lithium non-response [73]. Still, patients with late-stage BD are more likely to be treatment-resistant and more often need complex treatments such as clozapine or ECT [147,148]. In this sense, patients at late-stages present poorer prognosis, functioning and quality of life.

Chronicity is charaterized by persistent mood episodes (with at best only partial remission), continuous cycling, or persistent major functional impairment due to BD for at least 2 years. Chronicity implies that the duration of an illness episode exeeds what would be an expected duration of a manic or depressive episode. Moreover it also depends whether symptomatic or functional outcome is taken into consideration. In either case, chronicity refers to incomplete recovery having major impact on overall functioning and well-being. Although a time period of 2 years is arbitrary, it has been used in other contexts. In DSM-IV-TR a chronic specifier for a major depressive episode (in MDD, BD I or BD II) was defined as meeting full criteria for at least the past 2 years. DSM-5 no longer has this specifier, but instead classifies all depressive states that last more than 2 years (chronic major depressive disorder as well as dysthymia) as persistent depressive disorder. There is no similar category for BD, since cyclothymia, also lasting at least 2 years, is by definition of limited symptomatic severity and does not cover chronic BD I or II. In BD, a chronic course of illness may present as the abcense of symptomatic and functional recovery, even without persistently meeting full syndromal critera, which may be further complicated by persistent psychiatric and somatic comorbidity.

Since most patients will have received multiple treatments at this stage, chronicity and *treatment resistance* are overlapping phenomena.

Treatment-resistant bipolar disorder. Here we briefly comment on treatment-resistant BD. However, it must be born in mind that defining a disorder by its response to treatment is a complex and potentially flawed option. Treatment interventions evolve over time (e.g. recent additions include psychotherapies for BD, use of ketamine, novel pharmacotherapies) and operationalizing the construct of treatment-resistant is extremely difficult. For example, there is little agreement regarding the number of treatment interventions, classes of medications, adequate doses or exposures to treatments, and/or the duration of each treatment trial that is required. Given that the key problem for the individual patient is likely to be the clinical symptoms, functional impairment and social consequences of treatment-resistance, we suggest that, in staging models, it is better to consider these cases as chronic BD.

Most reports on treatment resistant mood disorders address treatment-resistant depression (TRD) as part of (unipolar) major depressive disorder (MDD) [149, 150]. Treatment-resitant BD (TRBD) is scarcely addressed in the literature, and even in TRBD, the focus is mostly on bipolar depression. As a result of consensus meetings of experts using a modified Delphi process, Hidalgo-Mazzei et al [151] defined TRBD criteria for depression as failure to reach sustained symptomatic remission for eight consecutive weeks after two different treatment trials, at adequate therapeutic doses, with at least two recommended monotherapy treatments or at least one monotherapy treatment and another combination treatment. They also defined multi-therapy-resistant bipolar depression (MTRBD), adding to the criteria of TRBD at least one completed course of cognitive-behavioural therapy (CBT) and a trial of at least 12 sessions of bilateral electroconvulsive therapy (ECT) if accepted and tolerated. Fornaro et al [152] reviewd the literature for TRBD and only found definitions for the depressive phase (TRBD-De), but not for acute mania (TRBD-MA) nor for refractoriness considering the long-term management of BD. Similarly, there are no definitions of treatment-resistant rapid cycling BD. The taskforce recommends use of the definitions of (M)TRBD for depression as described here, although with the cautionary statement made previously when using the concept of treatment-resistance in the context of staging.

Discussion

In this consensus paper we propose definitions for terms often used in research and clinical practice pertaining to the development, longitudinal course, and clinical staging with specific reference to BD. Given the complexity and heterogeneity of BD, there is a need for a clear nomenclature of anchor points in the illness evolution and hence staging. Our paper is not intended as a review of current staging models in BD as available elsewhere [14,38]. Of the existing staging models for BD, we briefly presented three with complementary perspectives. We restricted this nomenclature to the staging of BD, although many terms will be applicable to staging of other psychiatric disorders or to a transdiagnostic staging model. We realize that the understanding of the onset and progression of psychiatric illnesses, especially the optimal staging model for BD given its multifaced presentations, is in its relative infancy.

Therefore, the operationalizations we have provided for these key terms are likely to require further refinement as we increase our understanding of the developmental course, underlying pathophysiology, and the clinic-pathological boundaries between stages of illness in BD and between BD and other disorders [2]. The staging effort will also benefit from advances in biomarkers indexing staging and integration with findings from polygenic risk score research [153].

