



Risk syndromes, clinical staging and DSM V: New diagnostic infrastructure for early intervention in psychiatry

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1. Risk and the risk syndrome

The proposal to consider including the concept of the risk syndrome in the forthcoming revision of the DSM classification is innovative and timely. It has not come out of left field, however, and is based upon a series of conceptual and empirical foundations built over the past 15 years. Since the term “risk” is central to the proposal, let us initially consider the notion of risk and risk factors.

Kraemer (Kraemer et al., 1997) did the field great service in teasing apart the conceptual confusion concerning the term “risk”. She carefully distinguishes between risk markers, which can include biomarkers, and risk factors, and then further defines the causal risk factor. In the 1990s, Bell (1992), Eaton et al. (1995) and Mrazek and Haggerty (1994) made major contributions which helped us to move forward and create an empirical basis for the risk syndrome idea. Because we had relatively poor knowledge of causal or malleable risk factors for onset of disorder in psychiatry, unlike in cardiovascular disease for example, these authors, principally Eaton, suggested a major shift in strategy. This involved modifying the sophisticated new prevention framework of Gordon (1983) to allow sub-threshold syndromes to be regarded as risk factors for the full threshold syndrome such as psychosis/schizophrenia, or severe/major

depression. This strategy became known as “indicated prevention” and has been successfully pursued in psychosis (Yung et al., 1996; McGorry et al., 2002; McGorry et al., 2003) and in depression (Clarke et al., 1995; Clarke et al., 2001; Garber et al., 2009). While only a subset of those with “warning signs” or sub-threshold features progressed, the idea was to capitalise on the predictive power and the risk conferred by these features to intervene preventively. We have since built a clinical staging model to illuminate further the utility of this model for aetiological and intervention research (McGorry et al., 2006). The proposal to include a class of risk syndromes in the future DSM V is an expression of this idea and would take us forward heuristically and practically. Does it go far enough however? And, if introduced in too limited a manner, such as for psychotic disorders only, rather than as a class or generic concept, would there be unacceptable risks?

2. The early intervention imperative

It has long been recognised that the need for care in psychiatry substantially precedes the point that a diagnosis can be assigned according to classical concepts (Sullivan, 1927; Meares, 1959; Hafner, 1998). Waiting for perfect diagnostic clarity works against early intervention and is clearly hazardous to the health of patients (McGlashan, 2006). However, while we can agree that there is a need to intervene well before severe and more intractable illness and collateral psychosocial damage supervenes, how do we define the initial clinical stages to guide early intervention, and what should be the range and sequence of interventions offered?

The past 15 years have seen significant but incomplete progress in responding to these questions. Until recently we have lacked the diagnostic infrastructure, in the form of operational definitions, which characterise the early syndromal stages of the major psychiatric syndromes, and consequently clinical trial data to provide an evidence base for early intervention. This defect has been partly remedied, although

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much of the scientific progress and debate to date has been conducted within the “silo” of psychosis and schizophrenia (McGlashan, 2005; McGorry, 2008; McGorry et al., 2009a, 2009b). However the challenge of early intervention is a much broader one and extends to the full spectrum of mental disorders (Insel, 2007; Saraceno, 2007). The first issue that needs to be tackled is to define the boundary between those who are experiencing mental ill health and those who are not; i.e. the point for which a need for care can be clearly agreed upon.

3. The boundary with normality: when is the need for care first apparent?

“We want to know what to ask to split clearly between the people who are having trouble in living and the people who are at grave risk of psychosis” Harry Stack Sullivan (1927)

The majority of the psychiatric morbidity which manifests during adult life emerges for the first time before the age of 25 years, either evolving from childhood emotional and behavioural disorder, or appearing *de novo* from puberty through to the mid-twenties as a surge of new incident cases (Kessler et al., 2005; Kessler et al., 2007). Lifetime risk for mental disorder can reach as much as 50% (Kessler et al., 2005). There are many biological, psychological and sociological reasons for this pattern of onset (Arnett, 2004; Eckersley, 2008; Paus et al., 2008).

