A clinical trials agenda for testing interventions in earlier stages of psychotic disorders

Patrick D McGorry, Alison R Yung, Christos Pantelis and Ian B Hickie

ABSTRACT

- A fundamental shift in the design of clinical trials for psychotic disorders is desirable and feasible. Priority should be placed on evaluation of the efficacy of interventions targeting different phases of illness.
- A range of traditional therapeutic approaches needs to be augmented by an increased emphasis on the potential benefits of informational, e-health, behavioural and neuroprotective strategies.
- A new national clinical trials platform, based on *headspace*, the National Youth Mental Health Foundation, is outlined. It provides the opportunity for conducting large multisite clinical trials in young people with emerging major mental disorders.

MJA 2009; 190: S33–S36

The early phases of schizophrenia and other psychotic disorders usually manifest as sustained and prolonged periods of emotional and behavioural changes. Symptoms may be diffuse, mixed, and subthreshold in pattern and severity. Recent research has shown that the prodrome of schizophrenia is indistinguishable from that of major depression.[1] We contend that a kind of pluripotential prodromal stage exists. From this non-specific prodrome, there are essentially two ways a disorder can emerge. Firstly, an existing emotional or behavioural state can intensify in severity or persistence, causing distress or disturbance in the person's life. Secondly, new subjective experiences can emerge, intensifying with distressing and disruptive effects.

We have incorporated such thinking into a clinical staging model of mental disorders.[2] Within this model, the initial pluripotential prodromal stage can result in a range of outcomes, including spontaneous remission, progression to a non-psychotic disorder or development of subthreshold psychotic symptoms — the ultra-high risk (UHR) state.

In the case of psychotic disorders, there is a gradual or sudden emergence of hallucinations or delusions, which may initially appear in subthreshold or fluctuating forms. A series of studies has identified a set of clinical features that confer a UHR of proceeding to a first psychotic episode.[3] First-episode psychosis is said to have developed once psychotic experiences become persistent and are at full threshold level,[4] marking a point at which antipsychotic medications are indicated.[3] Hence, first-episode psychosis is a practical and useful diagnostic marker, and the concept of early or first-episode psychosis has proved popular as a structural basis for service reform and investment worldwide.[5]

First-episode psychosis can develop along a range of trajectories, including the subsequent development of schizophrenia. One implication of the staging model is that if interventions occur early, either during the non-specific prodrome or during the UHR state, then development of later stages, including schizophrenia, may be prevented. Importantly, we are not suggesting treating asymptomatic patients. Rather, because these early phases are associated with distress, disability and a range of psychiatric symptoms, they can be seen as targets for intervention in their own right, as well as potential precursors to later stages.

The need for clinical care can be identified well before a clear traditional diagnosis of frank psychosis or schizophrenia emerges. Clinical trials are urgently needed to define the safety and effectiveness of both psychosocial and drug therapies in these early, less clear-cut clinical stages. It is possible that delivering simpler, safer treatments for briefer periods at an early stage of illness will prove more effective than if treatment is withheld until a later stage. Clearly, a more permissive approach and a broader range of interventions are needed. Formal diagnosis of specific mental disorders and provision of some types of treatments (notably medications) potentially carry significant risks (eg, experiences of stigma, discrimination, physical health side effects). Failure to identify and treat severe mental illness in a timely manner increases other risks (eg, suicide, homelessness, unemployment, offending behaviour, comorbid drug or alcohol misuse, comorbid physical illness). Clinical trials will define the risk–benefit ratio associated with the provision of particular interventions at different time points, thereby allowing more informed patient- and family-oriented decision making.

