## BRIDGE Study Warrants Critique

The Bipolar Disorders: Improving Diagnosis, Guidance and Education (BRIDGE) study[1] by Angst et al has received coverage in psychiatric online media.[2-4] The message is that almost half the patients with a major depressive episode have undiagnosed bipolar disorder and are "not receiving necessary mood stabilizer treatment."[2] Such views are controversial and far from the mainstream as reflected in *International Statistical Classification of Diseases, 10th Revision* and *DSM-IV*. Yet the BRIDGE study findings were published without accompanying commentary or critique.

The study's findings are based on a "bipolar specifier" requiring "no minimum duration of symptoms" and "no exclusion criteria." Any subject who came to psychiatric attention with an angry, agitated, or elated response to environmental triggers or psychoactive substances might have met criteria for "bipolarity." The lack of duration requirements means any subject with episodic affective instability (eg, borderline personality disorder or posttraumatic symptoms) is liable to be mislabeled as having bipolar disorder. Not mentioned was that the self-report "bipolar-specifier" instrument was previously reported to have a specificity of only 51%.[5]

The study based "subthreshold mania" on just 3 symptoms (eg, "being more talkative, [having] decreased need for sleep, and increased goal-directed activity"). In the absence of core manic symptoms, many clinicians would inquire about anxiety and consider manic defenses to contextual stressors. The article does not define how behavior was determined to be an "unequivocal and observable change in functioning uncharacteristic of the person's usual behavior."[1(p793)] Patients with borderline personality disorder or substance abuse frequently report these sorts of behavioral changes.

Further, 23.2% of subjects were reported to experience elevated or irritable mood triggered by antidepressants and were defined as having bipolar disorder. Irritability is a common adverse effect of selective serotonin reuptake inhibitors. Angst et al presumed that anyone with this adverse effect actually had bipolar disorder. This conflicts with the literature[6] and with a 6-decade retrospective study by Angst of swings from depression to mania concluding "there is no evidence for a treatment-induced (manic) switch."[7(p140)] Yet Angst et al do not comment on this apparent change in perspective.

The article reports "the sponsor of this study (sanofi-aventis) was involved in the study design, conduct, monitoring, data analysis, and preparation of the report."[1(p798)] Participating psychiatrists were financially remunerated for patient recruitment. The article concluded with an appeal to use "mood stabilizers," presumably atypical antipsychotics, which are less efficacious than lithium.[8] The sponsor has a medication in this class. Other pharmaceutical company documents indicate a desire for a widening of bipolar diagnostic criteria.[9] Angst et al advocate treatment with such drugs for "symptoms that impair everyday functioning,"[1(p797)] but according to Table 2 in their article,[1(p795)] more than 40% of patients who met subthreshold bipolar criteria had no lifetime history of such impairment.

Angst et al state that a study limitation was that "participating centers were not randomly selected, which may have led to a bias through inclusion of psychiatrists with a particular interest in bipolar disorder."[1(p797)] This is not a trivial point. Opposing perspectives in psychiatry that consider or do not consider the influence of reactive dynamic forces on contextual factors have been labeled at the extreme as "brainless psychiatry" and "mindless psychiatry."[10] The ever-widening "bipolar spectrum" is the current focus for this debate.[11-13] The BRIDGE study findings would have been better presented with a critique couched within this debate.

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***In reply***

*We are pleased to respond to the points raised by Allen et al, some of which take material out of context and quote news media articles beyond our control. For example, the letter states that "The message is that almost half the patients with a major depressive episode have undiagnosed bipolar disorder and are 'not receiving necessary mood stabilizer treatment.'" Our actual statements are:*

Based on these studies and the major differences in treatment guidelines for MDD [major depressive disorder] and bipolar disorder, we recommend that, among patients with MDEs [major depressive episodes], the presence of bipolar features, including all those with significant predictive value reported in this study, should be investigated carefully before a decision is made to prescribe antidepressants. If patients exhibit bipolar symptoms that impair everyday functioning, treatment with a mood stabilizer or an atypical antipsychotic may be useful.[1(p797)]

*They assert that "The study's findings are based on a 'bipolar specifier' requiring 'no minimum duration of symptoms' and 'no exclusion criteria,'" and that "Any subject who came to psychiatric attention with an angry, agitated, or elated response to environmental triggers or psychoactive substances might have met criteria for 'bipolarity.'" The criteria, stated in the "Methods" section of our article,[1(p793)] were (1) an episode of elevated mood, an episode of irritable mood, or an episode of increased activity with (2) at least 3 of the symptoms listed under Criterion B of the* DSM-IV-TR *associated with (3) at least 1 of the 3 following consequences: unequivocal and observable change in functioning uncharacteristic of the person's usual behavior, marked impairment in social or occupational functioning observable by others, or requiring hospitalization or outpatient treatment. The minimum duration of symptoms required for a hypomanic episode was 1 day. We assessed the duration reported for hypomanic episodes in 5 groups. Among subjects with major depressive episode with hypomanic episodes, 7.8% reported episodes of 1 day's duration; 2 to 3 days' duration was more frequent than 4 to 6 days.*[2] *No exclusion criteria for manic/hypomanic episodes associated with antidepressant or other drug use were applied. Importantly, the initial eligibility criterion was that patients have presented to clinical settings for evaluation and treatment of a major depressive episode per* DSM-IV-TR *criteria. These sequential criteria, applied by senior psychiatrists in each country, are entirely inconsistent with the assertion that the psychiatrists conducting the assessments enrolled "any subject who came to psychiatric attention with an angry, agitated, or elated response to environmental triggers."*

*The statement that 23.2% of subjects experienced elevated or irritable mood triggered by antidepressants did not "define the subjects as having 'bipolar disorder.'" Rather, it addresses the* DSM *A criteria, which are essential, but not sufficient, for diagnosis of bipolar disorder. As Figure 1 in our article*[1(p794)] *shows, mood lability while taking antidepressants occurred in 55.8% of bipolar specifier–positive vs 23.0% of bipolar specifier–negative subjects (odds ratio, 1.7; 95% CI, 1.4-2.0) and mania/hypomania while taking antidepressants occurred in 37.2% of bipolar specifier–positive vs 3.4% of bipolar specifier–negative subjects (odds ratio, 5.7; 95% CI, 4.4-7.5).*

*Allen et al view their position as part of a "debate" about the "ever-widening bipolar spectrum." We consider data, not debates, as central to the progress in the scientific understanding of mood disorders. They make several references to borderline personality disorder. The BRIDGE study assessed for comorbid diagnoses in all subjects. Five hundred thirty-two patients (9.3%) met* DSM-IV-TR *criteria for borderline personality disorder. This large sample provides an opportunity to analyze patients who met borderline criteria vs those who did not. We are completing a manuscript that will provide useful evidence on this subject.*

*Allen et al cast unseemly aspersions that the BRIDGE study was a vehicle to promote sales of an antipsychotic drug sold by sanofi-aventis. sanofi-aventis has no antipsychotic with an indication for bipolar disorder. We know of no evidence that this was the case at any stage of development and execution of the BRIDGE study. sanofi-aventis ceased financial support for analyses of the study in 2010. All work subsequently conducted has been achieved by our local funds.*

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