Accurate diagnosis, as in other areas of medicine, requires more than just descriptions of acute syndromes and longitudinal course. Other aspects, some unique to BD, must be considered when thinking about concepts related to risk, the emergent clinical course, and later stages of bipolar illness. BD as currently conceptualized is heterogeneous, with different subtypes (beyond those as classified in DSM-5 and ICD-11) associated with comorbidities, characteristic family history, risk factors, antecedents, subthreshold syndromes, clinical course and response to treatment [98,147]. Typically, BD evolves in a clinical sequence moving from non-specific childhood symptoms and sleep and anxiety disorders to depressive disorders in adolescence, and then to hypomanic/manic episodes starting in late adolescence and early adulthood [13,15,82,93].

Since a staging model is only useful in clinical practice if it has prognostic value, we included in our proposed nomenclature only those terms that can be used for this purpose. In this context we therefore recommend the use of 'risk factors' instead of 'prodromes', 'antecedents', or 'precursors', terms that are often used interchangeably albeit with subtle nuances.

One of the major problems in diagnosing, classifying and staging BD is the separation of all forms of unipolar depression from bipolar disorders [154,155], especially given abundant evidence that most cases of BD present with depression as the first mood episode and experience one or more depressive episodes before the emergence of hypomanic or manic episodes. In our proposed nomenclature, this is revealed in several areas, such as defining 'age at onset' of both depressive and (hypo)manic episodes, and 'conversion' (in case of change to a formal diagnosis of a different class of psychiatric disorder) versus 'transition' (in case of illness progression within the spectrum of mood disorders). How many cumulative, specific and nonspecific risk factors for BD are predictive for and needed to define a major depressive episode as a first syndromal stage of manifest bipolar disorder? Is there a specific signature of a depressive episode that can differentiate between unipolar and impending bipolar mood disorder? We must recognize the inherent circularity of thinking in that we are limited by current classifications yet are using these and data related to these constructs to try to define terms for future advancement. An example of this is the evolution of BD-II, where the current diagnostic criteria require a prior history of MDD before the onset of hypomania [156].

At the other end of illness evolution, a key issue regarding illness progression and staging, is whether it is unidirectional or reversible, either spontaneaous or by treatment. It is clear that a patient can recover from a chronic stage of BD and move to a recurrent and remitting stage (Berk's model stage 4 to stage 3), or from major functional impairment to functional autonomy (Kapczinski's model stage IV to stage III). Hence, a 'chronic stage' need not be an 'end stage'. In terms of communication with caregivers and patients this is a critical message because staging could otherwise imply therapeutic nihilism which needs to be avoided. The key message needs to be one of

optimism, that only a subgroup of 'at risk' will become ill, and only a proportion of individuals who experience an illness will progress from one stage to the next, and importantly that these disorders, if treated appropriately and especially early, may remain stable for many years. In a retrospective study of the first five years after BD onset, van der Markt et al [149] found that 21 of 99 patients reached a chronic stage (i.e., non-remission for at least two years), of whom 8 subsequently recovered to a recurrent/remitting stage within those first five years. This study also showed that reaching a 'late' stage is not restricted to those with a long duration of illness. Especially in later stages it matters which outcome is taken into consideration: a symptomatic, disorder-specific (non-)recovery or a more generic functional (non-)recovery. In a second study, van der Markt et al [158] combined Berk's and Kapczinski's models in a sample of 1396 BD-I patients and found a low association between these models, suggesting that a multidimensional staging model may better address the complexities of illness progression in BD [25].

Moreover, when describing illness progression and staging, we have not taken into consideration the impact of treatment. As in many longitudinal observational ('naturalistic') studies in clinical samples that report on various aspect of the course of illness, one could argue that we are not looking at the natural evolution of the untreated illness but at illness progression that is potentially attenuated (e.g. by mood stabilizers like lithium) or accelerated (e.g. by antidepressants) depending on the individual treatment response. This is of importance since much of the research on staging has been performed in clinical samples, and may not only be pertinent in the later stages, but also in the pre-syndromal stages if early recognition and intervention are incorporated as standard of care.

