Moving Psychiatry From Clinical Studies to Everyday Health Care

Written by Brian Hoyle

Scott L. Rauch, MD, McLean Hospital, Belmont, Massachusetts, USA, provided an overview of the innovations in psychiatry that are increasingly translating findings from basic science and clinical studies to the real-life of public health care.

Modern neuroscience is diverse, encompassing recognized fields like behavioral pharmacology, genetics/molecular biology, and neuroimaging, as well as newer aspects. In all these areas, the path from information acquisition to health care arises from basic science, for which animal models have been and continue to be fundamentally important. Findings that are possibly relevant to humans are tested in the standard phases of clinical trials. Those that are validated can become incorporated into health care practices.

In this scheme, behavioral pharmacology drives novel drug-based treatments, genetics and molecular approaches lead into personalized medicine, and neuroimaging discoveries lead to techniques that modulate brain function. The goals are both better and faster patient care at lower cost.

This view of psychiatry is no longer in the realm of conjecture; real achievements have been made. One example is the use of D-cycloserine to boost the success of extinction-based therapy, in which a patient is exposed to the source of anxiety in a safe and supportive setting. Another is the use of buprenorphine in the recovery from opiate dependence.

D-cycloserine is an antibiotic that is active against *Mycobacterium tuberculosis*. As well as its efficacy against tuberculosis, D-cycloserine can penetrate into the central nervous system, where it acts on N-methyl-D-aspartic acid glutamatergic receptors in the amygdala region of the brain. Rodent models established the value of D-cycloserine in lessening the conditioned fear response, in which a stimulus is associated with a feared outcome; animal study findings have been translated to human therapies that include acrophobia. Meta-analyses have validated D-cycloserine in the reduction of a variety of anxiety disorders [Rodrigues H et al. *PLoS One.* 2014; Bontempo A et al. *J Clin Psychiatry.* 2012; Graham BM et al. *Br J Pharmacol.* 2011; Norberg MM et al. *Biol Psychiatry.* 2008].

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Buprenorphine was discovered a half-century ago. It is both an opiate agonist, like methadone, and an opiate antagonist, like naltrexone. Since there is little physical dependence, the likelihood of abuse is low. In the 1970s, the possible value of buprenorphine in weaning individuals off heroin was suggested and explored, first in rat models and then in humans. The research led to FDA approval of buprenorphine for opiate dependence in 2002. A subsequent multisite randomized controlled trial involving 653 patients reported the value of buprenorphine in a tapering schedule that weaned them from the abusive use of opiates, with a success rate (defined as total/near abstinence from opioids) near 50% at the end of treatment [Weiss RD et al. *Arch Gen Psychiatry.* 2011].

Personalized medicine denotes the tailoring of therapy to the individual based on that person's genetic predisposition to the particular disease. In psychiatry, as in other disciplines, this approach is in its early days, but already success has been apparent. One example is the use of methylfolate in the treatment of schizophrenia in patients harboring genetic variants that affect the metabolism of folate. Another example is the use of glycine in psychosis in individuals with gene-related deficiency in glycine metabolism.

Folic acid is supplied mainly in the diet. The methyl groups obtained from folate metabolism are important for brain development including the manufacture of neurotransmitters. A study published 40 years ago linked folate deficiency with schizophrenia, and spurred analyses that identified the genetic link between homocystinuria and schizophrenia [Allen NC et al. *Nat Genet.* 2008] and the benefits of folate supplementation in genetically compromised schizophrenia

patients, including those with the MTHFR 677C >T genotype [Roffman JL et al. *JAMA Psychiatry.* 2013; Hill M et al. *Schizophr Res.* 2011]. L-methylfolate supplementation may be a useful way of circumventing genetic deficiencies in folate metabolism.

Concerning glycine, the basis of the genetic mutation has been identified as excess copies of the gene affecting glycine decarboxylase. The result of the greater than normal catabolism of glycine, which lowers the brain levels of the compound, is reduced activity of the N-methyl-D-aspartate receptor, which in turn could exacerbate psychosis. Genetic therapy geared toward restoring the normal gene copy number would be anticipated to produce more normal levels of glycine; research toward this goal is ongoing.

Neuroimaging is also proving useful in psychiatric care. Being able to visually pinpoint brain activity can be valuable in defining the nature of the pathology and the targets of therapy. Depression has responded to the noninvasive neuromodulation treatment of transcranial magnetic stimulation (TMS). In TMS, an electrical current is used to create a magnetic field; in turn, the magnetic field can induce neuronal/brain activity. The observed efficacy of daily repetitive TMS on lessening symptoms of depression [George MS et al. *Arch Gen Psychiatry.* 2010] may reflect the capacity of TMS to "reset" the brain [Hanlon CA et al. *PLoS One.* 2013]. TMS was approved by the FDA in 2008 for treatment of mildly resistant depression.

Another neuromodulation technique is deep brain stimulation (DBS). The approach is invasive; electrodes are implanted in certain regions of the brain to deliver electrical impulses to targets, such as the subcallosal cingulated white matter. DBS for treatment-resistant depression was validated in a proof-of-principle study [Mayberg HS et al. *Neuron.* 2005]. However, to date, larger scale controlled trials are yet to prove efficacy of DBS for psychiatric indications.

Novel therapies include Internet-based cognitive behavioral therapy [Andrews G et al. *PLoS One.* 2010]. This approach and teletechnology may allow delivery of care to select patients in a way that reduces cost. Finally, the identification of new molecular targets will offer new avenues of therapy.

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