Pre-emptive psychiatric treatments: pipe dream or a realistic outcome of clinical staging models?

“Diagnosing schizophrenia or bipolar disorder with the emergence of psychosis (or mania) is analogous to diagnosing coronary artery disease after the occurrence of a myocardial infarct [1].”

In the 1990s, the growing acknowledgement that adolescence and early adulthood represent the peak ages of onset of psychosis helped drive clinical innovations such as early intervention services for individuals experiencing a first episode of severe mental disorder [2]. It also led to research that aimed to better understand the taxonomy of risk for ‘conversion’ from less specific symptomatic or prodromal presentations into psychosis [3]. A major impetus to continue the development of these clinical and research strategies was the conviction that psychiatry could learn fundamental lessons from general medicine, where clinical staging models are routinely employed to enhance not only the early detection, but also the systematic management of chronic diseases such as cancer, ischemic heart disease (IHD), arthritis and diabetes [Scott J, Leboyer M, Hickie I et al. Clinical staging in psychiatry: a cross-cutting model of diagnosis with heuristic and practical value (2012), Submitted] [3–6].

According to Gonella et al. staging defines “discrete points in the course of a disease” that are clinically detectable, reflect severity in terms of the risk of residual impairment or death, and possess clinical significance for choice of therapeutic modality and prognosis [6]. Critically, staging describes where an individual exists on a continuum from ‘at risk’, to ‘early illness’, through to ‘end stage’ [Scott J, Leboyer M, Hickie I et al. Clinical staging in psychiatry: a cross-cutting model of diagnosis with heuristic and practical value (2012), Submitted] [3,4]. It actively facilitates predictions about disease extension or progression that is...
largely independent of illness severity or duration. Clinical staging is therefore a more refined concept than cross-sectional diagnosis (which is largely blind to concepts such as age at onset or illness progression). For clinical psychiatry, it actively promotes greater attention to indicated prevention strategies (e.g., interventions for individuals at ultra-high risk of developing psychosis) [Scott J, Leboyer M, Hickie I et al. Clinical staging in psychiatry: a cross-cutting model of diagnosis with heuristic and practical value (2012), Submitted] [3,4]. We suggest that international adoption of clinical staging could move general psychiatry away from its traditional focus only on established disease. The benefits would include an active shift from the current focus on the development of ‘me-too’ psychological or pharmacological therapies. Clinical staging demands a greater appreciation of the need for novel research and treatment strategies that target the early stages of severe mental disorders [Scott J, Leboyer M, Hickie I et al. Clinical staging in psychiatry: a cross-cutting model of diagnosis with heuristic and practical value (2012), Submitted] [1,3–6].

In this editorial, we review how staging underpins modern medical approaches to chronic illnesses and highlight how applying this paradigm to psychiatry has major implications for innovative, pre-emptive interventions.

**Staging models in general medicine**

To understand the potential value of clinical staging, it is helpful to first illustrate the utility and implications of this model for a prototypical medical disorder, IHD (see also [1]). Individuals at high risk of IHD (i.e., stage 0 or the latency stage) can be detected by the presence of known risk factors, namely smoking, raised plasma lipid levels or family history. Even at this presymptomatic stage, appropriate dietary and lifestyle interventions are recommended. These may be augmented by specific medical therapies such as the selective use of statins. If a person with these risk factors develops hypertension, additional medications may be prescribed (e.g., β-blockers). Further interventions may follow based on evidence of overt illness onset (e.g., angina) or the results of electrophysiological, imaging and radiographic investigations. Ultimately, pre-empting the occurrence of a critical event, namely myocardial infarction, may be achieved with the insertion of cardiac stents. Such active and timely intervention may reduce the chances of illness progression to later clinical stages such as heart failure or of premature death [1].

As demonstrated, staging dictates that any intervention serves two overt goals—one to manage the current clinical stage, the other to prevent disease progression [Scott J, Leboyer M, Hickie I et al. Clinical staging in psychiatry: a cross-cutting model of diagnosis with heuristic and practical value (2012), Submitted] [3–6]. Further, there is an expectation that clinicians will actively engage with individuals presenting at the earliest stages (i.e., individuals perceived to be at risk of either premature death or progressing to late-stage IHD). Within this model, it is a failure of care if individuals experience the least desirable outcome (e.g., myocardial infarction) before interventions are provided [Scott J, Leboyer M, Hickie I et al. Clinical staging in psychiatry: a cross-cutting model of diagnosis with heuristic and practical value (2012), Submitted] [3,6,7]. Importantly, treatment for the initial stages should not simply rely on the earlier introduction of the same medications used for late stages. Early interventions are usually more benign, or more narrowly focused on risk factor reduction, than those recommended for later stages [4,7,8]. The overt expectation is that early stage treatments will be associated with better outcomes and fewer adverse effects (i.e., a larger benefit: risk ratio). Traditionally, later stage treatments are characterized by a greater risk: benefit ratio, but their use is accepted as the best option for avoiding or delaying progression to end-stage disease [9]. Lastly, as more individuals at risk of disorder or in the very earliest illness stages are detected and treated promptly, the model predicts that the proportion of late-stage cases requiring the most aggressive (and often more expensive) treatment or palliative care is likely to be reduced over time (Scott J, Leboyer M, Hickie I et al. Clinical staging in psychiatry: a cross-cutting model of diagnosis with heuristic and practical value (2012), Submitted) [6,9].

