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.

References

1. Pruessner JC, Collins DL, Pruessner M, Evans AC: Age and gender predict volume decline in the anterior and posterior hippocampus in early adulthood. J Neurosci 2001; 21:194–200
2. Sullivan EV, Marsh L, Pfefferbaum A: Preservation of hippocampal volume throughout adulthood in healthy men and women: Neurobiol Aging 2005; 26:1093–1098
3. Lupien SJ, de Leon M, de Santi S, Convit A, Tarshish C, Nair NP, Thakur M, McEwen BS, Hauger RL, Meaney MJ: Cortisol levels during human aging predict hippocampal atrophy and memory deficits. Nat Neurosci 1998; 1:69–73
4. Sullivan EV, Marsh L, Mathalon DH, Lim KO, Pfefferbaum A: Age-related decline in MRI volumes of temporal gray matter but not hippocampus. Neurobiol Aging 1995; 16:591–606

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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.

References

1. Juurlink DN, Mamdani MM, Kopp A, Redelmeier DA: The risk of suicide with selective serotonin reuptake inhibitors in the elderly. Am J Psychiatry 2006; 163:813–821
2. Benazzi F: Family history validation of a definition of mixed depression. Compr Psychiatry 2005; 46:159–166
3. Benazzi F: Suicidal ideation and depressive mixed states. Psychother Psychosom 2005; 74:61–62
4. Akiskal HS, Benazzi F, Perugi G, Rihmer Z: Agitated "unipolar" depression re-conceptualized as a depressive mixed state: implications for the antidepressant-suicide controversy. J Affect Disord 2005; 85:245–258
5. Balazs J, Benazzi F, Rihmer Z, Rihmer A, Akiskal KK, Akiskal HS: The close link between suicide attempts and mixed (bipolar) depression: implications for suicide prevention. J Affect Disord 2006; 91:133–138

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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-

ality defies existing literature as well as basic principles of drug safety. Our findings are consistent with the hypothesis that SSRIs can induce suicidality in a small minority of patients during the initial weeks of therapy.

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Comparing Antipsychotic Efficacy

TO THE EDITOR: Stephen Heres, M.D., and colleagues (1) succinctly summarized difficulties in integrating inconsistent findings from head-to-head industry-sponsored trials about comparative effectiveness of second-generation antipsychotics. They enumerate several study design and reporting elements that potentially bias studies and contribute to findings favorable for a sponsor's drug. One additional factor is the frequent discrepancy between the study outcome as reported in the study's abstract and the actual findings of the study (2). For example, in a study sponsored by the manufacturer of olanzapine that compared olanzapine to risperidone (3), the two medications were not different on 21 out of 25 efficacy measures, yet the abstract emphasized the greater efficacy of olanzapine. In contrast, in a study sponsored by the manufacturer of risperidone that compared the same set of agents (4), risperidone and olanzapine were found to be not different on 33 out of 37 efficacy measures, including the a priori primary endpoints of the study, yet the abstract emphasized the greater efficacy of risperidone!

The hope that nonindustry-sponsored studies will resolve these discrepancies remains to be realized. In reporting results from phase 1 of their landmark Clinical Antipsychotic Trials of Intervention Effectiveness (CATIE) study comparing first-generation and second-generation antipsychotics (5), Lieberman and colleagues concluded that "olanzapine was more effective than the other four drugs studied." The comparison between different second-generation antipsychotics was, however, biased by suboptimal dosing of quetiapine, ziprasidone, and risperidone (6, 7) and differences in switching rates (51% of olanzapine patients did not have to discontinue a previous antipsychotic in comparison to 45% of risperidone patients, 35% of quetiapine patients, and 30% of ziprasidone patients; the correlation between these switch rates and 8-week all-cause discontinuation was >0.95). Switching antipsychotics among relatively stable, moderately ill patients with schizophrenia always entails high risk (8). Neither of these issues was considered in the abstract, analysis, or conclusions.

