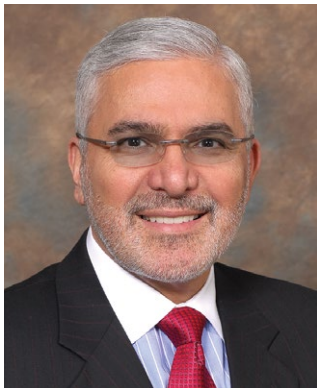
Psychopharmacology 3.0



Henry A. Nasrallah, MD
Editor-in-Chief

There is little doubt that the psychopharmacology revolution has been transformational for psychiatry and is also credited for sparking the momentous neuroscience advances of the past half century.

The field of psychiatry, dominated by Freudian psychology for decades, radically evolved from psychoanalysis to pharmacotherapy with the discovery that serious mental disorders are treatable with medications, thus dispensing with the couch.

Prior to 1952, the prevailing dogma was that "madness is irreversible." That's why millions of patients with various psychiatric disorders were locked up in institutions, which added to the stigma of mental illness. Then came the first antipsychotic drug, chlorpromazine, which "magically" eliminated the delusions and hallucinations of patients who had been hospitalized for years. That serendipitous and historic discovery was as transformational for psychiatry as penicillin was for infections (yet inexplicably, only the discovery of penicillin received a Nobel Prize). Most people today do not know that before chlorpromazine, 50% of all hospital beds in the U.S. were occupied by psychiatric patients. The massive shuttering of state hospitals in the 1970s and '80s was a direct consequence of the widespread use of chlorpromazine and its cohort of first-generation antipsychotics (FGAs).

That was Psychopharmacology 1.0, spanning the period 1952 to 1987. It included dozens of FGAs belonging to 6 classes: phenothiazines, thioxanthenes, butyrophenones, dibenzazepines, dihydroindolones, and dibenzodiazepines. Psychopharmacology 1.0 also included monoamine oxidase inhibitors and tricyclic antidepressants for depression, and lithium for bipolar mania. Ironically, clozapine, the incognito seed template of the second-generation antipsychotic (SGA) class, was synthesized in 1959 with the early wave of FGAs, and launched in Europe in 1972, only to be withdrawn in 1974 due to agranulocytosis-induced deaths not recognized during the clinical trials.

The late 1980s ushered in Psychopharmacology 2.0, which was also transformative. It began in 1987 with the introduction of fluoxetine, the first selective serotonin receptor inhibitor. Then clozapine was resurrected in 1988 as the first FDA-approved drug for refractory schizophrenia. Being the first SGA (no acute extrapyramidal side effects at all, in contrast to all FGAs), it became the "mechanistic model" for all other SGA agents, which were introduced starting in 1993. All SGAs were designed by pharmaceutical companies' medicinal chemists to mimic clozapine's receptor profile: far stronger affinity to serotonin 5HT-2A receptors than to dopamine D2 receptors. Three partial agonists and several heterocyclic antidepressants were also introduced during this 2.0 era, which continued until approximately 2017. Of the 11 SGAs that were initially approved for schizophrenia, 7 also were approved for bipolar

I remain excited about the prospects of astounding psychopharmacologic advances to treat the disorders of the mind

To comment on this editorial or other topics of interest:
henry.nasrallah
@currentpsychiatry.com

Current PSYCHIATRY

Editorial Staff
EDITOR Jeff Bauer
SENIOR EDITOR Sathya Achia Abraham
ASSISTANT EDITOR Jason Orszt
WEB ASSISTANTS
Tyler Mundhenk, Kathryn Wighton

Art & Production Staff
CREATIVE DIRECTOR Mary Ellen Niatas
ART DIRECTOR Pat Fopma
DIRECTOR, JOURNAL MANUFACTURING
Michael Wendt
PRODUCTION MANAGER Donna Pituras

Publishing Staff
PUBLISHER Sharon J. Spector
DIRECTOR eBUSINESS DEVELOPMENT
Alison Paton
SENIOR DIRECTOR OF SALES
Tim LaPella
CONFERENCE MARKETING MANAGER
Kathleen Wenzler

