# A plan for mental illness

The **Royal Society International Seminar Consortium** describes what the next decade of mental-health drug development should look like.

No chronic disease burdens the world more than mental illness[1]. In any given year, nearly 40% of the population in 30 European countries is affected. And yet, the world is experiencing a crisis in drug development for mental illness; drug companies are withdrawing from the field or redirecting their investments[2]. Last November, an eagerly awaited compound, called TC-5214, failed to significantly relieve major depression in a phase III trial[3]. The timing could not have been worse. Recognizing that the pipeline was starting to run dry, the Royal Society in London recently convened an international scientific seminar to find solutions to this pharmacological impasse. The meeting concluded that a fundamental change was needed in nearly every aspect of translational research in mental health.

For better treatments, better science is needed. Genetic studies are already identifying new molecular targets in other fields — for example, research in sickle-cell anaemia has uncovered a gene that represses fetal haemoglobin production, providing promising new drug targets[4]. The molecular mechanisms of mental disorders are very complex, but the latest genetic technologies should help to identify effective treatment targets, and offer alternatives to the monoamines that have dominated psychiatric medications for half a century.

Borrowing from the success of prevention in other medical areas, ways to identify risk factors of mental illness need to be developed so that intervention precedes disability. Identifying these factors at an early stage may mean psychosocial treatments (such as, family support and cognitive training) are more effective than medication. Early detection could emerge from neuroimaging, cognitive assessments, predictive biomarkers or rare genetic variants that signal risk or a prodromal stage.

Even therapeutic end points need to be refocused. Currently, treatment is not aimed at full recovery, and targets late stages of illness rather than using pre-emptive therapies in early stages when outcomes might be better[5]. Treatment should also address adherence, which remains a problem in 20–70% of patients with psychiatric illness[6].

One method for improving the effectiveness of treatment is integrating medical and psychosocial approaches. In a study of phobias, which combined the drug D-cycloserine and cognitive-behavioural therapy, people given medication during virtual-reality sessions designed to accustom them to fearful situations saw symptoms improve faster than those just given a placebo with virtual-reality sessions[7]. Other potential techniques and 'neurotechnologies' include video-game training to help people in the early stages of schizophrenia to retain function or to help children with autism to interact socially, for example by increasing eye contact[5].

From a research perspective, progress requires changes not only in what we do but also how we do it. As industry withdraws from the field of mental health, we have an opportunity to rethink how academia and industry can work together for the public good. One obvious way to do this is to allow academic scientists to investigate compounds that have been abandoned by industry. But we can not simply repeat the best efforts of a company-directed failed clinical trial without new strategies. We should consider new approaches to identifying potential drug targets and their validation — such as open-access drug development — to include industry and academia.

We must also reconsider our use of animal models; too many compounds that seem to treat a disease in animals end up having little impact in humans. Although animal models may be unable to model all disease symptoms — such as those of schizophrenia — they can help to understand the neural mechanisms of specific symptoms, such as impulsivity[5]. Effective treatment of impulsivity could have a significant clinical effect on neuropsychiatric disorders such as attention deficit hyperactivity disorder, mania and substance abuse. We need to recognize the promise and limitations of animal studies, so trials can move quickly into work with human cells and volunteers to define or eliminate targets for drug development.

To achieve this vision, we need a new cadre of clinical neuroscientists[8] to focus on integrating basic and clinical neuroscience, translational medicine, and new methodologies. Patients are becoming more involved in drug development through advocacy groups and allowing their information to be held in registries, providing research partnerships with an opportunity to identify biomarkers and specific phenotypes that pinpoint the patient subgroups most likely to benefit from a treatment[9,10].

The increasing public-health needs of those with mental illness, including chronic disability, high suicide rates and early death, demand that we do better in the next decade. ■

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1. Collins, P. Y. *et al. Nature* **475,** 27–30 (2011).
2. Cressey, D. *Nature* http://dx.doi.org/10.1038/news.2011.367 (2011).
3. Ledford, H. *Nature* **479,** 278 (2011).
4. Sankaran, V. G. *et al. Science* **322,** 1839–1842 (2008).
5. Sahakian, B. J., Malloch, G. & Kennard, C. *Lancet* **375,** 1854–1855 (2010).
6. Julius, R. J., Novitsky, M. A., Jr & Dubin, W. R. *J. Psychiatr. Pract.* **15,** 34–44 (2009).
7. Ressler, K. J. *et al. Arch. Gen. Psychiatry* **61,** 1136–1144 (2004).
8. Lehner, T. & Insel, T. *Acad. Psychiatry* **34,** 87–89 (2010).
9. Ledford, H. *Nature* http://dx.doi.org/10.1038/news.2011.324 (2011).
10. Saha, K. & Hurlbut, J. B. *Nature* **478,** 312–313, (2011).