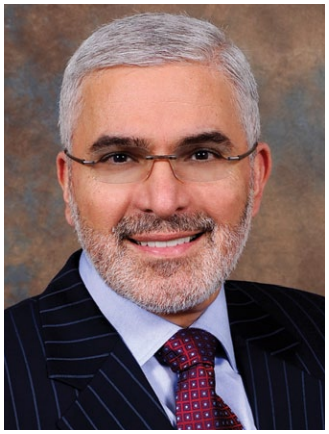

Henry A. Nasrallah, MD
Editor-in-Chief

Quo vadis, psychopharmacology?

The psychopharmacology era that began 6 decades ago has had a momentous and transformative effect on the identity and practice of psychiatry. It enabled community-based treatment and follow-up to supplant institutional warehousing of persons with serious mental disorders. The discovery of neurotransmitter pathways and receptors involved in the mechanism of action of antipsychotic, antidepressant, and anxiolytic agents sparked the neuroscience revolution that has become 1 of the fastest-moving frontiers in medicine.

Innovation in psychopharmacology depends on overcoming multiple challenges that stifle drug discovery and development

Over the past few years, the shine seems to have worn off and psychopharmacology appears to be in limbo between the serendipitous but aging discoveries of the past and the exciting but unfulfilled promise of future breakthroughs. Psychopharmacology is in urgent need of a renaissance to propel it into new directions that will maintain its credibility as the core of psychiatric therapeutics. The following are some issues and challenges that may influence how psychopharmacology can surge forward and restore its "mojo."

Scientific challenges. Psychopharmacology must decisively move from serendipity and its corollaries to rational, pathophysiology-based drug development. We need a translational "Marshall Plan" to exploit genetic and molecular neurobiology advances to develop radically new pharmacologic biotherapies for psychiatric brain disorders.

Conceptual challenges. As long as psychiatric diagnoses are based on clusters of symptoms assembled by committees, it makes little sense for the FDA to mandate that a drug must work for a DSM diagnosis instead of specific symptoms. Psychiatric disorders share many symptoms such as depressed mood, anxiety, agitation, hallucinations, delusions, insomnia, impulsivity, etc. Approving new drugs for target symptoms rather than a DSM diagnosis might eliminate the often deplored—yet necessary—practice referred to as "off-label" pharmacotherapy. Frankly, it is silly that an antipsychotic must be approved separately for schizophrenia, schizoaffective disorder, psychotic mania, delusional disorder, or brief reactive psychosis when these disorders all share delusions or hallucinations that respond to that same agent. The high cost of conducting redundant clinical trials for all antipsychotic drugs in

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each psychotic disorder is far better invested in discovering agents with new mechanisms of action.

Disease heterogeneity. Research strongly points to a substantial heterogeneity in practically every psychiatric disorder, with multiple genotypes and phenotypes that share common features. Therefore, there will always be full responders, partial responders, and refractory patients in any psychiatric illness. Rational psychopharmacology must develop strategies to prospectively identify these subgroups by using pharmacogenetic markers that should become a vital component of guiding treatment selection.

Big picture issues

Who will spearhead the psychopharmacology of the future? There is a tremendous unmet need, with >80% of psychiatric disorders having no FDA-approved medication, and a substantial proportion of patients who do receive an approved drug often remain disabled even after symptomatic improvement. This unmet need is not just for *new* drugs, but more *effective* drugs.

Funding. It is expensive to develop new mediations. Only the private sector (pharmaceutical industry) develops drugs for psychiatry. Unless the government decides to allocate a trillion dollars to take over that role, it should provide incentives to attract the private sector to invest in psychiatry instead of abandoning it, as some companies recently have done. One possibility is to substantially extend the patent life for a medication with a new mechanism of action. This will spur innovation and benefit millions of sick individuals.

Medico-legal liability. The antidote to innovation is a class-action lawsuit. All drugs will inevitably cause side effects. When millions of people receive a vaccine during an epidemic, a couple hundred may die or suffer serious side effects. Imagine if vaccine development stops and many millions die as a consequence. The FDA currently approves a drug after careful study. Therefore, shouldn't the FDA share liability for unexpected serious adverse effects or waive such liability altogether if these effects were completely unforeseen during the clinical trials?

So quo vadis, psychopharmacology? This temporary lull is worrisome but there is reason to believe brighter days lie ahead. However, it is obvious that innovative advances in psychopharmacology are not only dependent on scientific breakthroughs but also on completely new paradigms of clinical diagnosis, less rigid regulatory policies, creative financing, and a change in liability laws that stifle drug development. All these are feasible and achievable. This is a time to stop dithering and to start envisioning new directions. Millions of patients are eagerly awaiting the psychopharmacology of the future.

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