(4). Thus, an investigator allegiance effect was controlled for, and the results can be expected to be more representative than the results of many studies in which proponents of only one approach were included. In their letter, Hofmann et al. critically note that we used the Liebowitz Social Anxiety Scale to assess remission (and response) and not the absence of a social anxiety disorder diagnosis assessed by the Structured Clinical Interview for DSM-IV Axis I Disorders (SCID-I). Remission and response can be assessed in many ways (e.g., by standardized rating scales, by assessing reliable and clinical significant change, or by assessing the absence or presence of a diagnosis). We decided to use the Liebowitz Social Anxiety Scale because it can be expected to yield more reliable data on remission than a qualitative SCID-I diagnosis. Remission and response are assessed by use of established cutoff scores (4). We described the rationale and the design of our study long before any data were available (7). Hofmann et al. claim that the loss of patients during the follow-up was significantly higher in the psychodynamic therapy group than in the CBT group, questioning the assumption of missing at random on which multiple imputation is based. They apparently lumped together all losses over the whole follow-up period. However, it is more appropriate to compare the losses for each time of assessment. We did so and did not find a significant difference between CBT and psychodynamic therapy here— since multiple testing is involved, the alpha needs to be adjusted to control for type I error inflation (0.05/4). In order to examine whether estimating missing data by multiple imputation had an effect on the comparison of psychodynamic therapy and CBT with regard to remission and response, we included missing or not (0/1) as a covariate in additional analyses. Whereas the per protocol analysis takes only the data of the per protocol patients into account, this analysis includes both the per protocol patients and the dropouts whose data were estimated by multiple imputation. The analysis examines whether the comparison of CBT and psychodynamic therapy is affected by estimating missing data by multiple imputation. The results were corroborated for the three follow-up assessments with no significant differences ($p<0.05$) between CBT and psychodynamic therapy.

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Sex Difference in Response to Varenicline for Smoking Cessation

TO THE EDITOR: A major finding reported by Jed E. Rose, Ph.D., and Frédérique M. Behm, C.R.A. (1), in the November 2014 issue of the *Journal,* was a significant sex difference in response to the varenicline plus bupropion combination for smoking cessation, viz., men had a significantly better response to the combination than to varenicline alone (i.e., plus placebo), whereas women had a similar response to the combination and to varenicline alone. This finding is mentioned in the accompanying editorial by Potter (2) as extending to the finding of several previous clinical trials and meta-analyses that "male smokers benefit from nicotine replacement therapy to a greater degree than female smokers." However, neither the authors nor the editorialist mentions the between-sex comparison for varenicline alone (i.e., within the varenicline plus placebo group). The data in Figure 2 of the article (blue bars represent the varenicline plus placebo group for male and female participants) show a higher percent of abstinence for women (30%) than for men (19%) in the varenicline plus placebo group (i.e., a better response to varenicline in women than in men, contrary to the pattern for nicotine replacement therapy and previous trials with varenicline alone) (2). The error bars (standard deviation, not standard error of the mean) barely overlap, suggesting that this difference is statistically significant. Thus, at least part of the sex difference in response to varenicline plus bupropion may be a result of women responding better than men to varenicline alone, thereby reducing the opportunity for them to show enhanced response with the addition of bupropion.

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Response to Gorelick

TO THE EDITOR: Dr. Gorelick raises a reasonable question as to whether the sex-by-treatment interaction reported in our article on combined varenicline/bupropion sustained-release treatment could have been due in part to a lower efficacy of varenicline alone in men compared with women. Although we, along with the editorialist, highlight this possibility, two factors argue against it being a major contributor to the interaction effect. First, the previous literature has not reported sex differences in varenicline treatment. Second, the statistical argument advanced in Dr. Gorelick's comment is imprecise. Error-bar overlap is not a reliable criterion for assessing statistical significance. Using the information presented in Table 2 of our article, a chi-square calculation yields a p value of 0.27 for the difference between varenicline plus placebo treatment in men compared with women. Thus, although the possibility remains that there is an effect that contributed to the overall interaction effect, there is no compelling data in support of that interpretation at the present time.

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Association of a Brain Methylation Site With Clinical Outcomes in Depression Does Not Replicate Across Populations

TO THE EDITOR: In the December 2014 issue of the *Journal*, Ma-Li Wong, M.D., et al. (1) reported a strong association between the genetic variant rs1321744 and outcome of treatment with the antidepressants fluoxetine and desipramine in a small sample of Mexican Americans with major depressive disorder. They further reported that a predictive model based on this genetic variant, in addition to several other variants, predicts remission with a high accuracy (area under the receiver operating characteristic curve equal to 0.95). Such prediction would be highly clinically significant and applicable in practice. However, it is based on an analysis of only 65 genotyped individuals, which raises the question whether this might be a false positive or a highly population-specific finding.

The clinical applicability of the reported finding fully depends on whether it is replicable. Wong et al. reported no replication attempt. However, results from much larger samples are available. We previously reported a meta-analysis of three genome-wide pharmacogenetic studies of antidepressants with data on 2,256 individuals (2), and the results, summarized in Figures 1 and 2, are publicly available (http://www.broadinstitute.org/mpg/ricopili/) (3). We queried these data to test whether the finding reported by Wong et al. is replicable. Since the genetic association was reported to apply across the two antidepressant drugs from different classes, we used the whole combined sample analysis of 2,256 individuals from the United States and Europe with major depressive disorder treated with all types of antidepressants. In this large, combined sample, rs1321744 was not significantly associated with either reduction in depressive symptoms ($p=0.489$, uncorrected) or with remission ($p=0.556$, uncorrected).

This completely negative result in a large, combined sample suggests that the reported finding is extremely unlikely to replicate across populations. Because we have no access to results on other Mexican American samples, the currently available data do not allow us to distinguish between highly population-specific association and false positive findings. The comparison between the reported results and the publicly available meta-analysis cautions against accepting results from intensive analyses of small samples without replication. Future reports should take advantage of publicly available data to estimate the robustness of results in context.

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Dr. Müller-Myhsok is a consultant with HMNC and an inventor on several patents in the subject area of pharmacogenetics. Dr. Lewis has received consultant fees from Eli Lilly. Dr. Perlis has served on scientific advisory boards or received consulting fees from Genomind LLC, Healthrageous, Perfect Health, Pfizer, Proteus Biomedical, Psybrain, and RID Ventures, and he receives royalties through Massachusetts General Hospital from Concordant Rater Systems (now UBC). Drs. Uher and Ripke report no financial relationships with commercial interests.

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