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Dr. Woodside Replies

TO THE EDITOR: I read with interest the letter by Dr. Godart et al. concerning the rates of premature termination of inpatient treatment for anorexia nervosa. This issue, studied minimally in adults, has been neglected in adolescents. I expect that some of the differences in the findings of the study by Dr. Godart et al. and ours can be explained by the nature of the patient population. I would also be interested in knowing how Dr. Godart et al. established a failure in a patient's therapeutic contract, given that the patients were all adolescents and receiving treatment at least partly at their parents' behest.

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Brain-Derived Neurotrophic Factor in Patients With Remitted Depression

TO THE EDITOR: We read with interest the article by Alexander Neumeister, M.D., and colleagues (1). The neurobiology of brain-derived neurotrophic factor (BDNF) is complex and influenced by a number of different hormonal systems, including the hypothalamic-pituitary-adrenal (HPA) axis, which is known to be dysfunctional in patients with severe mood disorders. Stress-responsive corticosteroids, which are the end products of the HPA axis, have been shown to have important effects on the expression of BDNF in preclinical studies (2). We have also recently shown an interaction between cortisol and serum levels of BDNF in patients with bipolar depression and schizophrenia (3). Furthermore, tryptophan depletion has been shown to lower cortisol levels in patients with mood disorders (4) as well as in healthy comparison subjects (5). Of interest, sham tryptophan depletion has also been reported to cause a significant decrease of plasma cortisol (4). Changes in cortisol levels may, therefore, account for the increases in BDNF following sham depletion observed by Dr. Neumeister and colleagues.

The data presented by Dr. Neumeister et al. may indeed suggest an intimate link between the serotonergic and neurotrophic systems, but in the absence of any data regarding HPA axis function in these patients (and healthy subjects), it remains a possibility that the observed changes of expression of BDNF are secondary to differences in cortisol production. We advocate that further studies of BDNF in mood disorders also investigate HPA axis function.

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Drs. Neumeister and Manji Reply

TO THE EDITOR: We read with interest the letter by Dr. Mackin and Mr. Gallagher in which they suggest interpreting the interactive effects of BDNF and serotonin in major depressive disorder in the context of HPA axis function. Preclinical studies (1) have suggested major functional interactions between knockout mice with genetically induced alterations in serotonin (5-HT) transporters and heterozygous BDNF knockout mice and have also shown that this leads to enhanced stress responses with altered HPA axis function. Notably, a decrease in BDNF concentrations does not appear sufficient to lower extracellular 5-HT; similarly, constitutional changes in extracellular 5-HT because of differences in 5-HT reuptake by 5-HT transporters do not affect BDNF protein levels. This adds to the importance of identifying additional parameters that may contribute to the interactive effects of 5-HT and BDNF in major depressive disorder. There is a wide range of evidence supporting the idea that glucocorticoids play a key role in acute and chronic stress responses. For example, stress and glucocorticoids impair hippocampal neurogenesis; furthermore, in addition to directly causing neuronal atrophy, stress and glucocorticoids also impair cellular resilience that together may lead to the well-established morphological alterations in major depressive disorder. Notably, BDNF and other

neurotrophic factors are believed to counteract these effects (2). It has been previously demonstrated that in addition to glucocorticoids, BDNF is involved in the early response to acute stress (3). In our study, tryptophan depletion was used as a model to study the effects of acute stress in the context of reduced 5-HT function in major depressive disorder and healthy comparison subjects. Additional work is clearly necessary to delineate the causal relationships between altered 5-HT function, BDNF, and HPA axis function and the pathogenesis of major depressive disorder. Dysregulation of these cascades may be a key mechanism by which stress induces impairments of cellular plasticity. This highlights the interactive effects of different neurobiological systems in the pathogenesis of major depressive disorder, and all three of the referenced major neurobiological systems appear to be involved.

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Validity of the One-Criterion Threshold for an Alcohol Abuse Diagnosis

TO THE EDITOR: We were surprised to read the results of the article by Marc A. Schuckit, M.D., et al. (1). The authors concluded that all four DSM-IV alcohol abuse criteria perform equally well and that their results favored the threshold of one criterion for the diagnosis of alcohol abuse. This is remarkable because the validity of the abuse category has been one of the main controversies of the DSM-IV classification for alcohol use disorders (e.g., reference 2). We have serious reservations regarding the validity of the data of Dr. Schuckit et al. and their subsequent justification of the one-criterion threshold for alcohol abuse.

First, the study group in the article by Dr. Schuckit et al. was rather unusual, with more than 70% of the subjects being relatives of treatment-seeking alcoholics. This limited the generalizability of their findings. For example, in our recent study of a large general population sample (N=7,076) (3), subjects with a DSM-IV diagnosis of alcohol abuse could not be differentiated from subjects without a DSM-IV alcohol use disorder diagnosis with a broad range of external validators (e.g., psychiatric comorbidity, functional status, familial alcohol problems, treatment seeking). Subjects with two or more criteria, however, were significantly different from subjects without a DSM-IV alcohol use disorder, indicating better validity for a threshold of at least two criteria (3).

Second, most of the validators for the DSM-IV diagnosis of alcohol abuse in the article by Dr. Schuckit et al. are rather weak. The fact that subjects with abuse had a higher intake of alcohol than the subjects without an alcohol use disorder is hardly surprising and almost tautological. When the authors looked at drug-related history to compare subjects with one-criterion abuse to subjects without an alcohol use disorder, they did mention drug use (significant difference for cocaine use only) but failed to mention the more relevant prior history of drug abuse or dependence.

Third, when evaluating the 5-year outcome, the authors seemed to ignore the fact that over 70% of the subjects with a DSM-IV diagnosis of abuse at baseline did not endorse any abuse criterion at follow-up. In our general population study, even higher rates of spontaneous remission of DSM-IV alcohol abuse were observed: 81% and 85% at the 1- and 3-year follow-ups, respectively (unpublished report). In a prospective evaluation of the validity of current DSM-IV abuse criteria, these findings should at least be discussed.

In summary, we feel that the limitations of the study by Dr. Schuckit et al. call for a more cautious interpretation and that their findings cannot simply be used as support for the validity of the one-criterion threshold for the diagnosis of alcohol abuse.

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Dr. Schuckit Replies

TO THE EDITOR: Clinical issues are complex, and study results reflect the methods and subject groups used. Therefore, the "true" answer to a question is likely to be found only when one pays attention to differences as well as similarities across research reports. So if the unpublished study cited by Drs. de Bruijn and van den Brink generates some different answers than the current report, such disagreements may offer important insights into the questions raised. However, Drs. de Bruijn and van den Brink incorrectly asserted that in our study, 70% of the subjects with abuse at baseline endorsed no abuse criterion at follow-up. In Table 2 of our study, 54% of the subjects who had three or more experiences with any alcohol abuse item at study entry reported at least one problem at follow-up, 42% endorsed a dependence item, and 25% experienced at least one abuse item at least three times. Therefore, between 54% and as many as two-thirds may have had such experiences.

The letter also incorrectly states that we reported no differences between those with one versus two abuse items at baseline. The tables reveal that those with two or more items had