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Clinical Staging for Youth Mental Disorders: Progress in Reforming Diagnosis and Clinical Care

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Abstract

Current silo-based diagnostic systems for mental disorders lack utility and fail to fulfil a fundamental purpose of diagnosis: to guide treatment planning and predict outcomes. Diagnostic reform has gained momentum, and clinical staging has emerged as a promising framework to improve the precision of diagnosis, particularly in early illness stages, and fill current gaps in linking diagnosis to more personalized and effective intervention, prognosis, and neurobiological markers. Transdiagnostic clinical staging recognizes that the early development of mental ill-health is marked by substantial fluidity and that symptoms may, although not inevitably, evolve into more stable diagnosable syndromes. Staging facilitates the selection of interventions that are proportionate to the current need and risk of illness progression and provides an efficient framework to organize biomarker data and guide service delivery. Here, we provide an overview of transdiagnostic clinical staging and summarize key evidence supporting its ability to integrate biomarkers and guide mental health care.

Contents

INTRODUCTION

Early and accurate diagnosis is the cornerstone of effective clinical management. Recognizing the limitations of current diagnostic systems in guiding treatment selection and predicting illness course, particularly for young people, the concept of clinical staging in mental health was introduced to strengthen the utility of diagnosis. Guided by robust epidemiological evidence, transdiagnostic clinical staging acknowledges the dynamic nature of psychopathology and recognizes that illness progression can be altered via the deployment of timely and stage-appropriate interventions that target modifiable risk and protective factors (McGorry et al. 2014a). For over a decade, evidence has accumulated supporting the model's conceptual validity, its ability to integrate biomarkers, and its significance in guiding mental health care. We provide a summary of this evidence and outline future directions. First, we describe the concept of clinical staging, including its rationale and application in mental health.

OVERVIEW OF CLINICAL STAGING

Purpose of Diagnosis

At its core, diagnosis is classification with utility (Kendell & Jablensky 2003). Its central objective is to guide critical decisions regarding whether signs or symptoms of ill-health or illness are present and require professional care, the choice of management plan, and the prediction of illness trajectory. Despite the development and refining of internationally agreed upon and operationally defined criteria for mental disorders, traditional diagnostic categories have low clinical utility and are widely regarded as inadequate to guide treatment and prognosis (Maj 2020, McGorry & van Os 2013). The pursuit of precision medicine (Natl. Res. Counc. 2011), to strengthen the utility

of diagnosis in order to tailor the management plan to a patient's profile, has led to many medical disciplines advancing diagnostic techniques to improve patient outcomes. However, this progress has substantially lagged behind in psychiatry, which partly reflects that current diagnostic systems have not sufficiently facilitated, and have potentially hindered, the validation of biomarkers for clinical use. Current diagnostic systems rely on the assumption that multiple discrete pathways running in parallel lead to separate diagnoses (McGorry 2013). This assumption is not supported by the fact that traditional diagnostic categories map poorly onto the underlying biology and the patterns of treatment response (Hickie et al. 2013b), which significantly challenges the validity of these categories (Stephan et al. 2016). It is now increasingly clear that traditional diagnostic categories do not and will not optimize clinical utility and that further subclassification, such as staging (McGorry & Hickie 2019) and profiling, is crucial to deliver treatment in a more precise manner and to predict outcomes.

Emergence of Mental Disorders

An additional major limitation of current diagnostic systems is their failure to operationalize the earliest stages of emerging mental disorders, particularly in young people, which has impeded the capacity for early diagnosis and intervention. Prior to reaching threshold-level criteria, all major psychiatric disorders are preceded by early clinical stages or subthreshold states that are often associated with sustained distress and disability as well as a need for care (McGorry et al. 2006). The course of these early symptoms substantially varies. For some, they may be transient or intermittent. For others, they may persist and represent an increased risk for a potentially serious mental disorder (Iorfino et al. 2019), and in some cases, they are regarded as a disorder (Fusar-Poli et al. 2015). This subthreshold state is characterized by a fluctuating constellation of nonspecific symptoms, such as anxiety, depression, sleep disturbance, withdrawal, and apathy (Hartmann et al. 2019, van Os 2013). During the early stages of illness, these symptoms are largely transdiagnostic (Hartmann et al. 2019), and over time they may intensify and blend into diagnosable syndromes (McGorry & van Os 2013). This process is not linear and is characterized by substantial fluidity and heterogeneity (van Os 2013). This underlies the need for a transdiagnostic approach, particularly in the early stages of mental illness, that can appropriately inform early intervention and prevention strategies (McGorry & Nelson 2016).

The evolution from well to unwell is often gradual and challenging to demarcate. A hard, arbitrary boundary is incompatible with the emergence and progression of mental illness in young people. Traditional and current mental health services often inhibit access to care at the earliest stages of illness, predominately due to the adoption of hard entry criteria that favor established adult-type mental disorders over emerging and transdiagnostic phenotypes that are common among young people. This reflects the state of current diagnostic systems and their failure to capture early clinical phenotypes and their trajectories as well as the serious underresourcing of mental health care, which restricts access and rations care. These traditional diagnostic systems are based on cross-sectional symptoms that typically reflect established and long-standing mental disorders. As a result, they do not sufficiently support early diagnosis, early intervention, prevention, and prediction efforts, particularly in view of pluripotent risk (i.e., the potential of early symptoms to evolve into a range of different syndromes). While imposing a hard border may be argued by some as addressing potential stigma, overdiagnosis, and overtreatment, it ultimately maintains the treatment gap. A new diagnostic system is needed—one that adequately reflects epidemiological evidence, promotes early diagnosis, and tolerates and guides a fuzzy boundary between well and mental illness to facilitate a low threshold for care in combination with safeguards to ensure that treatment is proportional and that benefits are maximized and risks minimized (McGorry et al. 2018).

