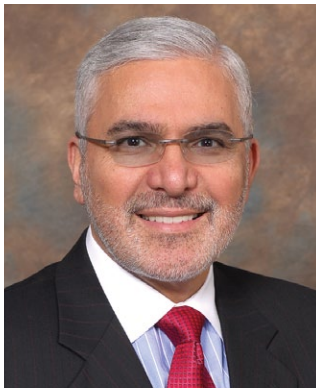

Henry A. Nasrallah, MD
Editor-in-Chief

BEYOND DOPAMINE
Brain repair tactics in schizophrenia

Let's be honest: No one is satisfied with current treatment outcomes in schizophrenia.

For the past 60 years, the standard of care has remained one-dimensional in this brain syndrome, even though the clinical and neurobiological complexities of schizophrenia are multidimensional. Dopamine D2 receptor antagonists, discovered serendipitously in the 1950s, have remained the mainstay of treatment, despite momentous insights about the neurodevelopmental and neurodegenerative processes of schizophrenia.

Why do we ignore abundant evidence that the brain in schizophrenia needs extensive structural repair, not simply a reduction in the activity of a single neurotransmitter in the mesolimbic dopamine tract? Perhaps the age-old dogmatic pessimism that neurodegeneration cannot be reversed has inhibited the field from attempting to escape the dopamine box, so to speak, and from developing innovative, even radical, approaches to repair of the brain of persons with schizophrenia.

But radical thinking is justified when dealing with a cruel brain syndrome that disables young adults in the prime of life.

We need to make progress in reversing or preventing neurodegeneration and clinical deterioration in schizophrenia

We should exploit neuroprotective tactics

Several neuroprotective approaches to preventing or reversing the degenerative changes across brain regions in schizophrenia are now recognized. Indirect evidence exists for such interventions in animal models, but the results of few controlled human studies have been published.

Here are my proposals for using neuroprotective tactics to address the unmet need to repair the brain of patients ravaged by neurotoxic psychotic relapses.

Promote 100% adherence to antipsychotic therapy. The simplest tactic to protect the brain from atrophy in patients with schizophrenia is to use long-acting injectable antipsychotic agents immediately after the first psychotic episode. The risk of a psychotic relapse is far lower (7-fold lower, according to a study performed at the University of California, Los Angeles, that soon will be published) with an injectable medication than with oral medication in first-episode patients. Preventing psychotic episodes is, logically, the most important neuroprotective tactic.

Enhance neurogenesis. The brain has 2 neurogenic regions that produce progenitor cells (stem cells) that gradually mature and differentiate into neurons and glia. That is how the brain naturally replenishes itself throughout life. This adult neurogenesis process, carried out in the dentate gyrus of the hippocampus and in the subventricular zone, stops during psychosis but resumes when psychosis remits.

Second-generation antipsychotics (but not first-generation agents) stimulate

To comment on this editorial or other topics of interest, visit www.facebook.com/CurrentPsychiatry, or go to CurrentPsychiatry.com and click on the "Send Letters" link.

neurogenesis in animals.[1] Haloperidol, in fact, does the opposite—suppressing neurogenesis and causing neuronal death via 15 different molecular mechanisms (see my editorial, "Haloperidol clearly is neurotoxic. Should it be banned?," in the July 2013 issue).

Other psychotropics also induce neurogenesis, including selective serotonin reuptake inhibitors (SSRIs), which increase hippocampal neurogenesis (atypical antipsychotics appear to increase neurogenesis in the subventricular zone).[2] SSRIs often have been used in schizophrenia patients for 2 common comorbid conditions: depression and anxiety. These agents can help regenerate brain tissue, in addition to providing their approved therapeutic indications.

Lithium and valproate have been shown to be neuroprotective[3] and to stimulate neurogenesis. Both are often used in schizoaffective disorder, bipolar type; they can exert a neuroprotective effect in addition to their clinical usefulness. The combination of an SSRI or lithium with a second-generation antipsychotic could be synergistic in turbocharging neurogenesis. This sounds like polypharmacy—but it is a rational approach that deserves to be put to the test.

