

Clinical Psychopharmacology: Advances and Challenges from 1965 to 2006

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In 1965, our psychotropic armamentarium consisted of phenothiazines for psychosis, tricyclic antidepressants and monoamine oxidase inhibitors for depression, and the first benzodiazepines, which had emerged as treatments for anxiety and insomnia. The major pharmacologic advances since then include a few agents with enhanced efficacy and a general trend in the introduction of psychotropics with fewer adverse effects and improved tolerability. For example, improved tolerability and ease in dosing with the serotonin-specific reuptake inhibitors has been associated with widespread treatment of depression and anxiety disorders.

Lithium and clozapine represent true advances in drug efficacy. The first report of lithium use in mania occurred in 1949; however, lithium was considered investigational until the 1970s. Although other mood stabilizers are now available, none has data to match those of lithium's efficacy in decreasing the long-term risk of suicide in bipolar disorder.

First abandoned because of agranulocytosis and then introduced in the US in 1989 for treatment-resistant schizophrenia, clozapine has become the antipsychotic that pharmaceutical companies attempt to mimic in efficacy, but not in adverse effects. Not only is clozapine more efficacious in treatment resistance, it decreases suicidality more than compared antipsychotics.

The myriad of other pharmacologic agents currently available for clinical use have improved adverse effect profiles, but superiority with regard to efficacy remains either elusive or open to debate. For example, the atypical antipsychotics that were developed since clozapine entered the market have a significantly decreased risk of neurologic adverse effects including dystonia, Parkinson-like symptoms, and tardive dyskinesia. However, superior efficacy in treating negative symptoms and cognition is modest and may be related to a lack of negative neurologic effects associated with the

first-generation antipsychotics rather than unique efficacy. Even these advantages have a trade-off, with some of the second-generation antipsychotics causing unacceptable weight gain and an increased risk of glucose intolerance and lipid abnormalities.

Much remains to be accomplished in the treatment of mental disorders. For the most part, the etiology and pathophysiology of mental disorders remain unclear. Obvious challenges in studying the living human brain pose difficulties that are just beginning to be addressed with modern imaging technologies and genomics. Much effort has been expended over the past 40 years studying psychotropic pharmacology and then attempting to infer disease pathophysiology based on drug mechanism. True advances toward achieving cures or even long-term remission for many severe mental disorders require identifying the biological targets that are associated with these disorders and then developing pharmacologic and nonpharmacologic treatments that impact these processes.

Clinical practice often does not reflect current scientific knowledge; the Institute of Medicine estimates that it often takes 12–15 years for research evidence to become common practice at the bedside. Mental disorders are often not diagnosed by primary care providers and medical specialists and, when diagnosed, treatment is often inadequate. When left untreated, mental disorders often progress, increase the risk and complicate the treatment of general medical disorders, and are associated with significant morbidity and increased mortality through suicide. Even within psychiatry, pharmacotherapy is often suboptimal. For some clinicians, clinical psychopharmacology is more of a “religion” than a science, and these clinicians may prescribe based on what they believe rather than on scientific evidence. Rampant antipsychotic polypharmacy is an example of such behavior. True, scientific evidence is often lacking when treatment proceeds beyond first- or second-line treatment recommendations, and good clinical care requires clinical judgment, often trial and error. However, rational pharmacologic treatment trials should be approached as objective individual patient studies, using

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objective assessment of clinical outcomes, and time-limited interventions during which to evaluate outcomes.

The other major challenge in the treatment of mental disorders lies in the public perception of mental illness. Unfortunately, significant stigma still exists, and many people continue to view mental illness as a sign of personal weakness rather than an actual disease. These perceptions are reflected in the use of such terms as behavioral disorders and behavioral health organizations, inferring that mental disorders are inappropriate behaviors rather than diseases. This view is manifested by the lack of parity that still exists in reimbursement for mental health care and the barriers that limit access to services. Some groups allege that psychiatry is a pseudoscience, and they lobby assertively to limit the types and kinds of services, including psychopharmacology, that are available. Unfortunately, when psychotropic medications are prescribed inappropriately, these examples are extrapolated to mental health care in general, and this negatively impacts efforts to improve parity.

Thus, if the ultimate goal of cures for mental disorders is to be realized, neuroscientists and clinicians must work in concert to make this reality. These efforts must take place in the laboratory and in the clinic, but they also must occur in educational efforts and positive and sustained interactions with elected government officials, healthcare payers, and the public at large.

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