inclusion waiting list comparison patients than in later-inclusion waiting list comparison patients.

The other issue on which Dr. Scheeringa comments is the sentence in our discussion section in which we concluded that our results further supported recommendations in two recently developed practice guidelines that for patients with a severe initial traumatic response, brief trauma-focused CBT may speed recovery and prevent PTSD if treatment begins 2 to 3 weeks after trauma exposure (1, 2). We believe that our results supported this recommendation, since we not only found early CBT to be more efficacious than late CBT, but also that CBT was more efficacious in patients with a comorbid major depression, which may indicate a more severe posttraumatic response.

Finally, as in our article, we would like to reemphasize that these results stem from exploratory subgroup analysis, which means that they should be interpreted with restraint. At best, they should tempt researchers to design new studies to test the hypotheses derived from these analyses, but they should not lead to changes in clinical practice (3).

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MARIT SIJBRANDIJ, PH.D.
MIRANDA OLFF, PH.D.
Amsterdam, the Netherlands

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The Relationship Between Obesity and Drug Use

TO THE EDITOR: The article by Melissa A. Kalarchian, Ph.D., et al. (1), published in the February 2007 issue of the *Journal,* reported that there is a prevalence of DSM-IV psychiatric disorders among bariatric surgery candidates, which is associated with greater obesity. The authors noted a "striking" discrepancy between lifetime substance use disorders (32.6%) compared with current use disorders (1.7%). They suggested a potential underreporting to explain the difference, but they also suggested an inverse relationship between overeating and drug use, citing the study by Volkow and Wise (2) on food- and drug-reward systems in the brain.

Our work is consistent with the latter suggestion of foods and drugs competing for reward sites in the brain. Overeating and obesity may in fact act as protective factors against drug reward and addiction. In similar patient populations, we found an inverse linear relationship between obesity and alcohol use (3). Additionally, as body mass index increased, the percentage of women who consumed alcohol in the past year decreased significantly. Similarly, as body mass index increased, the percentage of women who used marijuana in the past year significantly decreased (4). These findings are particularly interesting with the facts that alcohol and marijuana act as appetite stimulants in the acute intoxication setting.

The relationship between foods and drugs in the brain in competition for reward is complex. Hypothesis-driven research should be conducted in this area to explore possibilities for combating obesity and drug addiction.

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MATTHEW W. WARREN, PH.D.
MARK S. GOLD, M.D.
Gainesville, Fla.

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Drs. Kalarchian and Marcus Reply

TO THE EDITOR: The similarities and differences between aberrant eating and addiction have been debated for many years (1). As noted, recent work on the neurocircuitry of reward systems has stimulated new thinking on the potential commonalities in the biobehavioral impact of foods and drugs (2).

The studies by Drs. Warren, Gold, and colleagues that reported an inverse relationship between body mass index and alcohol (3) and marijuana (4) consumption appear to be consistent with the hypothesis that overeating and obesity may act as protective factors against addiction. However, the studies mentioned are restricted to chart reviews of substance use among obese, female weight-management patents. Additional research, including prospective studies of diverse, community-based cohorts, with research assessments of body weight, eating behavior, and patterns of substance use and abuse, is needed to evaluate this hypothesis fully.

Although our recently published article did not address this issue directly, we concurred that the possibilities for combating obesity and drug addiction with similar or overlapping strategies warrant further exploration. However, even if obesity and drug addiction share a common developmental vulnerability, effective treatments for obesity and addiction may differ.

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MELISSA A. KALARCHIAN, PH.D.
MARSHA D. MARCUS, PH.D.
Pittsburgh, Pa.

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Exacerbation of Schizophrenia by Varenicline

TO THE EDITOR: Schizophrenia is associated with heavy smoking. The replacement of tobacco by other forms of nicotine only occasionally achieves abstinence in persons with schizophrenia (1). The nicotinic agonist varenicline is a new alternative replacement agonist. There are no reports of its use in schizophrenia. We present the case of a patient with schizophrenia who received varenicline and experienced an activated psychotic relapse.

A 42-year-old woman with schizophrenia had been treated for 17 years with 1015 mg of thiothixene. She had several brief psychotic episodes per year, which seldom lasted for more than 3 days. She had no overt psychotic symptoms during an office visit one month previously. Her usual symptoms during acute psychotic episodes were voices commenting on her behavior, confusion, and angry outbursts. She smoked one to two packs of cigarettes per day and had made several attempts to discontinue the use of nicotine chewing gum and trandermal nicotine patches. The patient's mother reported a 5-day psychotic episode that began with increased activity, primarily the discarding of financial statements. At day 4, the patient ordered her daughter out of the house, and she threw away her thiothixene, which her daughter had insisted that she continue to take. She spent the next day screaming in her closet. Her mother administered thiothixene (20 mg) on the fifth evening and fed her because she had stopped eating. She appeared well groomed the next morning, without psychotic symptoms. She had no explanation for her sudden relapse and remission, but she announced with pride that her internist had prescribed a new medication, varenicline (2 mg), to help her stop smoking. The patient had been receiving varenicline for 5 days, and her quit day was the following day. She was advised to continue thiothixene, to avoid varenicline, and to return to nicotine chewing gum as a smoking substitute. She had no further exacerbations, but she continued to smoke cigarettes.

Nicotine activates several classes of brain cholinergic receptors. Many are high affinity presynaptic receptors, composed primarily of alpha4 and beta2 subunits, which cause the release of dopamine and other neurotransmitters. Nicotine produces profound tachyphylaxis at doses that are close to its agonist effect, which quickly ends its pleasurable effect. Heavy smokers, including persons with schizophrenia, respond by increasing their smoking to overcome the tachyphylaxis. Varenicline is principally an agonist at high affinity receptors, with a lower propensity to tachyphylaxis than nicotine (2). The more prolonged agonist effect of the drug was selected to increase its acceptance by smokers as a substitute for the briefer effects of cigarettes. Prolonged release of dopamine and norepinephrine may have resulted in the activated psychotic relapse in our patient. Her relatively low neuroleptic dose likely increased her vulnerability to this effect.

In addition to its pleasurable effects, smoking is a possible self-medication for cognitive dysfunction in schizophrenia. We have postulated the involvement of a different class of postsynaptic cholinergic receptors, composed primarily of alpha7 subunits, which activate inhibitory interneurons and thus inhibit response to extraneous sensory response. Pharmacological activation of these receptors by more alpha7-selective agonists improves cognitive performance in schizophrenia (3). Consideration of the unique neurobiological vulnerabilities of persons with schizophrenia is necessary in the design of cholinergic therapies for psychosis and smoking cessation.

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ROBERT FREEDMAN, M.D.
Denver, Colo.

Dr. Freedman, through the Department of Veterans Affairs, is co-inventor of a patent for genomic sequences for the alpha7 subunit.

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Varenicline-Induced Manic Episode in a Patient With Bipolar Disorder

TO THE EDITOR: We report a case of a manic episode in a patient with a history of bipolar disorder who was started on varenicline for smoking cessation. The case raises the possibility of inducing a manic episode with varenicline and using caution when prescribing it to patients with bipolar disorder.

A 63-year-old man with a history of bipolar disorder had been stable while receiving valproic acid for 5 years. The patient was admitted to an inpatient psychiatric unit and met criteria for a manic episode. He began exhibiting manic symptoms one week after starting varenicline (1 mg, twice daily) for smoking cessation. There was reported compliance with valproic acid, and his level on ad-