Increase neurotrophins, such as nerve growth factor (NGF) and brain-derived neurotrophic factor (BDNF). When neurotrophin levels decline, the brain starts shrinking because of apoptosis. Psychosis lowers neurotrophins drastically—by approximately 60%. Atypical antipsychotics have been reported to increase the level of neurotrophins; haloperidol actually lowers those levels.[4]

Decrease inflammation. Psychosis has been shown to be associated with neuro-inflammation, as reflected in a surge of pro-inflammatory cytokines (released from activated microglia).[5] A rise in interleukin-6, tumor necrosis factor-alpha, interferon-gamma, and other pro-inflammatory markers has been extensively documented in many studies.

With that observed rise in mind, several controlled studies have shown that adding an anti-inflammatory agent (aspirin, a nonsteroidal anti-inflammatory drug, a COX-2 inhibitor, or minocycline) to an antipsychotic can accentuate the therapeutic response, especially during a first episode of psychosis.[6] Note also that second-generation antipsychotics have anti-inflammatory effects[7] as well that might be part of their efficacy beyond blocking dopamine D2 receptors.

Decrease free radicals. Microglia are activated by psychosis to release free radicals, also known as reactive oxygen species; these include nitric oxide, superoxide, and peroxynitrate. All these species are destructive to brain tissue. Using an adjunctive strong antioxidant, such as *N*-acetyl cysteine,[8] with an antipsychotic might help neutralize destructive effects of free radicals and protect the brain from tissue loss during a psychotic episode.

Avoid apoptosis inducers. Several substances can initiate programmed cell death (apoptosis), which is triggered during psychosis (believed to be caused by increased dopamine and, possibly, glutamate, activity) and which leads to brain atrophy. Patients with schizophrenia must be protected from these apoptosis inducers:

- amphetamine
- cocaine
- *Cannabis*
- lipid peroxidation products
- inflammatory cytokines.

Apoptosis can be inhibited by maintaining high levels of neurotrophic factors. Atypical, but not typical, antipsychotics increase levels of neurotrophins, such as NGF and BDNF.[4] In

continued on page 73

Current Psychiatry

Editorial Staff
EDITOR John Baranowski
MANAGING EDITOR Erica Vonderheid
ASSOCIATE EDITOR Patrice Kubik
WEB ASSISTANTS
Connor Kennedy, 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
ASSOCIATE DIRECTOR, eBUSINESS DEVELOPMENT Joshua Norton
MARKETPLACE ACCOUNT MANAGER
Linda Wilson
CONFERENCE MARKETING MANAGER
Kathy Wenzler

Editor-in-Chief Emeritus
James Randolph Hillard, MD

Frontline Medical Communications
CHAIRMAN Stephen Stoneburn
EVP DIGITAL BUSINESS DEVELOPMENT/CFO
Douglas E. Grose
PRESIDENT/CEO
Alan J. Imhoff
PRESIDENT, CUSTOM SOLUTIONS
JoAnn Wahl
VICE PRESIDENT, CUSTOM SOLUTIONS
Wendy Raupers
VICE PRESIDENT, FINANCE
Dennis Quirk
EXECUTIVE DIRECTOR, OPERATIONS
Jim Chicca
VICE PRESIDENT, MARKETING & CUSTOMER ADVOCACY Jim McDonough
VICE PRESIDENT, CUSTOM PROGRAMS
Carol J. Nathan
CORPORATE DIRECTOR, RESEARCH & COMMUNICATIONS Lori Raskin
VICE PRESIDENT, AUDIENCE DEVELOPMENT
Donna Sickles
Subscription Services: (800) 480-4851

In affiliation with Global Academy for Medical Education, LLC.
VICE PRESIDENT, MEDICAL EDUCATION & CONFERENCES Sylvia H. Reitman, MBA
VICE PRESIDENT, EVENTS 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

Published through an educational partnership with Saint Louis University
SAINT LOUIS UNIVERSITY

continued from page 13

addition, the Bcl-2 family of proteins inhibits apoptosis,[9] and drugs such as lithium and valproate can induce Bcl-2 and protect against apoptosis and neuronal loss.[3]

Restore white-matter integrity. Numerous studies using diffusion tensor imaging have revealed that myelin is reduced or lacks integrity in schizophrenia. This results in loss of critical connectivity among brain regions, which might explain psychotic and cognitive symptoms. One possible way to repair white matter, which becomes more damaged after multiple psychotic episodes, is to use drugs indicated to treat the demyelinating disorder multiple sclerosis. Antagonists of LINGO-1, a negative regulator of axonal myelination, are a prominent possibility; a recent study reported altered signaling of LINGO-1 in schizophrenia.[10]

