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Dr. Douglas Replies

TO THE EDITOR: Drs. Hellerstein and Markowitz offer the important reminder that although supportive psychotherapy may be among the most widely prescribed and commonly practiced forms of psychotherapy, surprisingly few well-designed controlled trials examining its efficacy have been published in the literature. They correctly emphasize the need for further clinical trials to establish the legitimacy of supportive psychotherapy as an evidence-based form of psychotherapy with scientifically proven efficacy. However, while the field of supportive psychotherapy needs to be defined in a manual for the purposes of such research, it is not clear to me that the use of manuals is the best way to teach psychiatric residents. This will no doubt be an ongoing topic of debate for some time to come.

Ian Douglas Rushlau, Psy.D. brought to my attention the related point that in the psychological literature, there already exists a rather voluminous body of research pertaining to "non-directive" or client-centered therapy, a form of therapy carrying a different moniker, which is similar in many respects to supportive psychotherapy as I described it.

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Aggression, Suicide, and Lithium Treatment

TO THE EDITOR: In the April 2008 issue of the *Journal*, Larry J. Siever, M.D. comprehensively reviewed important studies regarding the neurobiology of aggression and violence (1). Dr. Siever suggested that the processing of stimuli in relation to past emotional conditioning encoded in the amygdala and related limbic regions will trigger the "bottom-up drive" to an aggressive action, while the orbital frontal cortex and anterior cingular gyrus will provide "top-down brakes" of the aggressive action.

Dr. Siever did not explicitly mention suicide, which is the most dangerous self-directed aggressive behavior. In studies of suicide, the orbital prefrontal cortex and anterior cingulate gyrus have been reported to play important roles in suppressing aggression via inhibitory projection to the amygdala (2). Actually, positron emission tomography studies have shown reduced response in the prefrontal cortex and anterior cingulate gyrus after fenfluramine challenge to individuals who have attempted suicide (2).

Although Dr. Siever briefly reviewed pharmacological treatment, lithium was regrettably omitted. Recent meta-analyses have revealed that lithium has antisuicidal effects (3, 4), which are probably stronger than those of other mood stabilizers such as valproate and gabapentin (5). As Dr. Siever pointed out, valproate and gabapentin may decrease limbic irritability ("bottom-up drive") and thereby improve both mood and aggression. On the other hand, lithium seems to reduce the rate of suicidal behavior independently of its mood-stabilizing effects (2). Taking the fact into consideration that lithium has been reported to increase the volume of the prefrontal cortex and anterior cingulate gyrus (6), it seems likely that lithium may at least partially exert its antisuicidal effect via reinforcing "top-down brakes" of aggressive action. Since lithium has been shown to increase the volume and function of the limbic system, such as the hippocampus (7), antisuicidal effects of lithium may consist of both reinforcing "top-down brakes" and decreasing "bottom-up drive." Therefore, lithium may have superior antisuicidal effects relative to other mood stabilizers.

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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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