Current PSYCHIATRY

Hazardous polypharmacy

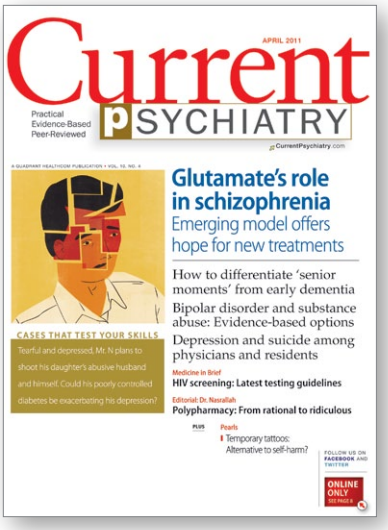
I am writing to compliment Dr. Henry A. Nasrallah for having the guts to write "Polypharmacy subtypes" (From the Editor, CURRENT PSYCHIATRY, April 2011, p. 10-12). I try hard to have patients on no more than 4 medications, 1 from each class if indicated. In California, what Dr. Nasrallah described as ridiculous and hazardous is all too rampant. I have inherited patients taking as many as 7 psychotropics and the initial evaluation of these patients usually begins with families stating that they are angry about their loved ones being "doped up to the point of being zombies." When I am finally able to get a good history of symptoms, I typically find that patients do not meet DSM-IV-TR criteria for some diagnoses. I then wean them off the medications, see what symptoms emerge, and then "reinvent the wheel" with their medication regimens. I was verbally reprimanded by the medical director at 1 job because he thought a patient was "doing well" on 7 medications despite the fact he was oversedated. I also have inherited patients on medications that interacted with other medications and were causing medical problems.

Problems with polypharmacy in California are, as I said, rampant.

Terry Roh, MD
Child and Adult Psychiatrist
Lutheran Social Services of Southern California
Big Bear Lake, CA

Ketamine and glutamate

I enjoyed the article "Glutamate: New hope for schizophrenia treatment" (CURRENT PSYCHIATRY, April 2011, p. 68-74) by Drs. Kantrowitz and Javitt. However, perhaps due to my own ignorance of the subject, I remain puzzled



April 2011

about their suggestion that the glutamatergic model of schizophrenia is supported by evidence showing that agonists at presynaptic mGluR2/3 receptors reverse the psychotomimetic effects of the *N*-methyl-D-aspartate (NMDA) receptor antagonist ketamine. Indeed, one would think that action of glutamatergic agonists at presynaptic autoreceptors would reduce glutamatergic activity and therefore mimic, rather than block, the effects of the antagonist ketamine.

Scott Mendelson, MD, PhD
Psychiatrist
Roseburg VA Hospital
Roseburg, OR

The authors respond

Thank you for your interest. We agree that this is a paradoxical effect of glutamate that is based largely upon the work of Bita Moghaddam, PhD, John Krystal, MD, and others. The basic finding is that blocking postsynaptic NMDA receptors leads to a rebound increase in presynaptic glutamate release that is pathological. Dr. Moghaddam showed that treatment with mGluR2/3 agonists reversed dopaminergic abnormalities and cognitive deficits induced by NMDAR antagonists in rodents.[1] Dr. Krystal showed that the presynaptic glutamate release antagonist lamotrigine blocked psychotomimetic effects of ketamine in normal human volunteers.[2] These findings have led to the hypothesis that blocking presynaptic glutamate may restore balance between glutamate and GABA systems, particularly in frontal brain regions. This theory also was supported by 1 successful clinical trial of a mGluR2/3 agonist,[3] although replication studies are ongoing. When interpreting these findings, it is important to keep in mind that glutamate acts at several receptor types in addition to NMDA, and it is the balance between these receptors, as well as the balance between excitatory glutamatergic vs inhibitory GABAergic neurotransmission, that may be critical in psychosis.

Joshua T. Kantrowitz, MD
Assistant Professor
Department of Psychiatry
Columbia College of Physicians and Surgeons
New York, NY
Schizophrenia Research Center
Nathan Kline Institute for Psychiatric Research
Orangeburg, NY

Daniel C. Javitt, MD, PhD
Director, Schizophrenia Research
Nathan Kline Institute for Psychiatric Research
Orangeburg, NY
Professor of Psychiatry and Neuroscience
New York University School of Medicine
New York, NY

References

1. Moghaddam B, Adams BW. Reversal of phencyclidine effects by a group II metabotropic glutamate receptor agonist in rats. Science. 1998; 281(5381):1349-1352.
2. Krystal JH, Abi-Saab W, Perry E, et al. Preliminary evidence of attenuation of the disruptive effects of the NMDA glutamate receptor antagonist, ketamine, on working memory by pretreatment with the group II metabotropic glutamate receptor agonist, LY354740, in healthy human subjects. Psychopharmacology (Berl). 2005;179(1):303-309.
3. Patil ST, Zhang L, Martenyi F, et al. Activation of mGlu2/3 receptors as a new approach to treat schizophrenia: a randomized Phase 2 clinical trial. Nat Med. 2007;13(9):1102-1107.

Send letters in care of Christina Thomas, CURRENT PSYCHIATRY, 7 Century Drive, Suite 302, Parsippany, NJ 07054, christina.thomas@qhc.com or visit CurrentPsychiatry.com and click on the "Send Letters" link. All letters are subject to editing for brevity and clarity.