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.

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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 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.

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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 Bitar 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 NMDA 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 an mGluR2/3 agonist, 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.

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References

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