Treatment of people at ultra-high risk for psychosis

The ultra-high risk (UHR) criteria were defined to identify young people at high and imminent risk of developing a first episode of psychosis[1]. The criteria have now been in use worldwide for over 20 years and have shown predictive validity for psychotic disorders across different countries and service settings. UHR individuals have a risk of developing a full psychotic disorder of 15-30% within 12 months, and over 36% after 3 years[2]. These "transition rates" are several hundredfold above that of the general population. Most individuals who develop a psychotic disorder have a diagnosis of schizophrenia or a schizophrenia-spectrum disorder. Identification of UHR individuals, therefore, presents the opportunity for prevention of onset of full psychotic disorder, or at least reduction in disability and delay of onset of first-episode psychosis.

Treatment of UHR individuals has two aims: to manage current symptoms and problems, and to reduce the risk of developing a psychotic disorder[1]. Intervention trials tend to have "transition to psychosis" as the primary outcome, with symptoms, level of functioning and distress sometimes included as secondary outcome measures. A recent meta-analysis studied 10 randomized trials that reported effects on transition rates of low-dose antipsychotic medication, cognitive behavioural therapy (CBT), omega 3 fatty acid and integrated treatment including family therapy, cognitive remediation, social skills training and CBT[3]. This study found that receipt of any specific intervention significantly reduced the risk of developing a first episode of psychosis both at 12 months and over the longer term (2-4 years), albeit with diminished effects over time. The reduced effect at long-term follow-up suggests that at least some UHR individuals remain at risk, and that interventions might delay, rather than prevent, onset of psychosis. Even so, such a delay could be of benefit, enabling people to, for example, finish education and develop supportive networks outside the family of origin. Additionally, individuals who develop a first episode of psychosis after having been treated in the prodromal phase have improved outcomes compared to their counterparts who did not receive such very early intervention[4].

Recently some novel treatments have also been piloted in the UHR group. These have had more targeted outcomes, based on hypothesized mechanisms of action of the intervention rather than global aims of reducing transition risk. For example, a small study of lithium postulated that it may have a neuroprotective effect and examined hippocampal T2 relaxation time and proton magnetic resonance spectroscopy as outcomes testing this hypothesis[5]. Glycine has been tested in two small pilot trials with outcomes of symptoms and neurocognitive functioning[6]. A study of biofeedback measured anxiety and distress as outcomes[7], and a trial of processing speed training examined improvement in processing speed and its correlation with social functioning[8]. A trial of a family intervention measured caregiver warmth, family communication and social functioning as outcomes[9]. All studies showed feasibility and either significant results or trends to significance, indicating future avenues of research.

The above approaches are moving towards developing interventions that are more tailored to underlying pathophysiology. Given the heterogeneity of the UHR group and our knowledge that poor outcomes include development or persistence of non-psychotic disorders and chronic social disability, this is a movement that should be welcomed. One problem is that we lack understanding of the factors that predict these different outcomes, including underlying biological mechanisms. This means that we are unable to individualize treatments. Thus, some UHR individuals are having unnecessary treatment, and others are having ineffective interventions that potentially delay initiation of effective treatment. There is, therefore, a need for investigation into factors that predict different trajectories and outcomes. The aim is to stratify the UHR group according to their underlying pathological processes and target treatment accordingly.

Clearly, we will also need to better understand the mechanisms of action of the interventions. Examples include determining if a subtype of the UHR group has high levels of oxidative stress and using an agent that has reduction in oxidative stress as its mechanism of action. For example, N-acetyl cysteine (NAC) is an antioxidant and may be indicated in such individuals. Studies will need to measure both reduction in oxidative stress and its correlation with improvement in symptoms and functioning as outcomes. We will need to investigate if the mechanism of action of NAC in the UHR group is through reduction in oxidative stress or through some other process (such as reduction in inflammation or an effect on neurotransmitters). Similarly, some UHR individuals may have high levels of dysfunctional metacognitive beliefs that lead to misinterpreting events and difficulty in dealing with stressful situations. These individuals could benefit from metacognitive therapy. Reduction in dysfunctional metacognitive beliefs should be measured as an outcome as well as symptoms and distress[10]. Transition to psychosis will also still be a relevant outcome in both scenarios.