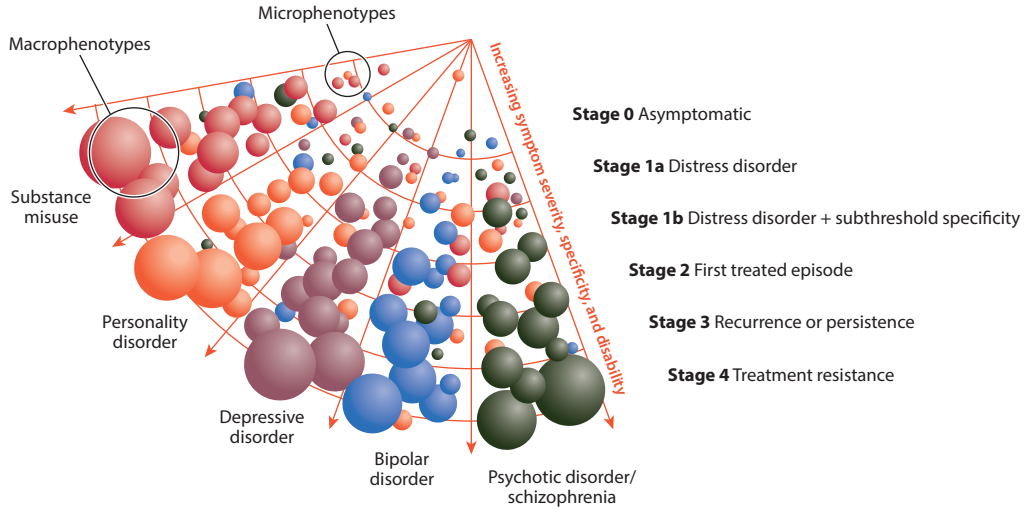

Figure 1

Clinical staging model depicting the emergence of undifferentiated microphenotypes that may progress to macrophenotypes (e.g., psychosis, depression).

Clinical Staging

Clinical staging is essentially a more refined form of diagnosis that is capable of addressing the limited clinical utility of current diagnostic systems for mental disorders (McGorry et al. 2006). It seeks to determine where an individual is situated on a continuum of illness, ranging from asymptomatic (Stage 0), to help-seeking with distress (Stage 1a), attenuated syndromes (Stage 1b), full-threshold disorder (Stage 2), recurrence and persistence (Stage 3), and severe, chronic mental illness (Stage 4) (**Figure 1**). Clinical staging acknowledges the early clinical presentations, which are characterized by mixed and fluid symptoms that overlap discrete syndromal boundaries or do not meet criteria for a full-threshold disorder, that are often not recognized by conventional diagnostic systems (McGorry & Nelson 2016). Transdiagnostic clinical staging acknowledges that these phenotypes may, over time, converge into traditional diagnostic categories while also recognizing the potential nonlinear progression of illness and substantial comorbidity.

Application of clinical staging in mental health. The concept of clinical staging has existed for nearly a century (Wright 2012). Its origins stem from the medical field, specifically oncology, where distinct stages of illness could be defined to appropriately inform treatment selection and prognosis (Gonnella et al. 1984). Staging has since spread to many branches of physical medicine (e.g., the management of diabetes and arthritis), where its value in guiding clinical management to improve survival and quality of life has been well recognized.

Nearly three decades ago, clinical staging for affective disorders was proposed by Fava & Kellner (1993) as a key missing element in psychiatric classification. They argued that staging, in comparison to widely used diagnostic systems, was superior due to its emphasis on characterizing mental illness according to its severity, progression, and features. Drawing on the learnings from the early psychosis paradigm, clinical staging for mental disorders has undergone extensive development to encompass a wide range of mental disorders, reflecting their pluripotent and transdiagnostic nature (Hickie et al. 2019, McGorry & Hickie 2019, McGorry et al. 2006).

Two approaches to clinical staging for mental disorders have been proposed: a single-disorder model that is confined to traditional diagnostic silos (e.g., Berk et al. 2007, Cosci & Fava 2013,

Fava & Kellner 1993, Hetrick et al. 2008) and a transdiagnostic model (McGorry & Hickie 2019). Transdiagnostic clinical staging fully recognizes the undifferentiated clinical phenotypes of emerging mental disorders in young people, thus addressing a major limitation of diagnostic systems that are grounded on a siloed approach (McGorry & Nelson 2016). Unlike a single-disorder approach, transdiagnostic staging models can accommodate both homotypic and heterotypic trajectories (e.g., a subthreshold state predicting its corresponding threshold-level syndrome or another quite different syndrome, respectively). This lumping approach aligns with the shared neurobiological architecture of mental disorders (Anttila et al. 2018, Goodkind et al. 2015). A transdiagnostic approach to staging, and diagnostic classification in general, is also consistent with the direction of other emerging approaches [e.g., Research Domain Criteria (RDoC), the Hierarchical Taxonomy of Psychopathology (HiTOP), and the general factor of psychopathology (p-factor)].

Developmental psychopathology and clinical staging. Clinical staging aligns with the contemporary epidemiology of mental disorders. Most mental disorders have their onset during childhood, adolescence, or young adulthood (Caspi et al. 2020, Kessler et al. 2005). Young people are particularly vulnerable to the onset of mental illness for complex neurobiological reasons; structural and functional maturational brain changes that occur during adolescence and early adulthood can increase susceptibility to psychopathology (Paus et al. 2008). Notably, genes implicated in cortical maturation are also enriched for psychiatric disorders (Parker et al. 2020). Early-onset mental disorder has been associated with a trajectory characterized by more years spent living with a disorder and the development of more diverse types of comorbid disorders (Caspi et al. 2020). Pure diagnoses are the exception, with all mental disorders being associated with an elevated risk of all other disorders (Caspi et al. 2020, Plana-Ripoll et al. 2019). Lifetime comorbidity begins to accumulate in adolescence (Caspi et al. 2020), with the risk of comorbidity heightened during the first year following the onset of a mental disorder (Plana-Ripoll et al. 2019). These data support the transdiagnostic nature of mental disorders and confirm that static, cross-sectional, and siloed diagnostic approaches are inefficient. The longitudinal and developmental approach of clinical staging captures the evolution of psychopathology and supports a preemptive and preventive strategy with multiple syndromal targets.

Key underlying principles of clinical staging. Clinical staging is guided by a number of principles and assumptions (Shah et al. 2020). The model does not assume that progression across stages is inevitable and is based on the premise of a differential risk of progression; that is, earlier stages are associated with a lower risk of progression to later stages. Long-term data indicate that 36.9% of help-seeking young people at Stage 1a transition to Stage 1b, 2.6% transition from Stage 1a to Stage 2, and 12.8% transition from Stage 1b to Stage 2 (Iorfino et al. 2019). The estimated rate of transition from Stage 2 to a later stage is 33.3% (Hickie et al. 2013a). Underlying the model is the notion that transition across stages can be linked to increasing severity and functional disability (Purcell et al. 2015) and biomarkers (e.g., neuroimaging and neuropsychological performance) (Sacks et al. 2021), as well as a change in treatment approach (Rohleder et al. 2019). In this respect, treatment in the earlier stages of illness is more likely to be effective than treatment in later stages; however, recovery or positive treatment outcomes are attainable at any stage. Early-stage treatments should be simpler and safer than later-stage treatments that are typically more intensive and pose more adverse effects. This reflects that later illness stages are characterized by greater symptom specificity, severity, persistence, and disability (Purcell et al. 2015). Stage-based interventions have two key functions: first, to target current need and ameliorate immediate impacts and short-term risks, and second, to reduce the risk of illness progression or extension via early effective treatments or preventive intervention.