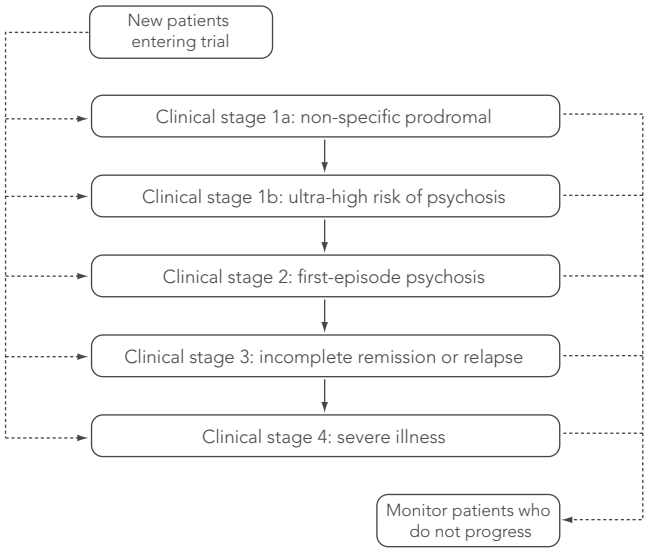
Designing clinical trials for early stages of illness

How, then, should we design trials for early stages of major disorders? We believe that adoption of the clinical staging model is an essential first step. Clinical staging augments conventional diagnostic practice in that it defines the extent to which disease progression at a particular point in time, and where a patient's current condition, lie along the continuum of the course of illness. The differentiation of early and milder clinical phenomena from those that accompany illness progression and chronicity lies at the heart of the concept. The model proposes that clinicians select treatments relevant to earlier stages, and assumes that such interventions will be both more effective and less harmful than treatments delivered later in the course of illness.

Health service developments that support new clinical trials

To progress this more flexible model of clinical research and related health care, much better access to health care is required for young people with emerging mental health problems. Fortunately, a change has occurred that will allow a new level of mental health clinical research in Australia. With the establishment of 30 new youth mental health service centres across Australia, *headspace* (http://www.headspace.org.au), the federal government's recent major funding initiative in youth mental health, has created a unique opportunity for longitudinal cohort studies and multicentre clinical trials focused on the earliest stages of emerging mental disorders. Although *headspace* is in its early stages of development, several thousand young people have

Design of a national clinical trials platform for testing interventions across various stages of psychotic and non-psychotic illnesses



The proposed clinical trials platform permits entry of participants at each stage of illness into a staged cascade of individual clinical trials. Other than at the initial intake, participants will enter the next stage because of the development of new and more specific symptoms, persistence of the disorder or failure to respond to previous treatment strategies. The goal of this approach is to have sufficient numbers of participants at each stage who are not only well matched to the content of the proposed intervention trial, but also are at high risk of progression to the next stage (ie, persistence or recurrence of their illness, or deterioration in their social functioning if they do not receive active intervention). Within such a model, responses to non-specific clinical care (ie, placebo responses) are also likely to be minimised, as a high proportion of each cohort will have participated in earlier clinical trials of less intensive or less specific interventions. All participants will receive informational, e-health, psychological and social interventions. Early pharmacological approaches are more likely to be generic in nature (eg, selective serotonin reuptake inhibitors, neuroprotective agents), particularly for those who have not yet developed psychotic phenomena. Later approaches will involve more specific interventions such as mood stabilisers and antipsychotic medications, including clozapine. ◆

already gained access to multidisciplinary care, many in the subset of services led by, or with close links to, clinical research centres. We expect this will allow the progressive creation of a firm evidence base for earlier diagnosis and treatment, and lead to a better understanding of a range of mental and substance-use disorders. Given the comorbidity and dimensionality that characterise the early stages of mental disorders in young people, a "wide-angle lens" is essential to allow a focus on those who are at greatest risk of persistent and disabling forms of mental disorder.

Implementing a national clinical trials platform

We propose a series of larger-scale cohort studies and multicentre effectiveness trials in young people with emerging mental and substance-use disorders (Box). Early interventions need to be simpler, safer and cheaper. In fact, with disorders of slow and diverse onset, there may be an optimal time to intervene — too early may be inefficient and trivialise the concept of what a disorder is, but delay may mean the disorder becomes refractory to intervention, either for biological or psychosocial reasons. Others have proposed that cost-effectiveness is superior to current severity or disability as a triage criterion.[6,7] The notion of an optimal point for intervention represents a testable hypothesis that may vary across types of disorder.

