

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-