Advantages of staging. Clinical staging offers a holistic framework that transcends traditional and static diagnostic systems. It recognizes the dimensional nature of psychopathology while superimposing a stage-based categorical framework that is linked to treatment decisions as well as potential neurobiological changes, as outlined below. This blended approach acknowledges the inherent role of categories in guiding patient management (Kendler 2018). The use of a stage-based continuum allows treatment to be proportional to illness stage and proactive to prevent illness progression and extension, guided by risk–benefit considerations. Because of this, it offers greater clinical potential than traditional diagnostic systems, facilitating early diagnosis as well as guiding treatment and prognostic decision-making.

CLINICAL STAGING AND BIOMARKERS

The longitudinal evolution, fluidity, overlap, and comorbidity of syndromes pose a serious challenge to the current approach to drug development and licensing. Taking the shortcut of equating syndromes, especially poorly validated, polythetic ones such as schizophrenia, with disease entities; failing to acknowledge neurobiological heterogeneity; and assuming a common substrate mean that the use of drugs that have a broader range of action is regarded as undesirably off-label. Conversely, a justifiable level of multiple drug prescriptions is labeled as polypharmacy. This is an example of spurious precision that can only be overcome by biomarker-guided personalized medicine, which must be transdiagnostic and trans-syndromal. Hence, the identification of biomarkers that can reliably predict risk of illness onset and progression is essential to personalize intervention and to achieve the ultimate goals of clinical staging. While this is at present aspirational, we summarize below evidence for promising biomarkers that may reflect clinical stage or risk of illness progression and may potentially represent therapeutic targets for stage-specific interventions. These markers support the validity of the model in that they can differentiate certain stages of illness, which may not necessarily involve a deterioration across clinical stages. We review evidence relevant to major mood and psychotic disorders and, where available, transdiagnostic clinical staging.

Neurocognitive Markers

Recent evidence has indicated that psychiatric disorders are associated with a common alteration in neurocognitive networks (Sha et al. 2019), supporting a transdiagnostic pattern of cognitive impairment across disorders (McTeague et al. 2016). In transdiagnostic cohorts, accumulated evidence indicates differential patterns of neurocognitive impairment across early and late stages of illness. Cross-sectional studies have indicated that young people classified at Stage 1b have lower composite neurocognitive scores than those at Stages 0 and 1a (Romanowska et al. 2018) and that, compared to healthy controls, those at Stage 1b show an intermediate neuropsychological profile, while those at Stage 2/3 have a significantly worse profile, particularly in verbal memory and executive functioning (Hermens et al. 2013). These findings were independent of current symptoms, level of distress, and diagnosis (psychotic or mood syndrome/disorder) (Hermens et al. 2013).

Longitudinal follow-up of young people at Stage 1b and Stage 2/3 has indicated that, despite the latter group showing a more reduced neurocognitive profile at baseline, both groups similarly improved in neuropsychological functioning across most measures at follow-up (3–51 months), especially in processing speed, sustained attention, and visual memory (Tickell et al. 2019). Verbal memory was an exception and may represent a treatment target for later stages. While individuals at Stage 1b significantly improved is this area, those at Stage 2/3 showed a slight decline at follow-up. Future longitudinal research that includes participants at Stage 4 is needed, particularly

given that individuals with major mood disorders may experience further progression of cognitive impairment during chronic stages of illness (Allott 2019). Across the course of psychotic disorders, unaffected siblings (Stage 0) have been found to show small deficits in cognitive functioning, while first-episode patients (Stage 2) show greater deficits than prodromal patients (Stage 1b) and slightly worse cognitive performance than established illness phases (Stage 3/4), suggesting some improvement over time (Velthorst et al. 2021). Neurocognitive impairments in first-episode psychosis are considered a trait marker since they are typically characterized by stability or developmental arrest, although a progressive decline may occur in a subgroup (Allott 2019). Another possibility is that decline occurs during the prodromal period, which then stabilizes (Reichenberg et al. 2010), at least in a proportion of patients. Finally, there may be a range of longitudinal patterns that are obscured in group data. While further research is also needed to examine the role of cognitive functioning in progression across clinical stages, neurocognitive and social cognitive deficits represent possible markers of transition to first-episode psychosis (Stage 2) in individuals at ultrahigh risk for psychosis (Stage 1b) (Allott 2019).

Neuroimaging Markers

A recent review of structural neuroimaging across clinical stages of schizophrenia-spectrum, bipolar, and depressive disorders identified a high degree of overlap in abnormalities across diagnoses, challenging the utility of diagnostic categories in neuroimaging research (Bartholomeusz & Pantelis 2019). Increasing evidence has highlighted the potential of transdiagnostic clinical staging to support the identification of neuroimaging biomarkers for early and late stages of illness in young people.

In Stage 1b participants, cross-sectional investigation of white matter integrity has revealed early white matter changes (reduced fractional anisotropy) in the left anterior corona radiata (particularly in the anterior thalamic radiation) (Lagopoulos et al. 2013) and in the body of the corpus callosum (Sacks et al. 2021). Disruptions in white matter integrity in these regions were greater in more advanced stages of illness (Stage 2/3 in Lagopoulos et al. and Stage 2 in Sacks et al.). Participants at Stage 2/3 also demonstrated significantly increased radial diffusivity in the left anterior corona radiata compared to controls, which, together with a reduction in fractional anisotropy but normal parallel diffusivity, suggested demyelination of fiber tracts (Lagopoulos et al. 2013). In another study, participants at Stage 2/3 demonstrated significant loss of gray matter volumes within frontal lobe regions compared to controls and Stage 1b (Lagopoulos et al. 2012). The largest loss occurred within an overlapping region bordered by the right superior and middle frontal gyri (Lagopoulos et al. 2012).

One study to date has used a transdiagnostic clinical staging model to examine whole-brain and frontal white matter changes longitudinally (Shakeel et al. 2020). This study identified no significant differences in fractional anisotropy and mean diffusivity at baseline and over a 12-month follow-up period between controls and young people at Stages 0, 1a, and 1b and those who had transitioned to serious mental illness. However, the latter group showed a trend of more reduced fractional anisotropy and increased mean diffusivity at both time points. The transition group also showed a significant increase in mean diffusivity at 12 months in the right anterior thalamic radiation; however, this did not survive correction for multiple comparisons. Only nine participants were included in the transition group, which likely reduced the study's power. Based on the same study cohort, cross-sectional analysis indicated no significant differences in brain activity (in regions known to be impacted by severe mental illness) between asymptomatic (healthy controls and Stage 0) and symptomatic participants (Stages 1a and 1b) (Metzak et al. 2021), although structural imaging revealed differential patterns of volume deficits in the limbic system (Nogovitsyn et al.

