Understanding pathophysiology is crucial in linking clinical staging to targeted therapeutics

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McGorry et al in Melbourne, and a select number of other groups around the world, have been instrumental in a paradigm change in the approach to schizophrenia over the last fifteen years or so. They have infused an illness that was seen as inexorably deteriorating with new hope, new data and new therapeutic optimism. The academia and the clinicians have responded to their idea. A quick search of PubMed shows that from 1993, when the first articles entitled “early intervention in schizophrenia” appeared, there have been at least 480 publications in the field. There were 22 in the field in the years before 1992. Mental health services around the world have reconfigured and invested in establishing early intervention teams for psychosis, and there has been an explosion in research in this area. Of course, there have been other developments over the same period that have contributed to clinical and research optimism – developments in neurobiological research, and the introduction of new therapeutic agents for example – but few others have linked the clinical and research domains so directly. McGorry et al, in their article in this issue, show they are still leading the evolution of thinking in research and clinical practice in this field.

It is worth reflecting on how what was recently inconceivable – the prevention of schizophrenia – has become conceivable, though not achievable. Currently

the best we can aim for is secondary prevention – intervention in individuals who are already symptomatic and functionally impaired to reduce the likelihood of their condition worsening. In this article McGorry et al draw on general medicine to introduce the concept of clinical staging to psychosis, with the proposal for three stages: ultra-high risk (putatively prodromal), first episode and recovery. However, a critical constraint on the applicability of a clinicopathological staging model to psychosis is our limited understanding of the underlying pathophysiology. Currently we rely on purely clinical factors to predict outcomes, for example which ultra-high risk patient will develop psychosis, or which first episode patient will respond to treatment. However, this approach still lacks satisfactory sensitivity and specificity and, in most cases, independent validation. More crucially, it does not suggest targeted, stage specific interventions.

Since our criteria for separating ultra-high risk from first episode are symptomatic, our treatments for the two must be distinct if we are to call one “secondary prevention” and the other “early treatment”. Since McGorry et al borrow from the rest of medicine, let's take an example from the rest of medicine to illustrate this point. Understanding the pathophysiology that leads to a heart attack has enabled clinicians to identify biomarkers for risk that can be combined to target intervention most appropriately. To prevent coronary artery disease, doctors identify patients with elevated cholesterol levels and treat them with dietary intervention or statins; or, if the patient has hypertension in addition, they are offered a beta-blocker. However, they are not

immediately offered a mini-angioplasty. The point being that the treatments used in secondary prevention are targeted at processes different from that used to treat the illness. We are not there as yet in psychosis. The treatments that are provided to patients in the first episode and have been evaluated in those with prodromal signs (antipsychotic drugs, cognitive-behavioural therapy and case management) are essentially the same interventions that are given to patients with established psychosis. Moreover, we do not know which form of intervention will work for whom, or what to give those who will respond poorly to treatment. Understanding the pathophysiology of risk factors, the prodromal signs of the illness, the first episode and determinants of recovery and response to treatment is a crucial first step towards the sort of clinical staging used in general medicine.

Nevertheless, there is some scope for optimism that the pathophysiology of these stages can be determined. The application of standardized criteria for characterizing people who are likely to be in the prodromal phase of psychotic illness (1,2) has provided a means of prospectively studying the development of psychosis, while the development of early intervention services has increased contact with patients in the early phases of psychosis. This has permitted the investigation of an area of clinical equipoise – whether to initiate treatment in people with prodromal signs – and informed the development of methods for secondary prevention. At the same time, it has enabled significant advances in the understanding the neurobiology of psychosis.

Structural and functional neuroimaging studies have shown that many of the abnormalities seen in chronic psychotic disorders are not only evident at the first episode of psychosis, but also in individuals with prodromal signs (reviewed in 3, 4). These include reduced frontal, cingulate and temporal grey matter volume (5-9), altered activation in these regions

during tasks that engage executive functions and working memory (10-11), and changes in the white matter tracts that interconnect them (12). Molecular imaging and magnetic resonance spectroscopy studies in people with prodromal signs have also revealed elevated pre-synaptic dopamine function, and alterations in glutamate levels and serotonin receptors (13-16). Moreover, longitudinal neuroimaging studies indicate that some of the structural anomalies evident in the prodromal phase progress as individuals make the transition to psychosis (5). Progressive reductions in grey matter volume appear to continue after the first episode and may be related to long term clinical outcome (17-19).

Whilst these studies are promising steps in identifying the neurobiology that might underpin a clinical staging model, a number of requirements need to be met before research findings can find clinical utility. Firstly, predictive findings need to be replicated in independent samples. This is beginning to happen for structural anomalies, but has yet to have been done for functional changes. Secondly, specificity not just to psychosis, but also to functional outcome and stage needs to be established. Biomarkers that meet these requirements can provide clear targets for the development of novel, stage specific therapies (20).

Progress in our field has come from many directions. Till now the major developments have been the result of astute clinical advances or new medications from the pharmaceutical industry. And while we should be truly grateful that this has happened, neither of them are explicitly linked to the underlying pathophysiology of the illness. As a result, the illness of schizophrenia has been a subject of constant reconceptualization and redefinition. Therefore, if the clinical staging model could be anchored to an evolving pathophysiology, it would offer the opportunity of a new conceptualization that might outlast its earlier counterparts.

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