Mounting large-scale multicentre studies with a sufficient overall sample size to rapidly test new therapies will require the use of practical trials that focus on effectiveness in real-world settings, rather than narrower efficacy trials.[8] From a theoretical perspective, there is a clear need to increase statistical power to conduct valid preventive and early intervention trials. We can achieve this by setting the main research boundary at the level of indicated prevention, which in turn can be accomplished by focusing on groups with multiple risk factors and early clinical changes; defining outcomes broadly and using briefer and more robust measures, with multiple exit syndromes and/or poor functioning as the key outcome to be prevented; and progressively strengthening the effectiveness of specific interventions and programs.

Novel therapeutic strategies

Engagement of young people who are in the earliest stages of mental disorders, including psychoses, means that safer and more acceptable interventions, including simpler e-health and psychosocial therapies, can be offered with better prospects of success. It also means that biological therapies with a better risk–benefit ratio can be explored.

Recently, we have seen a shift in views of neurodevelopment, neurodegeneration and adult brain functioning, with the revelation that the central nervous system can generate and remove progenitor, glial and neuronal cells across the lifespan, not only early in life as was previously thought.[9] Internal neurotrophins (eg, glutamate, dopamine, brain-derived neurotrophic factor, cytokines) and external factors (hypoxia, illicit drugs) influence whether the progenitor cells stop dividing, further differentiate, or die.[9,10] Regulation of these cellular survival processes is pivotal for connectivity, synapse formation, axon migration and pruning, and can be summarised under the term *synaptic plasticity*.

Synaptic plasticity is influenced by the neurodevelopmental stage of the brain, and supporting brain development and protecting this plasticity provides new therapeutic options for neuroprotection that may be relevant to the changes we have identified at various stages of mental disorder, particularly during the transition to fully fledged, sustained illness. Essential fatty acids (EFAs), mood stabilisers (particularly lithium) and some second-generation antipsychotics promote neurogenesis, reduce neuroprotective proteins and protect cells from excitotoxic death. Thus, we can examine these and other potential neuroprotective agents that are relevant to preventing onset, retarding progression or improving outcome (including neuropsychological function) for patients in the early illness stages. Among the key neuroprotective mechanisms that can be influenced in treatment studies are the neurotrophic processes generally (which may be dysregulated in mental disorders),[9,10] cell death, hypothalamic–pituitary–adrenal (HPA) axis function,[11,12] and the control of oxidative stress.[13]

Essential fatty acids and lipid metabolism

EFAs, such as eicosapentaenoic acid and docosahexaenoic acid, may have an adjunctive therapeutic effect in first-episode psychosis[14] and a primary therapeutic effect in prepsychotic or UHR states of psychosis.[15] Imaging studies suggest these benefits of EFAs may be mediated by reducing oxidative stress through an effect on glutathione metabolism.[16] Because EFAs have wider efficacy in a range of syndromes[17,18] and are safe and well tolerated, they are excellent candidates for trials in earlier stages of mental disorders.

Lithium as a neuroprotective agent

Lithium is a cornerstone in the treatment of mood disorders, and it has now become clear that it has potent neuroprotective properties.[19,20] Lithium treatment is associated with short-term increases in grey matter,[21] and has been shown to be dramatically effective in the treatment of degenerative neurological diseases, notably amyotrophic lateral sclerosis.[22] We studied use of lithium in young people at UHR of psychosis and found it to be associated with symptomatic improvement.[23] We also found that lithium was associated with positive central nervous system changes, as evidenced by significant reduction in T2 relaxometry and a trend for improvements in *N*-acetylaspartate–creatine ratios.[23] Hence, lithium could be the focus of clinical trials, particularly for use in the UHR state and subsequently in early treatment resistance.

Stress and hypothalamic–pituitary–adrenal axis dysregulation in early psychosis

We conducted a series of studies examining potential dysregulation of the HPA axis in response to stress and trauma in early psychosis.[24-27] We found evidence of relationships between HPA dysregulation and both clinical and neurobiological variables including changes in the volume of key brain structures, notably the pituitary and the hippocampus.[24] Possible interventions to be tested in clinical trials in this area include tianeptine (a novel antidepressant that affects the HPA axis),[28] glucocorticoid antagonists, and psychosocial interventions to reduce and moderate the effects of stress and trauma.