2020). Specifically, Stage 0 participants showed subtle but significant differences within the body of the hippocampus than did controls; Stage 1a participants showed volume reductions that were largely within hippocampal subregions compared to controls; and Stage 1b participants demonstrated more widespread volume deficits that included the hippocampal, amygdala, and thalamus subregions (Nogovitsyn et al. 2020). In a separate cohort, no volume changes in the hippocampus of participants at Stage 1b and Stage 2/3 were found compared to controls (Eggins et al. 2018). In this study, Stage 2/3 participants showed significantly reduced right amygdala volumes compared to controls (but not Stage 1b), whereas Stage 1b participants showed significantly reduced left caudate volumes than controls (but not Stage 2/3) (Eggins et al. 2018).

Although cross-sectional structural imaging studies generally support the validity of transdiagnostic clinical staging (i.e., differential patterns of brain changes across stages), further large longitudinal and functional imaging studies are needed to confirm neuroimaging markers of illness stage, remission, and progression.

Electroencephalography Markers

Electroencephalography (EEG), a measure of brain electrical activity, represents a promising approach to identify biomarkers of mental disorders. A recent review investigated the presence of resting state and event-related EEG abnormalities as markers of illness stage in psychosis spectrum and severe mood disorders (Lavoie et al. 2019). Specific EEG components examined were gamma phase synchrony, P50, mismatch negativity (MMN), and P300. The review found that the current evidence base is insufficient to support any EEG impairment across these components as a marker of illness stage for major psychiatric illnesses. For bipolar disorder and major depressive disorders, the evidence for early-stage disorder was too scarce for firm conclusions, while findings for chronic stages of these disorders were highly variable across the studies reviewed.

There were, however, notable event-related potential findings for schizophrenia in relation to frequency MMN (indexing preattentive auditory discrimination and sensory memory) and P300 (indexing endogenous cognitive processes). Frequency MMN is considered a state marker of psychosis (McGorry et al. 2014a). Frequency MMN abnormalities have been reported in individuals at ultrahigh risk for psychosis and show a deteriorating trend following transition to psychosis (Lavoie et al. 2018), although the evidence for this is inconsistent (Atkinson et al. 2017). For individuals with schizophrenia, MMN abnormalities have been consistently reported, with frequency MMN deficits in particular associated with illness duration (Umbricht & Krljes 2005). While MMN amplitude may be associated with disease progression, it has been speculated that this progression is not linear and may stabilize following the first few years of illness (Erickson et al. 2016).

In relation to P300, abnormalities have been reported in individuals with chronic schizophrenia (van der Stelt et al. 2005) and first-episode psychosis and schizophrenia (del Re et al. 2015, Hermens et al. 2010), as well as in individuals at ultrahigh risk for psychosis (Tang et al. 2020) and first-degree relatives of individuals with schizophrenia (Turetsky et al. 2007). However, there are indicators that P300 deficits demonstrate a progressive pathophysiological process. P300 is a promising marker of transition to psychosis (Hamilton et al. 2019), and P300 amplitude reduction and latency prolongation have been shown to worsen over the course of schizophrenia (Mathalon et al. 2000, Özgürdal et al. 2008). P300 and MMN are also both potential markers of remission from ultrahigh risk status (Hamilton et al. 2021).

Overall, the differential patterns of P300 and MMN across the illness course align with the clinical staging model, although further research, particularly longitudinal studies, is needed to confirm if P300 and MMN are markers of disease progression (Lavoie et al. 2019).

Sleep and Circadian Rhythm Markers

Sleep disturbance is a common antecedent of mental disorders (Hartmann et al. 2019). Across illness stages, there is evidence of a progressive disruption of sleep–wake and circadian systems (Grierson et al. 2019, Scott et al. 2016, Stowkowy et al. 2020). Three key findings have emerged from clinical staging studies utilizing subjective ratings of sleep in transdiagnostic samples. First, compared to healthy controls, individuals at Stages 1a and 1b report significantly worse subjective sleep quality, extended sleep onset latency, greater use of sleep medications, and greater daytime dysfunction (Stowkowy et al. 2020). Second, individuals at greater risk of severe mental illness (Stage 1b) report the highest levels of overall sleep dysfunction compared to Stage 0 and Stage 1a (Stowkowy et al. 2020). Third, depression severity and shared dimensions of sleep–wake disturbance and rumination are associated with transition to threshold syndromes (Grierson et al. 2019).

Corroborating these findings, objective (actigraphy) monitoring of sleep–wake patterns in transdiagnostic samples of young people has shown a progressive increase in rates of delayed sleep phase across clinical stages (Scott et al. 2016) and that sleep–wake disturbances are associated with transition from Stage 1b to Stage 2 (Iorfino et al. 2019). Specifically, young people with attenuated syndromes (Stage 1b) and established mental disorders (Stage 2+) had more significant sleep phase delays compared to healthy controls, with rates being more pronounced in those with more severe or persistent disorders (Scott et al. 2016). This finding is consistent with research examining the association between clinical stage and biological markers of the circadian system; that is, young people at Stage 2+ have significantly lower evening levels of melatonin secretion than those at Stage 1b as well as shorter phase angles, indicating the difference between melatonin onset and habitual sleep onset (Naismith et al. 2012).

While consistent evidence indicates that sleep–wake and circadian abnormalities are transdiagnostic markers of progression across stages, they may also represent pathophysiological mechanisms for a specific clinical phenotype. Combining a transdiagnostic clinical staging model with a pathophysiological framework has revealed a distinct, although not mutually exclusive from other pathways, circadian–bipolar spectrum pathway that is characterized by features such as delayed sleep–wake timing and disrupted sleep–wake behaviors and circadian rhythms (Carpenter et al. 2019). This is supported by evidence that has shown that young people with bipolar disorder are significantly more likely to have a delayed sleep phase than those with unipolar depression and controls (Robillard et al. 2013b) and that these delayed sleep–wake cycle disturbances are associated with circadian rhythm abnormalities (Robillard et al. 2013a), neurobiological changes (Naismith et al. 2014), and longitudinal manic symptoms (Robillard et al. 2016).