Another issue in treatment of UHR individuals is whether specialized services are indicated and if so, where they should be located. A major reform of early intervention in psychosis services has recently been implemented in England. All these services are now required to assess for presence of the UHR state (there called the "at risk mental state") and provide management of UHR individuals. Patients detected through this pathway are likely to have high levels of symptoms as they will have originally been referred as possible first-episode psychosis. They will likely resemble the original cohort of UHR patients identified mainly through this route over two decades ago[1]. It may be therefore that the transition rate in this group

is also higher than cohorts detected through more generalist pathways such as adolescent health services. Thus, it might be that the integration of UHR and early intervention in psychosis services is indicated, facilitating timely treatment of psychosis should that occur.

On the other hand, we now know that young people with depressive and anxiety disorders frequently experience psychotic-like symptoms and may meet criteria for the UHR state. For these individuals, who will most likely present to primary care or adolescent services, it may be that management is optimal in an enhanced primary care youth service, such as Headspace in Australia. Ideally we need to know more about the different subtypes of UHR individuals and move towards stratified pathways of care depending on need, risk profile and likely underlying pathophysiology.

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Persistent persecutory delusions: the spirit, style and content of targeted treatment

We believe that treatments for persecutory delusions can be substantially better. Current standard psychological and pharmacological treatments have small to moderate effects[1,2]. The severity of the problems associated with paranoia is typically considerable, but the treatments are less effective than those for problems such as anxiety disorders. The isolation, feelings of hopelessness, and missed opportunities for patients with persecutory delusions demand a step change in treatment outcomes.

This is a clinical area that is beginning to receive a degree of attention. There are innovations in understanding and treatment emerging[3-5]. Central to our own strategy for improving treatment have been three inter-connected elements: a sustained, specific focus upon persecutory delusions; the development of a precise theoretical model with causal elements amenable to intervention; and a style and content of intervention that follows from our understanding of delusions. Our objective has been to achieve a much higher recovery rate for persecutory delusions.

The strategy behind building a new treatment has been to target in separate interventions each key causal factor identified from our theoretical model, demonstrate that each reduces the delusion, and then bring the evaluated individual components together into one coherent framework – called the Feeling Safe Programme – that can be personalized for patients.

Persecutory delusions are conceptualized as threat beliefs, developed in the context of genetic and environmental risk, that are maintained by several psychological processes, including excessive worry, low self-confidence, intolerance of anxious affect (and other internal anomalous experiences), reasoning biases, and the use of defence strategies[6]. Therefore, the clinical strategy is first to limit the maintenance factors one by one, then enable patients to enter their feared situations in order to learn that they are now safe. Learning of safety counteracts the paranoia. The fundamental learning is that the difficulty is one of tolerating high anxiety, rather than that there is an external threat.

The spirit, style and content of the 20-session Feeling Safe Programme has emerged from theoretical understanding, patient feedback, and our own clinical experience[7]. To start, the three overarching goals of treatment, shared with patients, are simple: to feel safer, happier, and to get people back doing more of what they want to be doing. These positively framed goals are popular with patients, enhance engagement, and embed the mechanism of change – developing feelings of safety – from the outset. The goals also orient the intervention to the future. We are explicit that no significant time is spent going over the past, unless that is requested by a patient.

Secondly, our perspective that there are multiple causal factors, and the consequent development of multiple treatment modules, allows both individual tailoring of the intervention and patient preference. A brief assessment, combining clinical interview and questionnaires, identifies with patients the factors contributing to their difficulties, and leads to the presentation of a treatment menu. Patients choose which interventions they would like and in which order. This gives patients real control from the outset.

Thirdly, targeting each maintenance factor, focusing on one at a time, provides a method to address the undoubted complexity (and often associated feelings of hopelessness) of presenting problems. We acknowledge the complexity with patients, but explain that a way to deal with it is to tackle one problem, then move on to the next, starting with the most manageable. This reduces the influence of maintenance factors but also raises patients' capacity and confidence to face the demands of directly learning safety *in vivo*.