PERSPECTIVE

Retreat from the radical

Failures in the development of schizophrenia treatments don't justify the dramatic overhaul now being proposed, says **Stephen R. Marder.**

The past two decades have been a frustrating time for researchers developing drugs to treat schizophrenia and related psychotic illnesses. Ten antipsychotic medications have been introduced since the early 1990s, but large studies and meta-analyses[1] have shown that nearly all these so-called second- and third-generation antipsychotics are no more effective than agents that are more than 60 years old (the lone exception is clozapine). In the wake of these disappointing results, many companies have abandoned drug development for psychosis and other disorders of the central nervous system.

To get the field back on track, the director of the US National Institute of Mental Health (NIMH) suggested that researchers switch their efforts away from the short-term development of treatments that are only incremental improvements, and focus on understanding the core mechanisms of the disease[2]. This approach aims to foster discoveries in genetics and the functioning of neural circuits, and proponents argue that these firm foundations are required if future treatments are to be transformative.

The NIMH is asking scientists to adopt new approaches to better define schizophrenia. The latest edition of the *Diagnostic and Statistical Manual of Mental Disorders* (*DSM-5*) defines disorders by clinically observable phenomena, such as hallucinations, delusions and behavioural changes. But several illnesses can cause these symptoms, raising the risk of misdiagnosis.

The goal of the NIMH is to develop a set of diagnostic criteria based on measurable alterations in brain function. It is therefore discouraging grant applicants that use *DSM-5* to categorize subjects in clinical trials. Instead, it wants investigators to use its own proposed classification system, the Research Domain Criteria (RDoC), which includes constructs that are thought to reflect basic dimensions of behaviour. Proposed RDoC constructs include negative valence systems, such as anger and fear; positive valence systems, such as reward learning; and cognitive systems, such as attention and working memory. In addition, the NIMH has shifted its focus from large clinical trials of promising interventions to smaller studies that evaluate whether drugs or other interventions engage a neuroreceptor or alter a biological process relevant to a disorder.

These are major changes in the way schizophrenia is studied, and I think the NIMH may be moving too quickly. The path from genetics to diagnosis and treatment is uncertain. Although genome-wide association studies have linked many gene variants with schizophrenia (see 'Unravelling complexity', page S6), each variant is associated with only a small effect. Thus genetics research may yield little of benefit to schizophrenia patients for decades.

Similarly, an abrupt move to a new diagnostic system is no guarantee of better results. The RDoC's constructs may help to illuminate the relationships between the functioning of neural networks and psychopathology, but they have not yet been conclusively correlated to schizophrenia symptoms. The requirement that a drug engage a neural target may be misguided; although there are a number of promising biomarkers from neuroimaging, these have seldom been linked to the core symptoms of schizophrenia.

There is strong evidence that we are poised for substantial advances using the standard modes of research and patient categorization. Burdening investigators with an unproven diagnostic system, or a need to demonstrate the engagement of neural targets, could make this work difficult. But researchers who stick to their traditional methods may find it hard to obtain funding given the new NIMH criteria.

I am not arguing that all change is a mistake. Research has already benefited from approaches that challenge the *DSM-5* categories, but without abandoning altogether the link to symptoms. For example, focusing attention on domains other than psychosis — including negative symptoms, cognition and social cognition — is likely to lead to treatments that can improve functioning and quality of life. These advances will not prevent or cure schizophrenia, but they may mitigate the loss of function or disability associated with the illness. There are numerous active trials for drugs, devices and training interventions, so the fruits of this research are likely to reach patients in the next five to ten years.

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Some of the most promising research might not fit in the new NIMH research framework. For example, there is evidence that training interventions for schizophrenia, including cognitive remediation and cognitive behavioural training therapy, can improve outcomes and enhance the functioning of brain networks[3]. Other evidence suggests that training interventions delivered to recently diagnosed schizophrenia patients can protect the brain against the loss of grey matter in the early years of the illness[4]. These may be more than just symptomatic treatments; they could change the course of the disease[5]. More research is starting to show that neuroprotective agents might be able to alter the trajectory of the illness[6]. None of this work fits comfortably in an RDoC framework, so it might not be supported in the current environment.

The approaches endorsed by the NIMH may be able to transform the treatment and management of schizophrenia. If they pay off, the benefits will probably improve people's lives in the next few decades. But we are on the verge of less dramatic but nonetheless important improvements in the treatment of a devastating illness. Premature and radical changes in research methods may imperil these advances. ■

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