Inflammatory, Oxidative Stress, and Bioactive Lipid Markers

A strong body of evidence implicates immune dysfunction in the pathophysiology of psychiatric disorders (Fraguas et al. 2019, Khandaker et al. 2015, Miller et al. 2011). Across major psychiatric disorders, there are consistent reports of elevated levels of cytokines (inflammatory markers) (Goldsmith et al. 2016, Miller et al. 2011) and abnormal oxidative stress parameters (imbalance of oxidants against antioxidants) (Black et al. 2015, Brown et al. 2014, Upthegrove & Khandaker 2020). During acute and chronic phrases of schizophrenia, bipolar disorder, and major depressive disorder, there are similarities in the pattern of cytokine alterations, suggesting common pathways for immune dysfunction across these disorders (Goldsmith et al. 2016). In relation to schizophrenia, several cytokines (IL-1β, IL-6, and TGF-β) are considered state markers of acute illness, whereas others (IL-12, IFN-γ, TNF-α, and sIL-2R) may represent trait markers (Miller et al. 2011). In bipolar disorder, altered cytokine levels appear to be stage related (Berk et al. 2011). While proinflammatory cytokines IL-6 and TNF-α are increased during early- and late-stage

bipolar disorder, an increase in the anti-inflammatory cytokine IL-10 may be specific to early-stage bipolar disorder (Kauer-Sant'Anna et al. 2009). Further, TNF-α is significantly higher in the later stage of the disorder, indicating its potential as a marker of illness progression (Kauer-Sant'Anna et al. 2009).

Similarly, oxidative mechanisms may represent common pathogenic pathways across psychiatric disorders (Ng et al. 2008) and have demonstrated stage-dependent changes. Late-stage bipolar disorder has been associated with increased activity of glutathione reductase and glutathione *S*-transferase and increased levels of 3-nitrotyrosine, whereas early-stage bipolar disorder has been associated with increased 3-nitrotyrosine levels only (Andreazza et al. 2009). While oxidative stress may be increased in the early stages of psychosis, oxidative DNA damage increases in chronic unremitted schizophrenia (Copoglu et al. 2015, Nordholm et al. 2016).

Abnormally low levels of omega-3 fatty acids have been reported across psychiatric illnesses (Assies et al. 2010, van der Kemp et al. 2012) and have been detected prior to the onset of a first episode (Stage 2) (McNamara et al. 2016, Rice et al. 2015). In individuals at ultrahigh risk for psychosis, several classes of fatty acids have been associated with symptom severity (Berger et al. 2019). Decreased levels of nervonic acid (a monounsaturated omega-9 fatty acid) have been associated with transition to psychosis and attenuated psychotic symptoms (Amminger et al. 2012), although the evidence for this is unclear (Berger et al. 2019).

In schizophrenia and related disorders, strong evidence supports increased activity of phospholipase A2 (enzymes involved in the release of polyunsaturated fatty acids) (Berger et al. 2006), which may be more relevant to a first episode than chronic stages (Smesny et al. 2005, 2010). During the ultrahigh risk stage of psychosis, intracellular phospholipase A2 activity is significantly associated with levels of membrane omega-3 and omega-6 polyunsaturated fatty acids, and in some instances, these associations have been shown to vary according to the state of illness (Smesny et al. 2014). In particular, associations between omega-6 and arachidonic acid with intracellular phospholipase A2 activity were in opposite directions for those who transitioned to psychosis (positive correlation) and those who did not (negative correlation), suggesting that dysfunction in the omega-6 metabolic pathway may be a marker of psychosis onset.

Overall, the accumulated evidence suggests that neuroinflammation, oxidative stress, and bioactive lipids are markers of pathophysiological processes and are potentially stage dependent and may represent possible targets for preventive interventions.

STAGE-BASED MENTAL HEALTH CARE

Current therapies are largely targeted toward acute symptoms of mental disorders and are typically not directed toward early intervention, relapse prevention, and functional recovery. This is reflected by their short- and long-term effectiveness; up to half of help-seeking young people do not respond to first-line treatments (Maalouf et al. 2011), and approximately half experience multiple episodes (Gibb et al. 2010). To improve therapeutic outcomes, not only is better implementation of existing interventions needed, but equally so are novel interventions, including biotherapies, psychosocial innovations, and digital technologies.

Novel Biological Treatments

As opposed to psychosocial approaches that are predominately symptom based, biological treatments directly target the core biological processes (e.g., oxidative stress, inflammation) that may contribute to or underpin illness onset and progression. A key principal of clinical staging is that early-stage treatments should be safe and effective, and in particular, treatment should be more effective than when delivered at a later stage of illness when neurobiological damage or functional

decline has already occurred and may be harder to arrest or reverse. Omega-3 polyunsaturated fatty acids, *N*-acetylcysteine, and cannabidiol are promising novel biological treatments relevant to clinical staging (for a review of other putative neuroprotective treatments relevant to the staged progression of mental illness, see Robertson et al. 2019). Below, we provide a summary of the evidence supporting these three treatments, particularly in relation to mood and psychotic disorders. Their efficacy in transdiagnostic samples is an area of future research.

Omega-3 polyunsaturated fatty acids. Omega-3 fatty acids can influence core biological processes such as dopaminergic and serotonergic neurotransmission (Freeman et al. 2006, Sublette et al. 2014), and oxidative stress and inflammation (Calviello et al. 2013, Kiecolt-Glaser et al. 2013), which are relevant to illness progression transdiagnostically (Berk et al. 2011). Omega-3 fatty acids are considered safe and do not pose clinically relevant side effects (Amminger et al. 2017).

In the area of psychosis, one of the most promising randomized controlled trials of omega-3 found strong and sustained benefits following omega-3 supplementation in individuals at ultra-high risk for psychosis (Amminger et al. 2010). This was not replicated in a large multicenter trial (McGorry et al. 2017). However, this may have been because the psychosocial intervention was sufficiently effective to reduce the power of the study to detect any additional value of the omega-3 supplementation. Furthermore, analysis of biological samples in these trials demonstrated that an increase in omega-3 levels in participants predicted clinical improvement (Amminger et al. 2015, 2020), indicating that omega-3 fatty acids exert clinical benefits during the ultrahigh risk stage. Although the effects of omega-3 supplementation in individuals with first-episode psychosis seem modest or unclear (Berger et al. 2007), mechanistic studies have consistently reported improvements in hippocampal neuronal health and brain glutathione (Firth et al. 2018). In the treatment of acute depression, omega-3 (particularly eicosapentaenoic acid), either as a monotherapy or augmentation agent, has shown clinical benefits compared to placebo; however, a preventive effect was not found in nonclinical populations at risk for depression (Hallahan et al. 2016). Therapeutic effects have also been reported in young people with borderline personality disorder who are at ultrahigh risk for psychosis (Amminger et al. 2013) and in individuals with anxiety symptoms, regardless of diagnosis (Su et al. 2018).

***N*-acetylcysteine.** *N*-acetylcysteine targets a range of factors underlying the pathophysiology of neuropsychiatric disorders, including inflammatory pathways, oxidative stress, neurotrophins, apoptosis, mitochondrial function, and glutamatergic and dopaminergic neurotransmission (Berk et al. 2013). It has shown efficacy across several psychiatric disorders, including bipolar disorder and schizophrenia (Deepmala et al. 2015).