Oxidative stress and *N*-acetylcysteine

Recent studies have produced evidence that *N*-acetylcysteine, a neuroprotective treatment believed to act via the glutathione pathway and the reduction of oxidative stress, may be effective as an adjunctive therapy in established schizophrenia and bipolar disorder.[29,30] Thus, there are logical grounds for moving it forward in terms of stage of illness to earlier stages of psychotic illness.

Conclusion

As in many aspects of life, timing can be everything. The emerging field of early intervention in psychiatry and the clinical staging model describe a more flexible approach to diagnosis and clinical trial design. Defining discrete stages according to the progression of disease creates a preventively oriented framework for the evaluation of interventions. The key positive health outcomes are prevention of progression to more advanced stages (eg, persistent schizophrenia), or regression to an earlier stage. Although some factors may operate across several or all stage transitions, others may be stage-specific, with variable potency at different periods. We have described some exciting new approaches to treating early stages of mental disorders. Coupled with reforms in mental health service delivery, we now have the opportunity to test these novel treatments, and potentially prevent or minimise much ill health and disability in young Australians.

Competing interests

None identified.

Author details

Patrick D McGorry, MD, FRCP, FRANZCP, Professor of Youth Mental Health,[1] Clinical Director,[2] and Executive Director[3]
Alison R Yung, MB BS, MPM, FRANZCP, Medical Director, PACE Clinic[2]
Christos Pantelis, MD, FRANZCP, Professor and Scientific Director, Melbourne Neuropsychiatry Centre[1]
Ian B Hickie, MD, FRANZCP, AM, Professor of Psychiatry and Executive Director[4]
1 University of Melbourne, Melbourne, VIC.
2 ORYGEN Youth Health, Melbourne, VIC.
3 ORYGEN Research Centre, University of Melbourne, Melbourne, VIC.
4 Brain and Mind Research Institute, University of Sydney, Sydney, NSW.
Correspondence: pmcgorry@unimelb.edu.au

References

1 Häfner H, Maurer K, Trendler G, et al. Schizophrenia and depression: challenging the paradigm of two separate diseases — a controlled study of schizophrenia, depression and healthy controls. *Schizophr Res* 2005; 77: 11-24.
2 McGorry PD, Purcell R, Hickie IB, et al. Clinical staging: a heuristic model for psychiatry and youth mental health. *Med J Aust* 2007; 187 (7 Suppl): S40-S42.
3 Yung AR, Phillips LJ, Yuen HP, McGorry PD. Risk factors for psychosis in an ultra high-risk group: psychopathology and clinical features. *Schizophr Res* 2004; 67: 131-142.
4 Yung AR, McGorry PD, McFarlane CA, et al. Monitoring and care of young people at incipient risk of psychosis. *Schizophr Bull* 1996; 22: 283-303.
5 Edwards J, McGorry PD. Implementing early intervention in psychosis. A guide to establishing early psychosis services. London: Martin Dunitz, 2002.
6 Andrews G, Sanderson K, Corry J, et al. Cost-effectiveness of current and optimal treatment for schizophrenia. *Br J Psychiatry* 2003; 183: 427-435.
7 Wang PS, Simon G, Kessler RC. The economic burden of depression and the cost-effectiveness of treatment. *Int J Methods Psychiatr Res* 2003; 12: 22-33.
8 Insel TR. Beyond efficacy: the STAR*D trial. *Am J Psychiatry* 2006; 163: 5-7.
9 Berger GE, Wood S, McGorry PD. Incipient neurovulnerability and neuroprotection in early psychosis. *Psychopharmacol Bull* 2003; 37: 79-101.
10 Yao JK, Reddy RD. Membrane pathology in schizophrenia: implication for arachidonic acid signaling. *ScientificWorldJournal* 2002; 2: 1922-1936.
11 Phillips LJ, McGorry PD, Garner B, et al. Stress, the hippocampus and the hypothalamic–pituitary–adrenal axis: implications for the development of psychotic disorders. *Aust N Z J Psychiatry* 2006; 40: 725-741.
12 Corcoran C, Walker E, Huot R, et al. The stress cascade and schizophrenia: etiology and onset. *Schizophr Bull* 2003; 29: 671-692.
13 Ng F, Berk M, Dean O, Bush A. Oxidative stress in psychiatric disorders: evidence base and therapeutic implications. *Int J Neuropsychopharmacol* 2008; 11: 851-876.
14 Berger GE, Proffitt TM, McConchie M, et al. Ethyl-eicosapentaenoic acid in first-episode psychosis: a randomized, placebo-controlled trial. *J Clin Psychiatry* 2007; 68: 1867-1875.
15 Amminger GP, Schäfer MR, Papageorgiou K, et al. Relationship between reduced erythrocyte membrane fatty acids and transition to psychosis in ultra high risk individuals [abstract]. *Schizophr Res* 2008; 98 Suppl 1: 108.