The onset of mental disorder can be difficult to distinguish from transitory and normative changes in emotions and behaviour, especially in young people. In public and professional forums the question constantly arises: how does one tell the difference between a young person who is merely experiencing a troubling period, and one who is developing a mental disorder for which intervention is required? In a world where stigma still reigns, not only have we not clarified this boundary sufficiently, but there is anxiety and confusion about diagnosing mental disorders for the first time in young people. In the public mind this is partially based on a residual fear from the institutional era when many people were wrongly incarcerated for trivial or social reasons (Barry, 2008) and partially on the fear of overuse of psychotropic medications. Some have even suggested that since disturbances of this kind are common in young people, we should adopt a high threshold for defining onset of disorder. In my view, it would be a real mistake to set the bar too high for any of these reasons. Why should it be acceptable for young people to be persistently distressed or impaired and denied access to help simply because these are common experiences, because of stigma, relative weaknesses in the evidence base, or because of cost? We know this is the peak period of mental ill health across the lifespan (Kessler et al., 2005) and that such mental ill-health limits potential with damaging effects for several subsequent decades. If 51% of the population has a treatable infection, such as swine flu, do we withhold treatment because it is common and “normal”? The key question should be: is the experience undesirable or harmful, and can it be seen as evidence of poor mental health? This is critical, since not even all psychiatric symptoms, including hallucinations and

extreme beliefs, are necessarily associated with distress or impairment (van Os et al., 2001). On the other hand persistent depression in young people is demonstrably harmful, risky and relatively common.

If our focus is the full range of potentially serious mental disorders, then I believe the best approach is to not seek out the first signs of individual diagnostic syndromes, such as schizophrenia or bipolar disorder, but to decide when there is a need for care, independently of any specific syndromal content. This can be based purely on the dimensions of severity of distress, disturbed relationships and/or functioning, and/or persistence of such changes. The boundary for the initial offer of care should be set where there is a capacity to benefit from it and the potential benefits outweigh any risks of such care. A secondary question therefore arises, namely do we have effective interventions, which make sense and are acceptable to first time patients, and what are the risks of intervening in different ways? The risks still include stigma, though this has not been measured in this context. In our own recent experience this can be largely avoided with the right culture and context of care (McGorry, 2007). A final benefit of setting the bar on the low side is the potentially preventive effects of early treatment on secondary syndromes and disability; i.e. a disease-modifying effect. Cost-effectiveness of care may also be improved by earlier intervention. Clearly, however, care should be offered rather than imposed in these early stages. On the other hand, care should not be withheld. Is our diagnostic system currently able to support this endeavour?

4. The poor utility of psychiatric diagnosis for early diagnosis and treatment

In the current DSM and ICD systems, there are no agreed criteria at present for defining a threshold for an initial generic or specific “caseness” as proposed above. The definitions of the major mental disorders fail to acknowledge the complex and evolutionary nature of onset. How symptoms are acquired, intensify and cohere into syndromes, and how these ebb and flow, has not been widely considered (Eaton et al., 1995). We also lack valid definitions for distinguishing between benign and self-limiting states, which represent the early stages of what could become persistent and disabling conditions (Kessler et al., 2005). While some or even most distress may seem, initially at least, self-limiting (Eaton et al., 1995), it is important not to trivialise the significance of this since sub-threshold symptoms strongly predict future disorder (Eaton et al., 1995; Harrington and Clark, 1998; Yung et al., 2004; Hetrick et al., 2008; Seeley et al., 2009). In addition, even self-limiting distress and impairment usually warrants care or at least support of some kind.

We have been far too patient with the traditional diagnostic system, which, for the psychotic and mood disorders, was built during the age of steam. This system is characterised by artificial divisions based on cross-sectional symptom sets, propped up with course and outcome variables. The validity of categories, such as schizophrenia, even as end-state or target syndromes remains in question (McGorry et al., 1990; McGorry, 1991; Craddock and Owen, 2005). This is one reason why the debate about risk syndromes must be conducted beyond the confines of the psychosis/schizophrenia field. Until recently, early clinical features had not been differentiated from those

that become apparent once clinical disorder evolves and persists, and scant consideration had been given to the definition of the onset of a disorder and the initial clinical stage. The traditional diagnostic concepts in the mood and psychotic disorders have been derived “back to front” from the more prevalent subsamples of chronic patients, spuriously enhancing the impression of stability and validity. However, in everyday clinical practice this spurious precision breaks down in a fog of shifting comorbidity, and questions of validity and utility remain unresolved. Diagnoses like schizophrenia function largely as stable outcome variables, rather than useful tools for guiding early intervention or treatment of people with less severe illness, or uncovering underlying pathological mechanisms. The ubiquity of polypharmacy, a practice frequently criticised by purist adherents to the current diagnostic schema, provides evidence of the practical weakness of our current diagnostic concepts. The principal purpose of diagnosis is to guide treatment selection. In psychiatry however, drug therapies lack specificity for individual diagnoses, as reflected in high levels of off-label use and ever-widening indications. Psychosocial treatments appropriately focus on broader personal and social needs and hence range freely across the diagnostic landscape.

