whether lamotrigine could help some subgroups of people with borderline personality disorder. As requested, we have examined mean scores on the Zanarini Rating Scale for Borderline Personality Disorder (ZAN-BPD) at 12 weeks in subsamples of people who were adherent with medication during this period, those without coexisting substance misuse, and those who had a recent history of deliberate self-harm. While conducting this analysis, we identified a typographical error that appeared in our article (1) but not in the monograph that has subsequently been published that provides additional information about the trial (2). The number of participants in the placebo arm of the trial who reported deliberate self-harm in the 6 months prior to randomization was 87 (63%), not 51 (37%) as erroneously stated in our article. Among 98 participants who did not report substance misuse at baseline, the difference in the mean ZAN-BPD score at 12 weeks between those prescribed lamotrigine and those prescribed placebo was 0.90 (95% CI=−1.56 to 3.37). Among 181 participants who adhered to study medication during the first 12 weeks, the difference in the mean ZAN-BPD score between those prescribed lamotrigine and those prescribed placebo was 0.52 (95% CI=−2.41 to 1.36), and among the 143 participants who reported deliberate self-harm at baseline, the difference in the mean ZAN-BPD score at 12 weeks between those prescribed lamotrigine and those prescribed placebo was −0.60 (95% CI=−2.73 to 1.54).

Since the publication of the results of the LABILE trial, many people have told us of their surprise that the study generated negative findings and have asked us whether there was something about the group we recruited or the design of the trial that led to this result. In keeping with findings from previous research examining the views of psychiatrists (3), some clinicians have told us that they have seen firsthand how people with borderline personality disorder make a good response when prescribed medication. However, we would argue that this experience is entirely in keeping with the results of the LABILE trial that demonstrate that, when people are offered clear information by staff who provide structured follow-up, there are likely to be clinically important reductions in symptoms of emotional distress.

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Mike J. Crawford, M.D.
Rahil Sanatinia, Ph.D.
Wei Tan, Ph.D.

From the Centre for Psychiatry, Imperial College London, London; and the Nottingham Clinical Trials Unit, University of Nottingham, Nottingham, U.K.

Address correspondence to Prof. Crawford (m.crawford@imperial.ac.uk).

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The Influence of Unmeasured Confounding Effects in a Study of Antipsychotic Discontinuation in First-Episode Schizophrenia

TO THE EDITOR: In the August 2018 issue of the *Journal*, Tiihonen and colleagues (1) explored an important yet unresolved area concerning antipsychotic discontinuation in the treatment of first-episode schizophrenia. Because this was a nonexperimental study, the presence of systematic bias due to confounding variables was not surprising. The confounding effect of a significantly different frequency of clozapine use among users and discontinuers was apparent in one of the supplementary tables in the article. A chi-square analysis using a 2×2 contingency table would reveal values of 38.6, 25.6, 12.3, and 4.2, respectively, for comparisons between the four groups of users and discontinuers (i.e., <1 year, 1–<2 years, 2–<5 years, and ≥5 years). All of these values are significant at the level of $p<0.05$. The frequency of clozapine use was overrepresented in the users. Higher consumption of clozapine might be a proxy for higher severity or greater treatment resistance. Both of these variables could potentially confound the results. This would be an example of confounding by indication, in which the indication (treatment resistance) or severity is related to both the exposure (antipsychotic use) and the outcome (relapse or rehospitalization). The second measured but unaccounted for confounding effect stemmed from the inclusion of subjects with schizoaffective disorder. Compared with schizophrenia, schizoaffective disorder may have better outcomes (2). The authors could have mentioned and compared the number and distribution of subjects with schizoaffective disorder among the users and discontinuers to examine the effect of this potential confounder.

Another likely confounding effect that is known to influence the risk of relapse in schizophrenia but was not measured in this study is history of substance abuse. A meta-analysis in patients with first-episode psychosis, consisting of 29 studies with at least 12 months of follow-up, showed that persistent substance use disorder increased the odds of relapse by threefold (3). The odds of relapse were lower than those due to treatment nonadherence but higher than all other potential predictors of relapse. We believe that information regarding substance use status was available and that the authors could have included the same. Other factors, such as poor premorbid adaptation to school and social withdrawal, could predict relapse, but these are difficult to measure through medical records (4). Nevertheless, the authors could

have mentioned these in their discussion of limitations of the study.

One of the ways to estimate the effects of confounders is to calculate the variance in a multivariate regression analysis. The predictive value of even a highly significant covariate is judged to be low if the variance is small. In a Cox regression analysis, measurement of variance is difficult. In their article, Schemper and Henderson (5) proposed a model of estimating the predictive accuracy of covariates (risk factors) in a Cox proportional hazards model. There are other models as well (6). Had the authors of the present article used any of these models, the predictive accuracy of the risk factor (antipsychotic discontinuation) could have been measured. Influence of confounders could have been indirectly inferred from the predictive accuracy. In our opinion, in this kind of cohort study with a large number of unmeasured and unknown confounding effects, quoting only the hazard ratio (with confidence intervals) and the significance level is not enough.

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Abhishek Ghosh, M.D., D.M.
Dalton Noble, M.D.

From the Department of Psychiatry, Postgraduate Institute of Medical Education and Research, Chandigarh, India.

Address correspondence to Dr. Ghosh (ghoshabhishek12@gmail.com).

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Risk of Treatment Failure: Response to Ghosh and Noble

TO THE EDITOR: We thank Drs. Ghosh and Noble for their comments on our study. They state that treatment resistance or more severe illness, indicated by the frequency of clozapine use, could potentially confound the results of our study, as well as proportions of schizoaffective disorder and substance abuse. In the Discussion section of our article, we already considered these issues, as follows:

> We used the use of clozapine as a proxy for treatment resistance and the use of long-acting antipsychotic injection as a proxy for poor treatment adherence. These indicators suggested that the late discontinuers had a higher rate of treatment resistance compared with early discontinuers, while no signal was observed for poorer treatment adherence among late compared with early discontinuers. Therefore, the results suggest that the higher risk of relapse among late compared with early discontinuers may be attributable to more severe illness.

We also stated:

> Since clozapine's adverse effects, including metabolic syndrome, develop over a long period and the accurate cumulative exposure time for specific antipsychotics was not available in this analysis, the outcomes of treatment failure were not adjusted by using this rather crude proxy (at least one filled prescription of clozapine) as a covariate. However, we want to emphasize that the aim of this study was not to investigate clinical characteristics associated with treatment failure but simply to reveal how the risk of rehospitalization or death evolves after discontinuation of antipsychotic treatment in an entire nationwide cohort of first-episode patients.

Jari Tiihonen, M.D., Ph.D.
Antti Tanskanen, Phil.Lic.
Heidi Taipale, Ph.D.

From the Department of Clinical Neuroscience, Karolinska Institutet, Stockholm; the Department of Forensic Psychiatry, University of Eastern Finland, and Niuvanniemi Hospital, Kuopio; the Impact Assessment Unit, National Institute for Health and Welfare, Helsinki; and the School of Pharmacy, University of Eastern Finland, Kuopio.

Address correspondence to Dr. Tiihonen (jari.tiihonen@ki.se).

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