16 Berger GE, Wood SJ, Pantelis C, et al. Implications of lipid biology for the pathogenesis of schizophrenia. *Aust N Z J Psychiatry* 2002; 36: 355-366.
17 Ross BM, Seguin J, Sieswerda LE. Omega-3 fatty acids as treatments for mental illness: which disorder and which fatty acid? *Lipids Health Dis* 2007; 6: 21.
18 Young G, Conquer J. Omega-3 fatty acids and neuropsychiatric disorders. *Reprod Nutr Dev* 2005; 45: 1-28.
19 Bachmann RF, Schloesser RJ, Gould TD, Manji HK. Mood stabilizers target cellular plasticity and resilience cascades: implications for the development of novel therapeutics. *Mol Neurobiol* 2005; 32: 173-202.
20 Jope RS. Anti-bipolar therapy: mechanism of action of lithium. *Mol Psychiatry* 1999; 4: 117-128.
21 Moore GJ, Bebchuk JM, Wilds IB, et al. Lithium-induced increase in human brain grey matter. *Lancet* 2000; 356: 1241-1242.
22 Fornai F, Longone P, Cafaro L, et al. Lithium delays progression of amyotrophic lateral sclerosis. *Proc Natl Acad Sci USA* 2008; 105: 2052-2057.
23 Berger G, Dell'Olio M, Amminger P, et al. Neuroprotection in emerging psychotic disorders. *Early Interv Psychiatry* 2007; 1: 114-127.
24 Velakoulis D, Wood SJ, Wong MTH, et al. Hippocampal and amygdala volumes according to psychosis stage and diagnosis: a magnetic resonance imaging study of chronic schizophrenia, first-episode psychosis, and ultra-high-risk individuals. *Arch Gen Psychiatry* 2006; 63: 139-149.
25 Phillips LJ, McGorry PD, Garner B, et al. Stress, the hippocampus and the hypothalamic–pituitary–adrenal axis: implications for the development of psychotic disorders. *Aust N Z J Psychiatry* 2006; 40: 725-741.
26 Thompson KN, Phillips LJ, Komesaroff P, et al. Stress and HPA-axis functioning in young people at ultra high risk for psychosis. *J Psychiatr Res* 2007; 41: 561-569.
27 Thompson KN, Berger G, Phillips LJ, et al. HPA axis functioning associated with transition to psychosis: combined DEX/CRH test. *J Psychiatr Res* 2007; 41: 446-450.
28 Dupin N, Mailliet F, Rocher C, et al. Common efficacy of psychotropic drugs in restoring stress-induced impairment of prefrontal plasticity. *Neurotox Res* 2006; 10: 193-198.
29 Berk M, Copolov D, Dean O, et al. *N*-acetyl cysteine as a glutathione precursor for schizophrenia — a double-blind, randomized, placebo-controlled trial. *Biol Psychiatry* 2008; 64: 361-368.
30 Berk M, Copolov DL, Dean O, et al. *N*-acetyl cysteine for depressive symptoms in bipolar disorder — a double-blind randomized placebo-controlled trial. *Biol Psychiatry* 2008; 64: 468-475.

(Received 18 Jul 2008, accepted 28 Sep 2008) ❑