In summary, clinical staging should represent a substantial improvement over classical diagnosis by improving treatment selection and by linking the observed clinical phenotype with the extent of progression of the disease to guide therapy. The timing of intervention is a key determinant of the success of any specified treatment within a staging model. Clinical staging promotes the notion that interventions should not be delayed until after the individual has crossed a key clinical threshold that is indicative of poorer illness outcome. Evidently, staging...
in medicine has supported the development of novel, stage-appropriate interventions targeting potentially modifiable risk factors to reduce disease progression.

**Staging models & mental disorders**

Staging models have long been described for a range of neuropsychiatric disorders such as Alzheimer’s and Parkinson’s diseases. Obviously, if prognosis for the disorder in question is uniformly poor, the preventive perspective incorporated into staging may be viewed as unnecessary or possibly less helpful. As the outcomes of most early onset mental health problems are dynamic and variable (sociologically and neurobiologically), clinical staging assists clinicians to conceptualize the patient’s current mental state. If followed to its logical conclusion, it will lead to the development of stage-appropriate interventions for early subthreshold presentations. While these clinical scenarios are currently at the lower end of current diagnostic operational thresholds, they may represent the best opportunities for effective interventions [Scott J, Leboyer M, Hickie I et al. Clinical staging in psychiatry: a cross-cutting model of diagnosis with heuristic and practical value (2012), Submitted] [3,4,7–11].

In psychiatry, the identification of ‘at risk’ or ‘stage 0’ cases is hampered by the lack of discrete or easily modified risk factors, robust endophenotypes or biomarkers [Scott J, Leboyer M, Hickie I et al. Clinical staging in psychiatry: a cross-cutting model of diagnosis with heuristic and practical value (2012), Submitted] [1,12]. Consequently, to date, clinical staging has been appropriately limited to the early symptomatic presentations of psychosis and severe mood disorders in those presenting for clinical care [3,14]. Importantly, this early work confirms that while individuals may require short-term care to reduce risk or enhance function, only a subset of individuals move through the ‘gate’ at each stage so that those crossing traditional diagnostic thresholds (stage 2) or arriving at established, stable, end-stage disorder (stage 4) are very much the minority [1,2,13,14]. The major implication of this approach for clinical psychiatry is that stage-appropriate treatments can and should be devised for those help-seeking individuals who already demonstrate impairment in functioning and distress or are at significant risk of self-harm or suicide (even if their symptoms fail to reach the arbitrary criteria for a specified diagnosis). This clinical approach is clearly not an invitation to prescribe the major classes of psychotropics (e.g., antipsychotics, mood stabilizers such as lithium, or antidepressants) to prepubertal children or adolescents with undifferentiated syndromes that bear limited resemblance to those disorders for which these treatments were originally licensed. If staging is to help psychiatry move forward, we need to refine the goals of treatments for the early stages (0, 1a and 1b). This would represent the first attempt at pre-emptive psychiatric interventions designed to prevent or significantly delay conversion to severe mental disorders in those presenting with at-risk or attenuated mental states [11]. Although we do not know the optimal composition of these interventions, the broad-based goals will include ‘neuroprotection’ and ‘psychoprotection’ [7–10,13,15].

At this point, generic early stage treatments may include essential fatty acids or group and individual psychological therapies such as cognitive behavioral therapy. Both these interventions have been shown to be beneficial in reducing the rate of conversion to schizophrenia of those at ultra-high risk of psychosis [3,4]. The notional mechanism of action of ω-3 fatty acids is neuroprotection, which is especially important in early adulthood when a degree of excessive ‘pruning’ of networks is likely, which may have adverse future consequences for cognitive functioning [10–12]. Likewise, there is evidence that cognitive processing errors (e.g., negative self-perceptions, jumping to conclusions and rumination, among others) are transdiagnostic processes that increase the risk of developing a range of mental disorders from anxiety through to depression and psychosis, and are associated with the persistence of symptoms [7,8,15]. Hence programs that target these core cognitive dysfunctions and promote positive self-esteem and problem-solving skills may be helpful to a broad population of youths early in the course of illness (independent of which final illness point they may be at risk of reaching).

Currently, we do not have an evidence-based platform for personalized treatment in clinical psychiatry. We simply do not know which intervention will work for whom or what to give those who will respond poorly to early stage, generic treatments. Linking the underlying pathophysiology to risk factors, prodromal signs of illness and first-illness episodes and to treatment response has been the crucial next step for clinical staging models in general medicine [7,8,12,13]. This must remain a high priority for the potential impact of clinical staging in psychiatry. There is now some evidence that this critical research goal (detailing...wider adoption of clinical staging models to refine current diagnostic practice would revitalize the development of clinical practice guidelines.”
neuroimaging, neuropsychology and circadian biology parameters) has been advanced by the adoption of clinical staging in the early phases of major mood disorders (1,7,8,12–14).

For now, wider adoption of clinical staging models to refine current diagnostic practice would revitalize the development of clinical practice guidelines. That is, such clinical guides could incorporate stage-appropriate assessments and treatment choices. This would overtly acknowledge the true developmental trajectories of severe mental disorders and finally give hope to the notion that psychiatry can offer pre-emptive interventions. We should no longer wait for the mental equivalent of a ‘heart attack’ (e.g., attempted suicide, first manic attack and first psychotic episode) before clinicians are galvanized into action (Scott).

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