Another factor influencing the overall mental health state of an individual is the presence of comorbid psychiatric disorders, either preceding BD or emerging after illness onset, complicating the course of BD. In the context of illness progression, this has been addressed as 'illness extension'. This concept was introduced by Shah et al [25] as part of an international consensus statement on transdiagnostic clinical staging in youth mental health to describe how a mental illness expands beyond the original diagnostic boundaries. According to this proposed model, extension can be operationalized as one or more of the following: (a) the emergence of mental or physical health comorbidities; (b) a marked change in a linked biological construct; or (c) an independent neuropsychological construct reflecting cognitive deterioration. Extension is multidimensional and potentially independent of illness progression, and reflects the complexity of mental illness. Although described in the context of youth in the peak age range for onset of severe mental disorders, extension would also be applicable for older adults.

The potential overlap in symptomatology and course with other psychiatric conditions has been an argument for transdiagnostic models for staging, especially in early stages of illness. Whilst a trans-diagnostic model appears valid for non-specific or sub-threshold presentations, it does not appear to account fully for the varied supra-threshold trajectories of severe mood or psychotic disorders (i.e., presentations that meet current criteria for a specific diagnosis). The nomenclature definitions presented here are entirely compatible with the transdiagnostic model of early clinical stages, but diverge somewhat for later stages (e.g. stage 2 to 4). Given the existing evidence-base, our consensus view was that transdiagnostic and disorder-specific staging models have strengths and weaknesses. However, the group determined that detailing nomenclature for staging models of BD does not undermine future

dialogue about transdiagnostic models, whilst applying a transdiagnostic model to this project conferred no specific advantage to the target audience.

In a staging model, stepwise transition from one clinical stage to the next is more than just gradual illness progression and increasing symptom severity, but must be marked by meaningful differences, potentially reflecting changes in the underlying neurobiology, and having consequences for treatment and prognosis. Debates around where to draw the line between each clinical stage will be informed by advanced understanding of pathophysiology and associated biomarkers, and thus complementing clinical staging with pathological staging.

Given the complementary nature of current staging models for BD as described [41,44,45], all addressing clinically significant aspects of illness evolution (early trajectories, episode recurrence, and functional impairment, respectively), there is a need to combine these in multidimensional models [157]. A next step could be to develop a consolidated model incorporating these models and the evidence and where it makes sense bring this consolidated model in line with those in other areas of medicine [2,25].

Strenghts and limitations

In this narative review, a large panel of experts combining clinical and research expertise in BD integrated insights from the literature on course of illness and staging of BD into a proposed nomenclature for future staging research. A major limitation is the lack of empirical studies on staging and the fact that current clinical staging models in psychiatry are to a large extent theoretical given still unknown pathophysiology and lack of valid biomarkers.

Implications for research

The proposed nomenclature can be used in prospective studies addressing various stages of longitudinal illness evolution to test the underlying assumptions of the various staging models, measuring multi-level risk factors (e.g., psychological, physiological, genetic). Novel biomarkers may confirm or reposition the points of transition between stages. Furthermore, in treatment studies, staging according to one or more of the models described could be included as a descriptive clinical factor that may influence outcome. Finally, clinical staging and the identification of risk factors can inform the development of individualized risk prediction models.

Implications for clinical practice

Staging and profiling could guide treatment decisions on the level of treatment guidelines but also on the level of the individual patient, approaching the aim of a more personalized medicine. Timely diagnosis of BD may be improved if considering risk factors as described. Early stage interventions that share many trans-diagnostic targets such as sleep/circadian disruptions and rumination may be as effective as putative BD specific interventions [122] . Psychoeducation may be a key intervention for individuals at risk for BD and patients in early stages of manifest BD [159]. In addition, the overwhelming evidence identifying recurrent major depressive disorder as an early stage in those at familial risk, also informs the approach to treatment. Different treatment outcomes may be more relevant

in different stages, such as symptomatic recovery in early an middle stages and functional recovery and better quality of life in later stages [160] .

Conclusion

To advance research in the area of clinical (and subsequently pathological) staging in BD, a shared nomenclature is needed to integrate findings from studies in various groups of individuals at risk for or with already established BD. The proposed nomenclature complements that of prodomal [40] and syndromal [37] bipolar disorder.