N-acetylcysteine is a precursor of glutathione, a major antioxidant that has a potential role in the onset and progression of mental illness. In young people at ultrahigh risk for psychosis, low erythrocyte glutathione levels have been identified as a good predictor of transition to psychosis over the long term (Lavoie et al. 2017). While the efficacy of *N*-acetylcysteine in reducing transition to psychosis has yet to be determined, *N*-acetylcysteine has demonstrable benefits in established and later stages of illness (Yolland et al. 2019). In the treatment of early psychosis, it has been associated with improvements in processing speed and positive symptoms as well as an increase in brain glutathione levels, indicating good target engagement (Conus et al. 2018). In chronic schizophrenia, *N*-acetylcysteine has led to greater clinical improvement than placebo, especially for negative symptoms (Berk et al. 2008), and has improved auditory cortical functioning, as indexed by MMN (Lavoie et al. 2008).

Cannabidiol. Cannabidiol exerts anti-inflammatory, antioxidant, and neuroprotective effects (Campos et al. 2016), making it a promising treatment strategy during early-stage mental illness.

Cannabidiol has a favorable safety profile, particularly in comparison to common pharmacological treatments used to treat psychotic disorders (Iffland & Grotenhermen 2017).

Cannabidiol has been shown to reduce anxiety symptoms across several populations, including individuals with long-term and treatment refractory anxiety (Berger et al. 2020) and individuals at ultrahigh risk for psychosis (Appiah-Kusi et al. 2020). Further evidence indicates that cannabidiol can effectively treat subthreshold psychotic symptoms (Berger et al. 2020) and normalize brain function in regions associated with the pathophysiology of psychosis (parahippocampal, striatal, and midbrain) (Bhattacharyya et al. 2018). In individuals with acute schizophrenia, cannabidiol exerts antipsychotic effects (Leweke et al. 2012, McGuire et al. 2017) and is associated with fewer adverse effects than amisulpride (Leweke et al. 2012). However, in chronic schizophrenia, cannabidiol augmentation has not been associated with improvements in cognition or psychotic symptoms, potentially suggesting that it is more effective during earlier stages of illness (Boggs et al. 2018). In the field of mood disorders, there is a need for clinical trials investigating the effects of cannabidiol (Pinto et al. 2020).

Novel Psychosocial Treatment: Digital Interventions and Functional Recovery

Although a number of challenges remain in translating digital mental health interventions into models of care (Torous et al. 2018), the integration of digital technologies within youth stage-based models of care has the potential to improve service access, efficiency, and engagement, as well as the cost-effectiveness and scalability of care, while continuing to deliver personalized care (Burns et al. 2016, Lal & Adair 2014). Novel digital models of care and interventions can support and complement in-clinic service provision and provide an acceptable and efficient mode to expand the reach of services, overcoming waitlist times and geographical barriers, although some barriers may remain (e.g., access to a device, affordability of data, literacy skills). A substantial proportion of young people present with early-stage mental ill-health or mild symptoms that could potentially be effectively managed via online platforms (Alvarez-Jimenez et al. 2020), allowing for greater face-to-face resources to be directed toward later stages that are characterized by greater complexity or severity.

The integration of technology within models of care can assist in delivering stage-based strategies, including those relevant to mental health promotion, prevention, early intervention, and recovery (Burns et al. 2016). The use of technology can specifically support core components of care such as comprehensive multidimensional assessment; allocation of clinical stage; multidisciplinary management of mental ill-health or illness with the type, intensity, and duration of care aligned to clinical stage; and routine outcome monitoring (Davenport et al. 2019). Validation of an online platform delivering stage-based care is currently underway, and data collected will be used to validate algorithms designed to allocate clinical stage and match patients to the right level of care (Davenport et al. 2019). Preliminary data indicate that online clinical stage allocation in early intervention youth mental health services facilitates a more efficient and holistic systematic assessment of lifetime severity of mental illness and complexity of clinical presentation than face-to-face assessment (Ospina-Pinillos et al. 2018). This is due to the online assessment focusing more on indicators of illness progression (i.e., past history of mental health problems, previous suicide planning, and current cannabis misuse) (Ospina-Pinillos et al. 2018).

Novel online interventions, particularly social media and internet-based approaches that can parallel real-world social processes, provide a new avenue for improving functional recovery in young people (Firth et al. 2019). Targeting functioning across the stages of mental illness is fundamental given that functional impairment is a modifiable risk factor for illness progression across stages (Iorfino et al. 2019); young people with emerging mental disorders are frequently

not in education, employment, or training (O'Dea et al. 2014); and functional impacts often persist following symptomatic remission and can endure well into adulthood (Gibb et al. 2010). The internet and social media are highly utilized by young people and are an acceptable platform for mental health care, making them an ideal method for engaging with this population (Birnbaum et al. 2017). While the development of online social media–based interventions is an evolving area, current innovative models, which integrate online social media, interactive therapy modules, and peer and professional moderation, indicate that they are a feasible, safe, engaging, and potentially effective intervention approach for young people experiencing mental ill-health (Alvarez-Jimenez et al. 2020), major depression (Rice et al. 2018), and various stages of psychosis (Alvarez-Jimenez et al. 2013, 2018). Virtual reality is a further promising "real-life" intervention approach, which has demonstrable effectiveness across a range of psychiatric disorders and as early as Stage 1 in psychosis (Valmaggia et al. 2016). In psychotic disorders, virtual reality–based cognitive behavioral therapy has been shown to reduce paranoid ideation and anxiety (Pot-Kolder et al. 2018) and has been hypothesized to induce faster recovery of mental states than treatment as usual (Geraets et al. 2020).

These next-generation digital interventions and models of care could potentially assist in ensuring that young people, especially those at high risk of illness progression, remain engaged in mental health care. Despite presenting with greater clinical and social needs, help-seeking young people at Stage 1b (particularly those without a current *Diagnostic and Statistical Manual of Mental Disorders* diagnosis) have significantly poorer engagement with services than those at Stage 1a (Cross et al. 2016b), highlighting the need to tailor treatment modality to the individual needs of young people.