In summary, the concepts and definitions we have used to date, since they are quasi-syndromal, polythetic and descriptive, lack discriminant validity and therapeutic utility. Arbitrary strategies to force discriminant validity, such as hierarchies, merely obscured the problem and have been breaking down; however, the currently popular dimensional adjuncts seem to me just as unlikely to solve it. Overdue impatience with the traditional “purer” categories has produced a welcome desire to explore larger super-ordinate categories with a complementary dimensional cross-cutting matrix (Regier et al., 2009). However, no practical research strategy has yet been formulated to take us beyond the current impasse and the DSM and ICD revisions continue to occur within “silos” constructed, as mentioned above, in the age of steam. The best we can hope for from these revisions is a better steam engine.

What we really need is a heuristic strategy that aims to develop ground rules for clarifying as early as possible which people with emotional and behavioural disturbance are at specific risk of persistent and disabling mental illness and what sequence of established and novel therapeutic strategies is most likely to achieve remission of current symptoms as well as psychosocial recovery, and reduce the risk of persistence and recurrence.

Such a framework would aim to select treatments in a safer, sequential and more effective manner, to assess prognosis more accurately, and rearrange the confusing array of biological disturbances into something resembling a clinicopathological approach. Clinical staging, a deceptively simple and practical tool found useful in other areas of medicine, may provide a way forward (McGorry, 2007; McGorry et al., 2006, 2007). In a pre-emptive psychiatry based on this clinical staging paradigm (Insel, 2007; Insel, 2009), end-stage syndromes such as deficit schizophrenia may fade into the background as destinations to be avoided. This would be a welcome departure from the deterministic thinking that has plagued psychiatry for so long, and would also open the door to a better understanding of gene–environment interactions in the onset and course of psychiatric illness.

5. Clinical staging

Clinical staging is a more refined form of diagnosis. Its value is recognised in cancer and many other potentially serious medical illnesses, such as diabetes and arthritis, where limiting the extension and secondary impacts of the disease, and improving quality of life and survival, all rely on the earliest possible delivery of effective interventions. Clinical staging differs from conventional diagnostic practice in that it not only defines the extent of progression of a disorder at a particular point in time, but also where a person lies along the continuum of the course of an illness. The differentiation of early and milder clinical phenomena, from those that accompany illness extension, progression and chronicity, lies at the heart of the concept, which therefore makes it especially useful in adolescence and early adulthood, when most adult-type disorders emerge for the first time. A staging framework enables clinicians to select treatments relevant to earlier stages of an illness, and generally assumes that such interventions will be both more effective and less harmful than treatments delivered later in the course. Such an approach is worth consideration in psychiatric diagnosis given the range of problems described above.

Early successful treatment may change the original prognosis by preventing progression to subsequent stages, optimally resulting in remission and cure. In medicine, the boundaries and focus for a specific staging approach can be solidly based upon a pathological or tissue diagnosis. In psychiatry our current diagnostic categories are disconnected from the underlying substrates of the disorders, which remain elusive, and impose artificial boundaries without utility. In addition to guiding treatment selection, a staging framework, which spans the current “diagnostic silos” to encompass a broader range of clinical phenotypes, yet which introduces subtypes along a longitudinal dimension, has the potential to organise endophenotypic and biomarker data in a more coherent and mutually validating fashion. We need to cast the net wider to help us redraw these boundaries.

6. The risk syndrome as a new class or stage of disorder

The term “risk syndrome” has been proposed as a new class of disorders for inclusion in the DSM V (Carpenter, 2009; Woods et al., 2009). It has been suggested that there may need to be multiple definitions of risk for particular syndromes, though it remains unclear how separable these would be from one another. A pluripotential risk syndrome which is phenotypically broad and hard or impossible to subtype seems the most useful concept, even if it remains possible that it is underpinned with variable mixtures of biomarkers for later more specific syndromes. In fact, within a staging model each stage is in fact a risk syndrome for the next. So is the term risk syndrome helpful or misleading? If the features in question constitute a syndrome and there is a corresponding need for care, or if existing syndromes pose risk for other syndromes why does the term risk need to be included in the title? Is the momentum for risk a linear or more dynamic phenomenon? Many of these questions have been raised as a result of the work done on clinical risk syndromes in psychosis, where the proposal to include a specific psychosis risk syndrome in the DSM V has been made (Woods et al., 2009).

