EDITORIAL

Rapid and novel treatments in psychiatry: the future is now

Psychiatric illnesses are major public health problems and leading causes of disability and death worldwide. These illnesses often have their origins in childhood and adolescence, and account for over a third of disabilities across the human lifespan. Psychiatric disorders also contribute to premature aging and risk of dementias. Individuals with severe and persistent mental illnesses die years earlier than expected for their birth cohorts. Contributors to premature death include smoking, obesity, sedentary lifestyle, drug and alcohol use, cardiovascular illnesses, violence, and suicide. In 2021, "deaths of despair"—including suicide, drug overdoses, and drug and alcohol-related deaths—claimed the lives of over 185,000 individuals in the United States.

The devastation wreaked by psychiatric illnesses strongly underlies the need for novel, rapid, and more effective treatments. The latest treatments—including psychotropic medications, neurostimulation methods, and evidence-based forms of psychotherapy—clearly benefit patients, but must be viewed as good but not great treatments. Current standard treatments can take weeks or longer to produce significant benefits, and even then, responses are often partial and limited by side effects, poor treatment compliance, and relapse. As a graphic example, current data indicate that about 30% of patients with major depressive disorder (MDD) do not respond to current treatments and are considered "treatment resistant."

How do we address this pressing need? Optimistically, many in the field now believe that psychiatry is in the early phases of a revolution in therapeutics—a revolution that includes novel approaches to treatment that, in some cases, can act very rapidly (within hours to days) to produce benefits that can be sustained for several weeks or more. This current revolution began over 20 years ago with the advent of using the dissociative anesthetic ketamine as a psychotherapeutic with rapid and dramatic antidepressant effects in patients who are refractory to other treatments. This work has progressed dramatically, and ketamine use in clinical practice is becoming increasingly common. In March 2019, esketamine—the ketamine enantiomer that is more active as an antagonist at N-methyl-D-aspartate receptors (NMDARs)—was approved by the U.S. Food and Drug Administration (FDA) for treatment-resistant major depression in adults, and subsequently for depressive symptoms in adults with MDD with acute suicidal ideation or behavior. Other novel and rapid treatments are in development and show substantial promise, such as the neurosteroid brexanolone, approved by the FDA for treatment of postpartum depression in individuals 15 years and older. Zuranolone, an orally active neurosteroid for postpartum depression in adults, was approved in August 2023. Multiple other treatments are in development; some already in late phase clinical trials.

This issue of *Neuropsychopharmacology Reviews* (NPPR) presents an overview of the current state of rapid and novel treatments in psychiatry, with an eye on the future of this critical area. The papers that follow are grouped into three major categories. All authors provide their version of SWOT analyses highlighting current strengths of the field, weaknesses and limitations of the approach, opportunities to move forward, and threats to therapeutic development as we look beyond the present state to future opportunities.

We begin with a series of perspectives that highlight how we arrived at the present state, and factors that will be necessary to move the field forward. These perspectives are written by leaders in the field and describe academic, industry, patient, and regulatory considerations in new treatment development. This section highlights areas of success, as well as some significant problems that have plagued treatment development to date and some of the major challenges that will confront the field as it moves forward.

The second section presents more formal reviews and forms the heart of this discussion, focusing critically on four leading examples of novel treatment approaches: ketamine and glutamate system modulators, GABA receptor modulators including neurosteroids, the advent of psychedelic agents as treatments in psychiatry, and the rapidly evolving field of brain stimulation methods. Neuromodulation approaches include less invasive stimulation methods (e.g., transcranial magnetic stimulation) and invasive (surgical) therapeutic approaches (e.g., deep brain stimulation). In each of the four main topic areas, the first article provides a critical look at the current state of clinical data, the second paper describes the current mechanistic understanding of the treatment approach, and each section ends with an article looking specifically beyond the current state to future opportunities in that area of therapeutics.

The final group of papers give perspectives on what is necessary to move the field forward. These articles address the important issues of how to sustain the benefits of rapid treatments, the design of clinical trials for rapidly acting novel agents as we look to the future, the repurposing of existing drugs as psychotherapeutics, the use of pharmacogenomics to enhance treatment responses, and the opportunities presented by computational methods in treatment development. Other important considerations include how new treatments can be used ethically and equitably to serve the vast population of individuals with psychiatric illnesses who are underserved and presently have restricted access to the most effective treatments. In addition, the critical area of advancing treatments in child and adolescent psychiatry is addressed—a topic that is worthy of more extensive discussion, given the early age of onset and persistence of many psychiatric disorders.

We are now in a critical time in psychiatry. Mechanistic understanding of the neural basis of behavior and mental illnesses is evolving rapidly, including novel thinking about therapeutic targets that harness the incredible plasticity of the human brain. The efforts that are presently underway and that will be developed based on this rapidly evolving science offer great optimism for the future. We hope this issue of the journal moves this discussion and the necessary science forward quickly, serving as a road map to future opportunities.

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