Clinical Staging Informing Mental Health Service Delivery

Clinical staging is highly relevant to youth mental health systems of care because young people are most likely to experience the onset of mental illness, and traditional and current mental health systems fail to recognize the need for care during the earliest stages of illness. To effectively address the mental health needs of young people, a comprehensive approach is required that is capable of meeting the high level of demand and need. High-quality health systems should be patient centered, safe, appropriate, effective, and efficient to ensure that all individuals in need of professional help receive evidence-based care that is timely and tailored and leads to improved outcomes (Inst. Med. 2001). For young people seeking mental health services, acceptable systems of care are needed that acknowledge and effectively respond to the complexity and diversity of need, including the fluctuation of symptoms, the nonspecificity of early clinical phenotypes, the potential trajectory of illness, and the substantial comorbidity (McGorry et al. 2014b). A transdiagnostic clinical staging model recognizes these issues and provides a holistic framework to guide early intervention and prevention (McGorry & Hickie 2019). The model is also responsive to developmental phase; that is, it can differentiate between early illness phases (Stages 1a and 1b) that are commonly seen in younger ages and later, more established illness phases (Stage 2 and beyond) that are typical in older ages (Iorfino et al. 2019). A clinical staging service model ensures that help-seeking young people are provided with mental health care that is timely, safe, effective, and appropriately tailored to their stage of illness in terms of the type, intensity, and duration of intervention (McGorry & Hickie 2019). To ensure that interventions are matched to level of need, services need to be adequately resourced with a range of treatment options of varying intensity. As outlined earlier, digital platforms play a key role in ensuring that this level of care is scalable. It is important to recognize that a stage-based model of care is distinct to a stepped care model. The latter is largely focused on improving service efficiency and is a more reactive strategy, in which

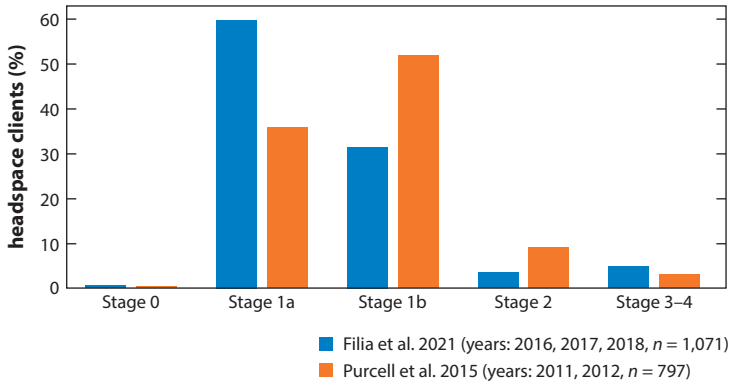

Figure 2

Clinical stages of young people (aged 12–25 years) attending headspace centers.

the lack of improvement at a step allows progression to the following step that involves a higher intensity of intervention. In contrast, stage-based models of care favor proactive or preemptive intervention that is personalized, appropriate, and timely.

In Australia, the clinical staging framework has been applied to headspace, an enhanced primary care model for youth mental health care (McGorry et al. 2014b). The proportion of headspace clients assigned to each stage is shown in **Figure 2**. headspace is a one-stop shop that provides young people aged 12 to 25 years with a range of services across four core streams: mental health, drug and alcohol, physical and sexual health, and vocational supports (Rickwood et al. 2019). Support is also available via headspace's nationwide online and phone service, eheadspace. headspace offers a stigma-free soft entry to primary mental health care and is guided by the principle that care should be appropriate to a young person's stage of illness, culture, and diverse identity (Rickwood et al. 2019). In line with the clinical staging model, a key focus is on providing appropriate and effective care well before a disorder emerges or during the earliest stages of mental illness to prevent progression or extension. headspace and other integrated youth models of care have shown positive outcomes in terms of service access, symptomatic and functional recovery, and client satisfaction (Hetrick et al. 2017) and have provided the blueprint for a global framework for youth mental health (Killackey et al. 2020).

Key elements of a primary-level stage-based model of care include comprehensive assessment, clinical stage allocation, evidence-based treatment planning with a focus on shared decision-making, stage-matched interventions, routine outcome assessment, integration with specialist mental health services, and planned exit from care to promote full recovery and secondary prevention (Cross et al. 2019) (see the sidebar titled Key Components of Stage-Based Mental Health Care for Help-Seeking Young People). Decisions concerning the type, intensity, and duration of intervention are considered together with the risk–benefit ratio of the intervention as well as the risk of illness progression. Simple and benign interventions (e.g., brief psychosocial approaches, education, and support) are typically used as first-line treatments, with more intensive psychosocial and/or pharmaceutical approaches, which may pose more risk, delivered in instances when initial psychosocial interventions are ineffective or when a young person presents with severe symptoms or risk (McGorry et al. 2014b). Young people presenting with fluctuating and nonspecific blends of symptoms typically require a different treatment approach than full-threshold disorders (e.g., psychosocial interventions for Stage 1 versus antipsychotic medication for Stage 2+).

KEY COMPONENTS OF STAGE-BASED MENTAL HEALTH CARE FOR HELP-SEEKING YOUNG PEOPLE

- Assessment should be multidimensional to ensure that intervention (type, intensity, and duration) is matched to level of need (Cross et al. 2019).
- Assessment domains to consider are mental health (illness type, stage, and trajectory); functioning, education, training, and employment needs; risk of self-harm and suicide; use of alcohol and other drugs; physical health; and objective measures of circadian rhythm, neuropsychological function, brain structure and function, and metabolic and immune markers (Rohleder et al. 2019).
- Allocation of clinical stage should be based on operationally defined criteria (e.g., Hickie et al. 2013a, McGorry & Hickie 2019).
- Through a shared decision-making process, the type and intensity of intervention should be matched to the patient's stage of illness and their needs and preferences.
- Early-stage psychological interventions should be transdiagnostic, while specific psychological therapies and medications should be provided for more established illnesses (e.g., clozapine for schizophrenia).
- Effectiveness of intervention and patient progress should be routinely monitored, with results informing changes to treatment type or intensity when indicated. At a service level, data can be used for quality improvement purposes (e.g., identifying service gaps and informing resource allocation) (Cross et al. 2019).
- Primary and specialist mental health services should be integrated to ensure that young people preemptively receive the most appropriate level of care according to their clinical and functional needs as well as their risk profile (Cross et al. 2014).

Application of clinical staging in headspace services has demonstrated the model's ability to guide service delivery, particularly in terms of resource allocation, duration of care, and stage-specific intervention and prevention strategies. Young people seeking headspace services at the earliest stages of illness (Stage 1a) show more favorable symptomatic and functional outcomes following treatment that is more benign and less intensive than young people at Stage 1b+ (i.e., attenuated or discrete mental disorders) (Cross et al. 2016a). This is in line with the model's principle that the right care at the right time leads to improved outcomes (McGorry et al. 2006). However, an important minority of young people at Stage 1a present with more complex clinical presentations (e.g., manic-like experiences, psychotic-like experiences, self-harm, and low social and occupational functioning) and have a heightened risk of early transition to Stage 1b (Iorfino et al. 2019). While young people at Stage 1a generally benefit from brief and low-intensity interventions (Cross et al. 2016a) for a minimum of 3 months (Cross et al. 2019), non-headspace data indicate that half of help-seeking young people at this stage may require specific interventions to effectively treat symptoms (Addington et al. 2021). In comparison to Stage 1a, young people at Stage 1b use significantly more services and typically receive more treatment combinations (including psychotropic medication). They also show similar treatment patterns to young people at Stage 2 (e.g., treatments received, professionals consulted), indicating that greater service resources should be directed toward individuals at higher risk of progression to mental illness (Stage 1b) and toward later stages (Stage 2+) (Cross et al. 2016a). This similarity between Stages 1b and 2 is in line with the notion that the type or dose of treatment for Stage 1b may be increased to reduce illness progression. Stepped care models are increasingly popular but inferior to staged care because a preemptive approach like this would not be supported in stepped care and a change in treatment would only occur reactively. A minimum 12-month duration of care is recommended for Stage 1b in recognition of the greater clinical needs and higher risk of progression to disabling

