

The first factor is an important methodological one. If patients had one or more brief hypomanias and then progressed to having full duration or more severe episodes, only the latter, most severe episode was counted. Thus, the apparent decrease in minor or subthreshold switches appears to be related to the fact that more patients receiving venlafaxine progressed to full duration hypomanias or manias relative to the patients given the other drugs.

Also consistent with this interpretation are the findings, based on this same cohort, that were analyzed using conventional cross-sectional measures of manic severity as reported in a companion article (1). If one used a two-point or greater increase in the Clinical Global Impression Scale for Bipolar Disorder mania severity rating as indicating a clinically meaningful switch, this criterion occurred in more patients receiving venlafaxine ($p < 0.01$). Similarly, if one used the criterion of a Young Mania Rating Scale score of > 13 as an indication of clinically meaningful hypomania or mania, this also occurred more frequently with venlafaxine ($p = 0.05$), especially in rapid cyclers. Moreover, Vieta and colleagues (2) also found higher switch rates with venlafaxine than paroxetine in a randomized open study.

Thus, the graded Young Mania Rating Scale and Clinical Global Impression Scale for Bipolar Disorder manic severity ratings used by Post and colleagues (1) and the methodological clarification that only the most severe form of manic switch observed was counted suggest that there is an increased proclivity for full switches with venlafaxine relative to the other two drugs (particularly bupropion). On the basis of both analyses, we would conclude that greater caution is warranted (particularly in those patients with a prior history of four or more episodes in the year prior to study entry) in the use of antidepressant adjunctive treatment with venlafaxine than sertraline or bupropion in the treatment of depressed patients with bipolar disorder who are already receiving a mood stabilizer.

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Reduced Hippocampal and Amygdalar Volume in Dissociative Identity Disorder: Not Such Clear Evidence

TO THE EDITOR: As experimental psychologists trained in research methodology, we read the article by Eric Vermetten, M.D., Ph.D., and colleagues (1) with mixed feelings. The authors employed magnetic resonance imaging (MRI) to measure the volumes of the hippocampus and amygdala in 15 female patients with dissociative identity disorder and 23 female nonpsychiatric women. Dr. Vermetten and colleagues concluded from their data that, relative to comparison subjects, patients with dissociative identity disorder had smaller hippocampal and amygdalar volumes. They admit that their

study suffers from a number of shortcomings. Most important, the patients with dissociative identity disorder were significantly older than the comparison subjects. Although group differences in hippocampal and amygdalar volumes disappeared when the authors statistically controlled for age, they try to convince the reader that their results are nonetheless valid. They argue that there is generally no age-related reduction in hippocampal and amygdalar volumes in healthy women aged 20–50. This point is reiterated in an editorial by David Spiegel, M.D. (2, p. 566), who stated that the article by Dr. Vermetten and colleagues offers “clear evidence of smaller hippocampal and amygdalar volume among those with dissociative disorders” (2). Unfortunately for Dr. Vermetten and colleagues as well as Dr. Spiegel, there have been reports that this population also exhibits significant, albeit moderate, hippocampal volume decreases in a 5-year follow-up design (3). In relation to this, there is good evidence that suffering from a major psychiatric disorder may lead to accelerated aging in middle-aged people (4, 5). Therefore, MRIs of healthy, younger individuals do not constitute the ideal control condition for those of patients with dissociative identity disorder. It is with these considerations in mind that we fundamentally disagree with Dr. Spiegel when he claims that the study by Dr. Vermetten and colleagues offers “clear evidence.” It does not.

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Dr. Vermetten Replies

TO THE EDITOR: We acknowledge that the design of every study is strongest when groups that are studied are matched for several dependent variables. However, we argue that the data disputed by Drs. Smeets, Jelicic, and Merckelbach are strong and valid. Hippocampal volume was 19.2% smaller and amygdalar volume was 31.6% smaller in the patients with dissociative identity disorder relative to the healthy subjects. Statistical rigor required us to control for the age difference (dissociative identity disorder patients [42.8 years] versus comparison subjects [34.6 years]). In doing so, our findings left only the right amygdalar volume significantly smaller across groups. However, we argue that the comparison data for the hippocampal and amygdalar volumes are valid without correction for this factor. Even though age-related structural alterations in the hippocampus have been identified, there are no