Editor-in-Chief Emeritus
James Randolph Hillard, MD

Frontline Medical Communications
PRESIDENT/CEO Alan J. Imhoff
CFO Douglas E. Grose
SVP, FINANCE Steven Resnick
VP, OPERATIONS Jim Chicca
VP, SALES Mike Guire
VP, SOCIETY PARTNERS Mark Branca
VP, EDITOR IN CHIEF Mary Jo Dales
VP, EDITORIAL DIRECTOR, CLINICAL CONTENT
Karen Clemments
CHIEF DIGITAL OFFICER Lee Schweizer
VP, DIGITAL CONTENT & STRATEGY
Amy Pfeiffer
PRESIDENT, CUSTOM SOLUTIONS JoAnn Wahl
VP, CUSTOM SOLUTIONS Wendy Raupers
VP, MARKETING & CUSTOMER ADVOCACY
Jim McDonough
VP, HUMAN RESOURCES & FACILITY
OPERATIONS Carolyn Caccavelli
DATA MANAGEMENT DIRECTOR Mike Fritz
CIRCULATION DIRECTOR Jared Sonners
CORPORATE DIRECTOR, RESEARCH
& COMMUNICATIONS Lori Raskin
DIRECTOR, CUSTOM PROGRAMS
Patrick Finnegan

AllMedx
PRESIDENT Douglas E. Grose
EXECUTIVE VICE PRESIDENT, SALES
John Maillard
EDITORIAL DIRECTOR/COO Carol Nathan

In affiliation with Global Academy for Medical Education, LLC
PRESIDENT David J. Small, MBA

FRONTLINE MEDICAL COMMUNICATIONS
7 Century Drive, Suite 302
Parsippany, NJ 07054
Tel: (973) 206-3434
Fax: (973) 206-9378
www.frontlinemedcom.com

Subscription Inquiries:
subscriptions@mdedge.com

Published through an educational partnership with Saint Louis University

SAINT LOUIS UNIVERSITY. EST. 1818

mania, and 2 received an FDA indication for bipolar depression, thus addressing a glaring unmet need.

Psychopharmacology 3.0 has already begun. Its seeds started sprouting over the past few years with the landmark studies of intravenous ketamine, which was demonstrated to reverse severe and refractory depression and suicidal urges within hours of injection. The first ketamine product, esketamine, an intranasal formulation, is expected to be approved by the FDA soon. In the same vein, other rapid-acting antidepressants, a welcome paradigm shift, are being developed, including IV scopolamine, IV rapastinel, and inhalable nitrous oxide.

Three novel and important pharmacologic agents have arrived in this 3.0 era:

• **Pimavanserin**, a serotonin 5HT-2A inverse agonist, the first and only non-dopamine–blocking antipsychotic approved by the FDA for the delusions and hallucinations of Parkinson's disease psychosis. It is currently in clinical trials for schizophrenia and Alzheimer's disease psychosis (for which nothing is yet approved).

• **Valbenazine**, the first drug approved for tardive dyskinesia (TD), the treatment of which had been elusive and remained a huge unmet need for 60 years. Its novel mechanism of action is inhibition of vesicular monoamine transporter 2 (VMAT2), which reduces the putative dopamine supersensitivity of TD.

• **Deutetrabenazine**, which was also approved for TD a few months after valbenazine, and has the same mechanism of action. It also was approved for Huntington's chorea.

Another important feature of Psychopharmacology 3.0 is the repurposing of hallucinogens into novel therapies for posttraumatic stress disorder, anxiety, and depression.[1] The opioid system is being recognized as another key player in depression, with many studies showing buprenorphine has antidepressant and anti-suicidal properties[2] and the recent finding that pre-treatment with naloxone blocks the rapid antidepressive effects of ketamine.[3] This finding casts doubt on the notion that the antidepressant mechanism of action of ketamine is solely mediated via its antagonism of the glutamate *N*-methyl-D-aspartate (NMDA) receptor. Another imminent innovative antidepressant mechanism of action is represented by brexanolone, an allosteric modulator of GABA-A receptors (which are known to become dormant during pregnancy and are not reactivated after delivery in women who develop postpartum depression).

