lease, paroxetine, or placebo in conjunction with mood stabilizers (3). Lack of efficacy appears to be an overall greater risk than induction of mania for most depressed bipolar patients who receive adjunctive antidepressants. The STEP-BD study did not evaluate depression outcomes with highly noradrenergic antidepressants, such as venlafaxine, but their apparent higher risk for induction of mania relative to predominantly serotonergic or dopaminergic antidepressants (4) would seem to prompt caution if one chose to expose a bipolar patient to other noradrenergic agents, especially those not studied in bipolar disorder, such as atomoxetine.

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Analysis of Mechanisms Underlying Depressive and Addictive Comorbid Disorders in Adolescents Should Not Ignore Nicotine Use and Dependence

TO THE EDITOR: In the March 2009 issue of the *Journal*, Uma Rao, M.D., et al. (1) tackled a very important issue pertaining to the comorbidity of affective disorders and substance use. The authors analyzed the role of stressors and urinary cortisol in predicting the onset of substance use disorders and depressive disorders in adolescents at risk, depressed adolescents, and healthy comparison subjects. Somewhat surprising was that the characterization of the participants did not include nicotine use and dependence, nor did the authors report that adolescents who smoked were excluded. Similarly, substance use disorder was a major outcome, but the most prevalent substance use disorder, tobacco dependence (2), was not mentioned. Dr. Rao et al. did not cite an assessment instrument for nicotine dependence. Although the Schedule for Affective Disorders and Schizophrenia for School-Age Children—Present and Lifetime Version (K-SADS-PL) does assess nicotine consumption, it does not cover nicotine dependence. Actually, nicotine use and dependence are ignored by most psychiatric instruments (e.g., Schedules for Clinical Assessment in Neuropsychiatry, Mini-International Neuropsychiatric Interview).

Cigarette smoking has been discussed as a "gateway drug" to substance use disorders (3). Furthermore, nicotine is a potent acute stimulator of the hypothalamic-pituitary-adrenal (HPA) axis through induction of corticotropin-releasing hormone release. Regular consumption of nicotine could therefore lead to chronically elevated adrenocorticotrophic hormone and/or cortisol levels (4). Thus, it seems pertinent to discuss nicotine as a factor with a possible effect on several assessments within this study. Although the authors referred to a separate nicotine study they conducted, they did not mention or discuss nicotine use and dependence in their present study.

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Drs. Rao, Hammen, and Poland Reply

TO THE EDITOR: We appreciate the comments by Drs. Schütz and Sepehry. We agree with their statement that cigarette smoking is frequently associated with alcohol and drug use disorders and that it also may be a "gateway drug" to other substance use disorders. For example, in one review article (1), the investigators reported that the prevalence of smoking in individuals with substance use disorder exceeded 75%. We also agree that most psychiatric instruments, including K-SADS-PL, do not assess nicotine dependence.

Nicotine dependence was not assessed in our study. However, cigarette consumption was documented both at intake and during follow-up assessments. Some of these data were presented at a scientific meeting (2). Specifically, 20.5% of adolescents in the sample reported a lifetime history of smoking, and 9.9% reported current smoking at intake. Of the adolescents who had follow-up data, 28.6% reported smoking during follow-up. Consistent with previous reports, there was a higher prevalence of smoking in adolescents who reported drug or alcohol use than those without a history of drug or alcohol use, both at baseline and follow-up (three- to four-fold higher).

At intake, adolescents who smoked and adolescents who did not smoke did not differ significantly with respect to HPA activity (the primary predictor variable of substance use disorder during follow-up). When follow-up clinical data were incorpo-