Decrease excessive glutamate. Because glutamate is neurotoxic and might contribute to brain-tissue loss during psychosis, it is important to reduce glutamate activity in schizophrenia. Lamotrigine and valproate are both known to do that.[11] Several studies indicate that adjunctive lamotrigine might be helpful in schizophrenia.[12]

Inhibit caspase-3, also known as the "death cascade," which is involved in brain-tissue loss. Eicosapentaenoic acid is an omega-3 fatty acid that inhibits caspase-3. Interestingly, omega-3 levels in patients with schizophrenia are significantly lower than in healthy subjects.[13] Lithium also can inhibit caspase-3.

Do these proposals sound radical?

Most of the recommendations I've made here are not employed in the clinical practice of psychiatry. These ideas must be put to the test in controlled clinical trials.

The crux of my argument is that we need to think outside the "dopamine box" and focus on brain repair if we are to make progress in reversing, even preventing, neurodegeneration and clinical deterioration in this disabling brain syndrome. Just as cancer often is treated with rational polypharmacy, schizophrenia might need a similar approach. To vanquish schizophrenia—a goal that has eluded us—it is imperative to pursue radically novel and disruptive therapeutic strategies. The ideas I've listed here sound the call that the quest to repair the brain in schizophrenia must begin, and soon.

Henry A. Nasrallah, MD
Editor-in-Chief

To vanquish schizophrenia, it is imperative to pursue radically novel and disruptive therapeutic strategies

References

1. Agius N, Nandra, KS. Do atypical antipsychotics promote neurogenesis as a class effect? Psychiatr Danub. 2012;24(suppl 1):S191-S193.
2. Nasrallah HA, Hopkins T, Pixley SK. Differential effects of antipsychotic and antidepressant drugs on neurogenic regions in rats. Brain Res. 2010;1354:23-29.
3. Chiu CT, Wang Z, Hunsberger JG, et al. Therapeutic potential of mood stabilizers lithium and valproic acid: beyond bipolar disorder. Pharmacol Rev. 2013;65(1):105-142.
4. Parikh V, Khan MM, Terry A, et al. Differential effects of typical and atypical antipsychotics on nerve growth factor and choline acetyltransferase expression in the cortex and nucleus basalis of rats. J Psychiatr Res. 2004;38(5):521-529.
5. Monji A, Kato TA, Mizoguchi Y, et al. Neuroinflammation in schizophrenia especially focused on the role of microglia. Prog Neuropsychopharmacol Biol Psychiatry. 2013;42:115-121.
6. Sommer IE, deWitte L, Begemann M, et al. Nonsteriodal anti-inflammatory drugs in schizophrenia: ready for practice or a good start? A meta-analysis. J Clin Psychiatry. 2012;73(4):414-419.
7. Bian Q, Kato T, Monji A, et al. The effect of atypical antipsychotics perospirone, ziprasidone and quetiapine on microglial activation induced by interferon-gamma. Prog Neuropsychopharmacol Biol Psychiatry. 2008;32(1):42-48.
8. Berk M, Copolov D, Dean O, et al. N-acetyl cysteine as a glutathione precursor for schizophrenia—a double-blind, randomized, placebo-controlled trial. Biol Psychiatry. 2008;64(5):361-368.
9. Huang J, Fairbrother W, Reed JC, et al. Therapeutic targeting of Bcl-2 family for treatment of B-cell malignancies. Expert Rev Hematol. 2015;8(3):283-297.
10. Fernandez-Enright F, Andrews JL, Newell KA, et al. Novel implications of Lingo-1 and its signaling partners in schizophrenia. Transl Psychiatry. 2014; 4:e348.
11. Zink M, Correll CU. Glutamatergic agents for schizophrenia: current evidence and perspectives. Expert Rev Clin Pharmacol. 2015;8(3):335-352.
12. Kremer I, Vass A, Gorelik I, et al. Placebo-controlled trial of lamotrigine added to conventional and atypical antipsychotics in schizophrenia. Biol Psychiatry. 2004;56(6):444-446.
13. McEvoy J, Baillie RA, Zhu H, et al. Lipidomics reveals early metabolic changes in subjects with schizophrenia: effects of atypical antipsychotics. PLoS One. 2013;8(7):e68717.