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.

Alison R. Yung
Division of Psychology and Mental Health, Faculty of Biology, Medicine and Health, University of Manchester and Greater Manchester Mental Health NHS Foundation Trust, Manchester Academic Health Science Centre, Manchester, UK

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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*.

Fourthly, throughout the programme, we monitor the causal mechanism targeted in a module, as well as the three overarching goals of the intervention. This enables us to track and demonstrate change with patients. Scores are also used in the regular, frequent supervision, particularly to rapidly identify cases requiring greater discussion.

Fifthly, the style that has evolved from this systematic step-by-step approach is akin to interval training: bursts of activity and intensity followed by periods of reflection and integration. Of course, within this approach, the absolute pace of the intervention remains tailored to the individual's needs and preference. Time is predominately dedicated to the implementation of strategies in day-to-day life. Substantial additional contact (e.g., telephone calls) between weekly sessions is expected. This is *not* "low intensity" working.

Finally, the clarity of the model, and strong evidence-base for each element, enables the therapeutic style to be encouraging and optimistic, often holding hope when the patient struggles (e.g., many patients with persistent delusions, right at the start, are not expecting improvement). Transparency, offering direct answers to questions, and providing expert opinion (that is accurate), in tandem with the monitoring of progress and collaborative style, helps substantiate that optimism for patients. All written materials are shared between therapist and patient. There is no separate therapist manual. The therapy booklets provide the framework and key messages of the intervention, but are not prescriptive. Creativity by both the therapist and patient is often fostered, ensuring personal meaning and successful embedding of strategies for change.

We are currently testing the full Feeling Safe Programme in a randomized controlled trial[8]. There are, of course, caveats. The approach does not benefit all patients: our target at this stage is recovery in half of patients with persistent delusions. If this is achieved, there will then be a problem of accessibility. We have developed the programme in a highly manualized form to aid later dissemination, but technological solutions may also prove important. For example, we have found that immersive virtual reality can help patients learn safety[9]. Mobile apps and web-based programs also offer alternative delivery methods[10].

New treatments for persecutory delusions obviously require empirical testing in rigorous trials. Different forms of treatment should not be regarded as a single class, given the varied mechanistic targets, delivery methods, and outcomes pursued. We believe that the concept of specificity, inherent in our approach, should be retained when evaluating treatment developments. In this way, promising routes to improved outcomes for patients with persistent delusions will not be obscured.

Daniel Freeman, Felicity Waite
Department of Psychiatry, University of Oxford, Warneford Hospital, Oxford, UK

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Does neuroimaging have a role in predicting outcomes in psychosis?

A key difficulty in the management of psychotic disorders is that clinical outcomes are difficult to predict on the basis of the patient's clinical features. As a result, patients with psychosis are generally treated in a similar way, even though there may be marked differences in their course of illness or response to medication. However, recent research using neuroimaging suggests that, within a sample of patients with psychosis, the pattern of abnormalities may vary in relation to different clinical outcomes. This raises the possibility that neuroimaging could be used to stratify patients according to clinical outcome; subgroups of patients could then be offered different forms of treatment.

Data from a number of structural magnetic resonance imaging (MRI) studies suggest that patients with relatively poor outcomes have, compared to those with good outcomes, more marked reductions in total and regional grey matter volume, and greater ventricular enlargement[1]. However, other studies have not found a relationship between alterations in brain structure and clinical outcomes[2]. This inconsistency may reflect the use of patient samples that were small, and heterogeneous for age, stage of illness, and pharmacological treatment, all of which can affect neuroimaging findings. Moreover, clinical outcomes have often been determined retrospectively, on the basis of clinical records.

Recent neurochemical imaging studies have suggested that the response to antipsychotic medication in patients with psychosis is related to both subcortical dopamine function, as measured using positron emission tomography, and regional brain glutamate levels, as assessed using magnetic resonance spectroscopy. A good therapeutic response has been associated with elevated dopamine function and relatively normal glutamate levels, whereas a poor response has been linked to normal dopamine function and elevated glutamate levels[3]. Independent work has also linked the response to antipsychotic medication to differences in cortical gyrification[4], and to diffusion tensor imaging measures of white matter integrity[5]. However,