Since we first operationalised the clinical criteria denoting risk for early transition to psychosis in 1994 (UHR or “ultra high risk”) as part of our early psychosis clinical research strategy, there has been substantial progress in confirming the predictive validity of these criteria and in showing that the risk they confer for transition can be reduced by both psychosocial and drug therapies, at least in the short term and while such treatments are being adhered to (McGorry and Singh, 1995; Yung and McGorry, 1996; McGorry et al., 2003; Yung et al., 2003; Yung et al., 2006; Yung and McGorry, 2007; Yung et al., 2008; Woods et al., 2009; McGorry et al., 2009b; Amminger et al., 2010).

The relative risk for transition to psychosis for those who meet the criteria for this risk syndrome is as high as 400 (Cannon et al., 2008), and even lower estimates based on falling transition rates are around 200 (Yung, 2008). It is true, however, that the most common outcome of the UHR state is not psychosis per se but persistence or emergence of non-psychotic illness, typically a blend of anxiety and depression (Phillips et al., 2007). So even when the target syndrome is “non-affective psychosis” not only affective psychoses but also non-psychotic affective disorders are caught in the net. This indicates that a common risk syndrome may precede the different trajectories to more specific target syndromes such as mania, psychosis, schizophrenia and severe or chronic depression (and perhaps other candidate syndromes), and that intervention at this stage is a more logical first step. Risk syndromes with greater specificity for schizophrenia or psychosis on the one hand and for severe mood disorders on the other may take shape as way-stations beyond this common risk syndrome, but prior to reaching full threshold for the target. The boundary or definition of this common risk syndrome might ideally correspond with the initial need for care, but perhaps not. Regardless, this stepwise approach reflects the thinking behind the clinical staging model and effectively defuses the false positive issue, which has caused anxiety in relation to the psychosis risk syndrome (Yung et al., 2007).

Persistence and progression beyond such a common risk syndrome, especially if this occurs despite exposure to broad spectrum interventions such as stress management, CBT and practical case management, and particularly if associated with the emergence or intensification of greater syndrome specificity such as psychotic or manic symptoms, might allow sub-typing of risk syndromes. This could also be progressed in a dimensional rather than purely categorical fashion, allowing for comorbid risk.

7. Proposal

My own proposal for the new classification systems begins with the project to operationalise an initial syndrome linked to need for care of the simplest type. This might connote levels of risk for the major syndromes which are actually far too low to justify the term “risk syndrome”, since the risk might prove to be less than say 10% and even then risk may not be imminent or short term. A possible term for this might be “Entry Syndrome” or “General Distress Syndrome”. We would then need to define a second stage, which not only would capture a greater (or at least more persistent) level of distress and/or impairment, but also a more compelling level of risk, say 50% or more, of combined risk for one or more of the more serious syndromes (disorders such as psychosis/schizophrenia, bipolar disorder or

chronic depression). This is a multiple target strategy. We could call this pluripotential stage the “Common Risk Syndrome”. Beyond this stage there may be value in sub-definitions of the risk syndrome concept linked to specific target or exit syndromes, e.g. “Psychosis Risk Syndrome”. This feasibility and utility of this step will depend upon the separability and independence of the trajectories of the putative exit syndromes at this point in the illness course.

Whether we need to insert the word risk in the terminology is debatable, since each stage, even the first, is above the threshold of need for care. Thus, intervention is justified on the merits of the presenting symptoms and problems, and the clinical staging model implies that earlier stages connote risk for later ones. However I do favour the insertion of the term risk in the title of the two putative stages post-entry but sub-threshold for the major target syndromes. This would make explicit and highlight the (additional) preventive target of reducing the risk of progression as well as the immediate or proximal one of relieving current symptoms, distress and impairment.

For this proposal to progress, we need to move outside our research silos and conduct additional careful work to operationalise the stages and concepts involved. This will take time. How should we respond in the meantime to the more modest proposal to create a class of risk syndromes in the DSM V of which the first version would be the Psychosis Risk Syndrome (PRS) based on the UHR concept? The main objections have been linked to the potential for harm, though I have pointed out a number of conceptual problems earlier in this article. Personally I believe that the PRS should be endorsed as an interim platform for further work, provided the contextual issues I have explained are kept in mind. I agree with Carpenter (2009) who points out that endorsing in some way the class of risk syndromes enables a framework for early detection and intervention and consequently evidence-based treatment. Potential for misuse is an insufficient argument against inclusion, since many other categories would have to be deleted if this were to be the criterion for inclusion or retention in the DSM. It is, however, important to be aware of the pitfalls and potential for harm arising from the use of risk syndromes, notably the assumption that the treatment needs are the same as for the fully-fledged disorders. It is vital that we actively explore via sophisticated clinical trials the treatment options and sequences for this crucial stage of illness (McGorry et al., 2008; McGorry et al., 2009b).

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