and persistent illness (Cross et al. 2016a). Factors associated with transition from Stage 1b to Stage 2, which can become targets of intervention, include psychotic-like experiences, circadian disturbances, and not being in education, employment, or training (Iorfino et al. 2019). For individuals at Stage 2, the 2- to 5-year period postdiagnosis is critical for early intervention, while individuals at Stages 3 and 4 require longer-term care that is matched to the patient's needs (Cross et al. 2019). In recognition of the accumulation of comorbid diagnoses across the life span (Caspi et al. 2020), treatment (even during Stages 3/4) should be multifaceted to prevent and respond to comorbidity.

FUTURE DIRECTIONS AND CONCLUSIONS

Personalized Intervention

The ultimate objective of clinical staging in mental health is to optimize health and well-being outcomes by preventing the onset and progression of mental illness via early and personalized intervention. This largely relies on the identification of reliable and modifiable markers that underlie the pathophysiology of mental illness, which can then become the targets of biological and psychosocial interventions (McGorry et al. 2014a). A future goal is to transform clinical staging into an evidence-based clinicopathological model that can be refined as new evidence emerges and that can allow each stage to be accompanied by comprehensive neurobiological, psychological, and clinical phenotyping and profiling. This would provide the basis for stage-specific and personalized intervention and prevention, as well as prediction of illness trajectory (McGorry et al. 2006). Here, we reviewed evidence for a variety of potential biomarkers that could be integrated into such a model. Other markers not reviewed here (e.g., neuroendocrine markers) may also be of relevance. Further biomarker research that is longitudinal and crosses diagnostic boundaries is needed to elucidate distinct trajectories and the pathophysiology of mental illness, which may reveal new therapeutic targets (McGorry et al. 2014a). This may also clarify the gene–environment interactions that underpin the onset, progression, and persistence of illness. Epigenetics may further illuminate gene–environment interactions and offer avenues for intervention. Polygenic risk scores may also play a role in personalized intervention; however, at present, they have relatively weak predictive power (Crouse et al. 2021).

Clinical Staging Across the Life Span

The current application of clinical staging to youth mental disorders aligns with the fact that the majority of mental disorders emerge before young adulthood and that traditional diagnostic systems have not been designed for young people with early or emerging mental disorders. This approach is supported by the accumulated evidence indicating a distinction between early and later clinical stages in transdiagnostic samples of young people, as reviewed above. There is, however, value in exploring the extension of clinical staging across the life span (Shah et al. 2020). This would require either expansion of the current model to include other relevant variables or the development of distinct but compatible models for the various developmental stages.

Alternative and Complementary Approaches

In addition to clinical staging, other new approaches have sought to address the limitations of traditional diagnostic categories and systems. These include RDoC and HiTOP. Unlike clinical staging, these approaches do not include a developmental perspective of psychopathology or a dynamic or longitudinal dimension. RDoC provides a framework for psychiatric research that seeks to identify biopsychological explanations of clinical problems, which can then inform classification

systems (Kozak & Cuthbert 2016). It is not currently intended for clinical purposes. HiTOP proposes a hierarchical dimensional approach to organizing psychopathology. It identifies dimensions based on the observed covariation of symptoms and combines co-occurring syndromes into larger spectra. While HiTOP has the advantage of being empirically driven compared to traditional diagnostic systems, its clinical utility is a work in progress (Kotov et al. 2021). RDoC and HiTOP are complementary approaches to staging that may be suitable for different purposes. Of active collaborative interest is the potential to integrate these approaches. Clinical staging can also be complemented by dynamic prediction approaches, based on cross-disciplinary methods, that are consistent with the fluid, fluctuating, and transdiagnostic emergence of psychiatric symptomatology (Nelson et al. 2017). This includes network theory, which could potentially be combined with clinical staging to examine psychopathology and further refine the emergence and progression of symptoms (Wigman et al. 2013).

Future Directions for Research

While substantial progress has been made over the last decade in advancing and validating the clinical staging framework for youth mental disorders, additional research is needed to strengthen the model's utility and realize its full potential. Future research should include a variety of innovative methodologies and designs and may, for example, involve large, well-powered prospective studies of transdiagnostic cohorts utilizing multidimensional data collection approaches (e.g., ecological momentary assessment, multiple biomarker measures), a range of analytical tools (e.g., network analysis, joint modeling, machine learning), and sequential clinical trial designs. Broad-spectrum youth mental health primary care services (e.g., headspace and similar models of care) that offer a low-threshold or soft entry point are a key platform for this research.

The growing interest in clinical staging has led to the development of various frameworks, from the transdiagnostic model described here to clinical staging models confined to diagnostic silos. A harmonized approach to staging is needed, which would facilitate the pooling of data into large data sets and enable comparisons across various cohorts. This endeavor will be facilitated by the International Working Group on Transdiagnostic Clinical Staging in Youth Mental Health, which recently proposed an international consensus statement for transdiagnostic clinical staging and a clinical research agenda (Shah et al. 2020).

The strength of clinical staging lies in its ability to not only heuristically guide neurobiological and intervention research, but also underpin clinical care and service delivery. Its integration into mainstream mental health care, especially early intervention services, will realize the ultimate benefits of staging in predicting illness trajectory and selecting highly personalized intervention and preventive strategies, which are tailored to an individual's current need and risk of illness progression and extension and are deployed in a more efficient and timely manner. Traditional diagnostic frameworks have failed to facilitate this preemptive approach. Clinical staging is a viable strategy to restore the utility of diagnosis and to accelerate personalized and preventive psychiatry.

DISCLOSURE STATEMENT

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the National Association for Research on Schizophrenia and Depression, The Stanley Foundation, the National Institutes of Health, the Wellcome Trust, and the Australian and Victorian governments. He has been granted patents for the prevention of psychotic disorders using omega-3 polyunsaturated fatty acids in Australia and in the United States (AU 2015203289, 2017; US 9884034, 2018), with an additional claim in the United States (US 15/844444) and a pending patent application in Canada (CA 2773031).

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