These early developments in Psychopharmacology 3.0 augur well for the future. Companies in the pharmaceutical industry (which are hated by many, and even demonized and kept at arm's length by major medical schools) are, in fact, the only entities in the world that develop new medications for psychiatric disorders, 82% of which still have no FDA-approved drug.[4] Psychiatric researchers and clinicians should collaborate and advise the pharmaceutical companies about the urgent or unmet needs of psychiatric patients so they can target those unmet needs with their massive R&D resources.

In that spirit, here is my wish list of therapeutic targets that I hope will emerge during the Psychopharmacology 3.0 era and beyond:

1. New mechanisms of action for antipsychotics, based on emerging neurobiological research in schizophrenia and related psychoses, such as:
   - Inhibit microglia activation
   - Repair mitochondrial dysfunction
   - Modulate the hypofunctional NMDA receptors
   - Inhibit apoptosis

- Enhance neurogenesis
- Repair myelin pathology
- Inhibit neuroinflammation and oxidative stress
- Increase neurotropic growth factors
- Neurosteroid therapies (including estrogen)
- Exploit the microbiome influence on both the enteric and cephalic brains

2. Long-acting injectable antidepressants and mood stabilizers, because there is a malignant transformation into treatment-resistance in mood disorders after recurrent episodes due to nonadherence.[5]

3. Treatments for personality disorders, especially borderline and antisocial personality disorders.

4. An effective treatment for alcoholism.

5. Pharmacotherapy for aggression.

6. Vaccines for substance use.

7. Stage-specific pharmacotherapies (because the neurobiology of prodromal, first-episode, and multiple-episode patients have been shown to be quite different).

8. Drugs for epigenetic modulation to inhibit risk genes and to over-express protective genes.

It may take decades and hundreds of billions (even trillions) of R&D investment to accomplish the above, but I remain excited about the prospects of astounding psychopharmacologic advances to treat the disorders of the mind. Precision psychiatry advances will also expedite the selection of the right medication for each patient by employing predictive biomarkers. Breakthrough methodologies, such as pluripotent stem cells, opto-genetics, and clustered regularly interspaced short palindromic repeats (CRISPR), promise to revolutionize the biology, diagnosis, treatment, and prevention of various neuropsychiatric disorders.

The future of psychopharmacology is bright, if adequate resources are invested. The current direct and indirect costs of mental disorders and addictions are in the hundreds of billions of dollars annually. Only intensive research and disruptive discoveries will have the salutary dual effect of healing disease and reducing the economic burden of neuropsychiatric disorders. Psychopharmacology 3.0 advances, along with nonpharmacologic therapies such as neuromodulation (electroconvulsive therapy, transcranial magnetic stimulation, vagus nerve stimulation, and a dozen other techniques in development). Together with the indispensable evidence-based psychotherapies such as cognitive-behavioral therapy, dialectical behavior therapy, and interpersonal psychotherapy, psychopharmacology represents the leading edge of progress in psychiatric treatment. The psychiatrists of 1952 could only fantasize about what has since become a reality in healing ailing minds.

The psychiatrists of 1952 could only fantasize about what has since become a reality

Henry A. Nasrallah, MD
Editor-in-Chief

References

1. Nasrallah, HA. Maddening therapies: How hallucinogens morphed into novel treatments. Current Psychiatry. 2017;16(1):19-21.
2. Serafini G, Adavastro G, Canepa G, et al. The efficacy of buprenorphine in major depression, treatment-resistant depression and suicidal behavior: a systematic review. Int J Mol Sci. 2018;19(8). doi: 10.3390/ijms19082410.
3. Williams NR, Heifets BD, Blasey C, et al. Attenuation of antidepressant effects of ketamine by opioid receptor antagonism. Am J Psychiatry. 2018. doi: 10.1176/appi.ajp.2018.18020138. [Epub ahead of print].
4. Devulapalli KK, Nasrallah HA. An analysis of the high psychotropic off-label use in psychiatric disorders. The majority of psychiatric diagnoses have no approved drug. Asian J Psychiatr. 2009;2(1):29-36.
5. Post RM. Preventing the malignant transformation of bipolar disorder. JAMA. 2018;319(12):1197-1198.