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Stage	Berk et al. staging model	Stage	Kapczinski et al. staging model
0	Increased risk of bipolar disorder	Latent	Increased risk of bipolar disorder;
1a	Mild or non-specific symptoms of mood disorder		mood or anxiety symptoms without criteria for threshold BD
1b	Prodromal features: ultra-high risk		
2	First threshold mood episode	I	Well-defined periods of euthymia without overt psychiatric symptoms
3a	Recurrence of sub-threshold mood symptoms		
3b	First threshold relapse	II	Symptoms in interepisode periods related to comorbidities
3c	Multiple relapses	III	Marked impairment in cognition and functioning
4	Persistent unremitting illness	IV	Unable to live autonomously owing to cognitive and functional impairment

Table 1: Comparison of complementary staging models of bipolar disorder as proposed by Berk et al. (2007) with emphasis on episode recurrence, and Kapczinski et al. (2009) with emphasis on interepisode functioning; the respective timing and numbering of stages do not fully correspond due to different focus.

Dufffy et al Staging Model	Classical bipolar disorder *	Bipolar spectrum**
Stage 0 Confirmed Familial Risk	Well, but at confirmed familial risk for episodic bipolar or recurrent mood disorder	Well, but at confirmed familial risk for chronic fluctuating bipolar spectrum disorder
Stage 1 Positive Family History + Non-specific disorders and symptoms	non-specific syndromes: episodic anxiety and sleep disorders, clinically significant anxiety & sleep symptoms	non-specific & developmental disorders: chronic fluctuating anxiety and sleep disorders, ADHD, learning and motor disabilities
Stage 2 Positive Family History + Minor Mood Disorder and/or clinically significant mood symptoms	minor mood disorders and symptoms (often episodic): depression NOS, dysthymia, cyclothymia, adjustment disorders, clinically significant depressive and hypomanic symptoms	Minor mood disorders and symptoms (often chronic fluctuating) with negative syndrome features: Depression NOS, dysthymia, cyclothymia, hypomanic symptoms, apathy, anhedonia, flattened affect, emptiness, irritability
Stage 3 Positive Family History + Major Depressive Disorder, Single or Recurrent	Single or recurrent (remitting) major depression (with or without psychotic features in episodes), good quality of remission	Single or recurrent (non-fully remitting) major depression often with attenuated psychotic features: cognitive dysfunction, decline in functioning (academically, socially),
Stage 4	A. Classical episodic bipolar disorder (BDI, II, NOS) with or without psychotic features in episodes and good quality of remission B. Bipolar disorder with residual symptoms: Reflecting burden of illness effects (addiction, medical comorbidity, non-optimal treatment)	A. Non-classical bipolar disorder (cyclic mania, mixed mania, BDI, II, NOS) typically not fully remitting and often attenuated psychotic symptoms B. Psychotic spectrum bipolar disorders (schizoaffective: poorly remitting) chronic fluctuating and cognitive and functional decline

* classical bipolar disorder: family history of episodic remitting mood disorders; predominantly depressive episodes; good quality of spontaneous remission; psychotic symptoms in minority of patients and limited to mood episodes; low rate of comorbidity; excellent response to lithium prophylaxis.

** bipolar spectrum: family history of chronic psychotic illness or chronic atypical depression and substance use disorders; manic episodes predominate; chronic fluctuating course of illness with significant residual symptoms; not uncommonly psychotic symptoms; cognitive and functional decline; poor response to lithium prophylaxis.

Table 2. Staging model for bipolar disorder as proposed by Duffy (2014) with an emphasis on early development towards classical bipolar disorder or psychotic bipolar spectrum disorder

(1) General definitions	**(2) Nomenclature for clinical presentations subthreshold for diagnosis of BD**
Staging	At risk
Clinical staging	*homotypic risk factors*
Pathological staging	*heterotypic risk factors*
Profiling	*(not to be used in a staging context: prodrome; antecedent; precursor)*
Illness progression	Positive family history
Neuroprogression	Prevention
Biomarker	*selective primary prevention*
Transition	*indicated primary prevention*
in a clinical staging model	*secundary prevention*
in clinical diagnosis/classification	*tertiary prevention*
(not to be used in a staging context: conversion)	Early intervention
(3) Nomenclature for clinical presentations that meet diagnostic criteria for BD	**(4) Late stages of established BD**
Full syndromal bipolar disorder	Late-Stage Bipolar Disorder
subthreshold/subsyndromal disorder	Chronicity
threshold/syndromal disorder	[Treatment-Resistant Bipolar Disorder]
Age at onset	
of depression	
of hypomania / mania	
Duration of illness	
duration of Bipolar Disorder	
duration of Untreated Bipolar Disorder	
duration of Illness	
duration of Untreated Illness	
Inter-episode period	
Functional recovery	

Table 3: Overview of terminology for staging of BD that have been defined by ISBD Staging Taskforce