Genetics and Suicidal Ideation During Antidepressant Treatment

TO THE EDITOR: In the October 2007 issue of the *Journal*, Gonzalo Laje, M.D., et al. (1) presented thought-provoking data regarding the possible prediction of treatment-emergent suicidal ideation by two deoxyribonucleic acid (DNA) sequence variants. They were appropriately cautious about the need for replication of such findings, since these findings alone would not justify using the two DNA markers to test for the risk of treatment-emergent suicidal ideation. For future meta-analyses, it would be helpful if the *Journal* would include the genotype counts (and joint counts for the two markers) in such studies or online as a data supplement.

The authors thoughtfully acknowledged the difficulty of measuring treatment-emergent suicidal ideation with a single self-report questionnaire item, but perhaps more attention should be paid to whether this measure is valid. Because treatment-emergent suicidal ideation has not been shown to be a heritable phenotype by any definition, the prior probability of an association is very low, and modest statistical evidence for genetic association must be viewed with caution. Subjects with treatment-emergent suicidal ideation were defined in the study as patients who denied suicidal ideation at baseline but then endorsed suicidal ideation at some point during 12 weeks of treatment. But might a patient be embarrassed or afraid to admit suicidal ideation at a first visit with a new treatment team and then decide to acknowledge it several weeks later? How many of these patients would report (if asked) that their suicidal ideation actually began earlier or had been present off and on for some time? In a controlled study, one would expect measurement error to be similar in treated versus untreated patients, and thus any group difference would have meaning. However, in this uncontrolled study, the findings rested on a non-validated measurement. Before large placebo-controlled studies are undertaken, as suggested by the authors, it would be helpful to validate a measurement strategy in patients beginning a new treatment.

Perhaps Dr. Laje et al. also could have clarified the control phenotype. All 1,862 genotyped patients with no missing data on the suicidal ideation item were considered either treatment-emergent suicidal ideation subjects (N=120) or comparison subjects (N=1,742). Comparison subjects "scored 0 on [the suicidal ideation item]...during up to 12 weeks of...treatment" (1, p. 1531), including 765 subjects with no suicidal ideation at any visit and 977 with some suicidal ideation at baseline. Did these 977 subjects also include those who reported suicidal ideation at baseline and also during at least one treatment visit? One assumes that there were such individuals.

Problems in defining treatment-emergent suicidal ideation underscore the difficulty of determining whether or not some people experience suicidal ideation because of antidepressant treatment. It would be premature to assume that treatment-emergent suicidal ideation is common and well established or that attempting to prevent it through genetic tests would be possible or useful at this time. (The article by Dr. Laje et al. mentions the reported incidence in children and adolescents, but data for adults are controversial and often show no treatment effect [2–4].) In this regard, one might question the appropriateness of the decision (made by the National Institutes of Health [NIH] Office of Technology Transfer [http://www.ott.nih.gov/db/abstract.asp?RefNo=1670] and not by NIH investigators) to allow the genetic test to be commercialized at this stage.

References

1. Laje G, Paddock S, Manji H, Rush AJ, Wilson AF, Charney D, McMahon FJ: Genetic markers of suicidal ideation emerging during citalopram treatment of major depression. Am J Psychiatry 2007; 164:1530–1538
2. Hammad TA, Laughren TP, Racoosin JA: Suicide rates in short-term randomized controlled trials of newer antidepressants. J Clin Psychopharmacol 2006; 26:203–207
3. Saperia J, Ashby D, Gunnell D: Suicidal behaviour and SSRIs: updated meta-analysis. BMJ 2006; 332:1453
4. Moller HJ: Is there evidence for negative effects of antidepressants on suicidality in depressive patients? a systematic review. Eur Arch Psychiatry Clin Neurosci 2006; 256:476–496

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Dr. Levinson reports no competing interests.

This letter (doi: 10.1176/appi.ajp.2007.07111699) was accepted for publication in November 2007.

Dr. McMahon Replies

TO THE EDITOR: We agree that very little is known about treatment-emergent suicidal ideation as a phenotype. Since it is an uncommon and transient event, treatment-emergent suicidal ideation cannot be assessed by the usual genetic epidemiologic methods of family and twin studies. Thus, as Dr. Levinson correctly observes, treatment-emergent suicidal ideation has not been shown to be a heritable phenotype. He states that the lack of data on heritability indicates that "the prior probability of [a genetic] association is very low." This may be true, but the same could be said even for conditions in which heritability has been clearly established; for example, experience with disorders such as schizophrenia and autism demonstrates high heritability of a trait that does little to ensure that genetic associations will be valid (1). In contrast, much less heritable conditions such as type 2 diabetes have produced several robust genetic associations (2). For tests of association, it is not so much the general heritability (of the liability) but rather the heritability attributable to a specific marker that is relevant. Thus, the relationship between the heritability of the trait and valid genetic associations is, in our view, not clear.

We defined subjects with treatment-emergent suicidal ideation as those participants who initially denied suicidal ideation but then endorsed it during treatment, which is the definition commonly used by regulatory agencies and in the literature. (Participants who endorsed suicidal ideation both initially and during treatment were not considered to be subjects with treatment-emergent suicidal ideation and were indeed included—as Dr. Levinson correctly assumes—among the set of comparison subjects who endorsed sui-