previous findings of a relationship between age and hippocampal or amygdalar volume in healthy women in the 20–50-year age group (1, 2), the age group represented by the subjects in our study. A significant negative correlation of age with both left and right hippocampal volumes has been found only in men (a reduction in hippocampal volume of about 1%–1.5% per year). No significant effect of age has been found for amygdalar volume in either men or women. Even when some of these women have entered menopause, no difference in hippocampal volume in pre- versus postmenopausal women has been found (2). The study they cite by Raz and colleagues found differences only for individuals over age 50. There is some evidence in elderly individuals (aged >70) for modest reductions in hippocampal volume with late stages of aging (3, 4). Even if our comparison group had been older, the difference in volumes would still have been present. Accordingly, we argue that the significance levels for the between-group comparisons of both hippocampal and amygdalar volumes are valid without correction for this factor.

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Antidepressant-Induced or Clinician-Induced Suicidality in Depression?

TO THE EDITOR: The article by David N. Juurlink, M.D., Ph.D., and colleagues (1) reports that selective serotonin reuptake inhibitors (SSRI) have a 4.8-fold risk of inducing suicide during the first month of therapy relative to non-SSRI antidepressants. In the abstract of the article, it also states that “the absolute risk of suicide with all antidepressants [is] low” (1, p. 813). The statistical data regarding this “low risk” should have been provided, since without in-depth study of the article, readers may be misled and thus undertreat their patients with depression. In addition, undertreatment may be supported by the Food and Drug Administration (FDA) warning about a possible relationship between antidepressants and suicidality (not suicide). The statistical data reported in the article are 1/3,353 (29/100,000) in SSRI-treated patients versus 1/16,037 (6.2/100,000) in non-SSRI antidepressant-treated patients. The authors state that “many suicides during the first month of treatment likely result from depression,” so that the “actual risk of suicide due to antidepressant therapy is probably far lower” (1, p. 817). Reporting specific data here would have been much more useful to clinicians than reporting that SSRIs are more risky than non-SSRI antidepressants. Despite the worrying abstract, the statistical data presented suggest

that very few patients may become suicidal using antidepressants. Then, there are “speculations” about the “mechanisms” underlying the association between SSRI antidepressants and suicide (p. 818). Among them, there is “treatment-emergent agitation or dysphoria” (p. 818). A recent series of studies has shed some light on the possible mechanisms related to suicidality and antidepressants. Among possible precursors to suicidality, the FDA lists features typical of mixed depression (depressive mixed states), such as irritability, psychomotor agitation, and bipolarity. In mixed depression, defined as a major depressive episode plus three or more intradepression, noneuphoric, DSM-IV hypomanic symptoms, irritability and psychomotor agitation are among the most common hypomanic symptoms, along with racing/crowded thoughts (2). The bipolar nature of mixed depression has been validated (2). In a large, psychoactive drug-free bipolar II and major depressive disorder sample, it was shown that psychomotor agitation and racing/crowded thoughts are independent predictors of suicidal ideation (3, 4). Furthermore, it has been shown that most suicide attempters have a mixed depression before acting (5). These findings suggest that there are features of depression that should always be assessed and may make some individuals at risk for antidepressant-induced suicidality, and this is related to the worsening of these intradepression hypomanic symptoms. Therefore, it is not antidepressants that induce suicidality, but the poor use of them. Mood stabilizing agents have been recommended prior to using antidepressants for treating patients with mixed depression (3, 4). In addition, systematic probing for intradepression hypomanic symptoms is suggested by the FDA and by findings of these previous studies.

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Dr. Juurlink Replies

TO THE EDITOR: Dr. Benazzi suggests presenting the absolute risks of suicide during the first month of treatment with SSRI and non-SSRI antidepressants in the abstract of our manuscript. These numbers, however, are only estimates, and their proper interpretation requires the context we provide in the accompanying discussion. This is beyond the scope of an abstract.

Dr. Benazzi offers his speculation about a variety of causal pathways linking SSRIs and suicide. We agree that SSRIs are often used inappropriately, but his hypothesis that prescribing practices are the sole explanation for SSRI-related suicid-