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Dr. Terao reports no competing interests.

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Dr. Siever Replies

TO THE EDITOR: I indeed thank Dr. Terao for the thought-provoking comments. As Dr. Terao explicitly notes, the overview did not attempt to comprehensively review treatment for aggression, nor did it address suicide. However, I agree that lithium may decrease limbic irritability, as do anticonvulsants, and increase “top-down brakes,” perhaps in part by enhancing serotonergic activity (1). There is indeed limited evidence that lithium is superior to anticonvulsants in the prevention of suicide (2), although a suicide-protective effect was not found in the data for 4,360 bipolar patients in the Systematic Treatment Enhancement Program for Bipolar Disorder (STEP-BD) study (3).

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Cannabis and the Course of Schizophrenia

TO THE EDITOR: While the correlations between schizophrenia and cannabis abuse are well corroborated, evidence for a causal correlation remains lacking. In their study, published in the April 2008 issue of the *Journal*, Monica Rais, M.D., et al. (1) found a more pronounced brain volume reduction over a 5-year follow-up period among cannabis using schizophrenia patients relative to schizophrenia patients without cannabis use. Dr. Rais et al. stated that their “study could not address the issue of direction of causality” (1, p. 494). Subsequently, they suggested “that some of the detrimental effects of cannabis on the course of illness may be explained by its effect on the progression of brain changes in schizophrenia” (1, p. 494).

If there was a specific effect of cannabis related to the outcome of schizophrenia, this should not be the case for other widely abused drugs, such as nicotine or alcohol. However, dose-dependent gray matter reductions have been described for individuals who smoke tobacco and abuse alcohol (e.g., 2). Although Dr. Rais et al. excluded patients who were addicted to alcohol at baseline, they did not exclude individuals who smoked tobacco, which admittedly would have been difficult to exclude because of the prevalence of smoking among schizophrenia patients. Neither alcohol nor tobacco consumption during follow-up was entered in the analyses. This may be particularly problematic concerning tobacco smoking because of its high prevalence among cannabis users (e.g., 3).

Since several addictive drugs seem to have similar effects on brain volume, the effect should not be considered specific. There is a possibility that there are discrete neurotoxic effects of different addictive drugs, and there is also a possibility that there are addiction-related factors common to each of the drugs that may contribute to volume loss. Consideration of these two possibilities might help to advance future studies in this area.

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