All studies have design constraints which impact their internal validity and generalizability. To obtain an accurate answer to a clinical question, we consequently need to critically examine and properly integrate all data pertinent to that question. The important findings of CATIE are most usefully considered in the context of the vast database to which it adds.

References

1. Heres S, Davis J, Maino K, Jetzinger E, Kissling W, Leucht S: Why Olanzapine beats risperidone, risperidone beats quetiapine, and quetiapine beats olanzapine: an exploratory analysis of head-to-head comparison studies of second-generation antipsychotics. Am J Psychiatry 2006; 163:185–194
2. Tandon R, Fleischhacker WW: Comparative efficacy of antipsychotics in the treatment of schizophrenia: a critical assessment. Schizophr Res 2005; 79:145–155
3. Tran PV, Hamilton SH, Kuntz AJ, Potvin JH, Andersen SW, Beasley C Jr, Tollefson GD: Double-blind comparison of olanzapine versus risperidone in the treatment of schizophrenia and other psychotic disorders. J Clin Psychopharmacol 1997; 17: 407–418
4. Conley RR, Mahmoud R: A randomized double-blind study of risperidone and olanzapine in the treatment of schizophrenia and schizoaffective disorder. Am J Psychiatry 2001; 158:765–774
5. Lieberman JA, Stroup ST, McEvoy JP, Swartz MS, Rosenheck RA, Perkins DO, Keefe RSE, Davis SM, Davis CE, Lebowitz BD, Severe J, Hsiao JK: Effectiveness of antipsychotic drugs in patients with chronic schizophrenia. N Engl J Med 2005; 353:1209–1223
6. Davis JM, Chen N: Dose response and dose equivalence of antipsychotics. J Clin Psychopharmacol 2004; 24:192–208
7. Nasrallah HA, Targum SD, Tandon R, Ross RA: Clinical effectiveness in the treatment of schizophrenia: an evolving paradigm. Psychiatr Serv 2005; 56: 273–282
8. Tandon R: Comparative effectiveness of antipsychotics in the treatment of schizophrenia: What CATIE tells us- Parts 1 and 2. International Drug Therapy Newsletter 2006; 41: 51-58; 67–74

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Dissociative Disorder Underdiagnosed Due to Undescriptive Criteria?

TO THE EDITOR: In his editorial, David Spiegel, M.D. states that the DSM-IV workgroup on dissociative disorders improved the name and diagnostic criteria of dissociative identity disorder (formerly multiple personality disorder), but that the disorder continues to be "underdiagnosed" (1, p. 567). Why is that?

Dr. Spiegel begins the answer when he notes that this is a "disease of hiddenness" in which patients "hide rather than reveal their symptoms." Let me complete the answer by noting that the diagnostic criteria don't even mention this camouflaged presentation. In addition, if the diagnostic criteria don't describe or even mention the typical presentation, how can clinicians be expected to recognize the disorder and make the diagnosis?

Like the diagnostic criteria, the new name for the disorder is not very descriptive. "Dissociative identity disorder" omits a key feature: multiplicity. Persons with this disorder have more than one "I." They have multiple subjective identities.

I have previously proposed a more descriptive name (dissociative disorder, multiple identity type) (2) and a set of more diagnosis-oriented criteria (3, 4), but I don't insist on the particulars or consider them the last word. All I respectfully insist on is that the name and diagnostic criteria for this disorder be made more descriptive of the typical presentation and more relevant to the actual process of making this diagnosis. Otherwise, it will continue to be underdiagnosed.

References

1. Spiegel D: Recognizing traumatic dissociation. Am J Psychiatry 2006; 163:566–568
2. Nakdimen KA: Renaming multiple personality disorder. Am J Psychiatry 1995; 152:1104
3. Nakdimen KA: Diagnostic criteria for multiple personality disorder. Am J Psychiatry 1992; 149:576-577
4. Wetsman H, Nakdimen KA: Diagnostic criteria for multiple personality disorder; Dr. Nakdimen replies [letters]. Am J Psychiatry 1993; 150:354–355

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