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.

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Dr. Levinson reports no competing interests.

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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-

cidal ideation at the initial visit.) Dr. Levinson questions whether some of the participants who met our case definition might have been "embarrassed or afraid to admit suicidal ideation at a first visit with a new treatment team." While this is a possibility, it seems to us unlikely. As shown in Table 2 of our article, treatment-emergent suicidal ideation subjects showed no general tendency to deny symptoms, since they had baseline symptom scores that were similar to those of the other participants. Moreover, they often endorsed other potentially embarrassing symptoms such as marital discord and sexual dysfunction (data not shown in the article). More detailed, longitudinal studies of suicidality during treatment may shed some light on this issue, but suicidal ideas, similar to most psychiatric symptoms, are fundamentally a subjective phenomenon. We are all limited by our patients' ability to reveal to us the contents of their conscious minds (3).

Dr. Levinson questions the decision of the NIH Office of Technology Transfer to license the markers reported in our study for commercial development. Such licensing gives the NIH some control over how the markers are used commercially. All data produced by laboratories within the NIH Intramural Research Program are the property of the people of the United States. The professionals in the Office of Technology Transfer have devoted their careers to protecting and managing this common property for the public good. We respect their decision.

However, we agree with Dr. Levinson that it is premature to introduce a test based on these results to the clinic until they are independently replicated. Independent replication serves two vital roles for genetic association findings: 1) verification of true positive associations and 2) better estimation of the true effect size. Experience and statistical theory show that highly significant p values alone are poor indicators of true associations and that the first study to detect an association will typically overestimate the effect size—the so-called winner's curse (4). Thus, independent replication is the essential next step.

But is independent replication sufficient to justify offering a genetic test in the clinic? What other criteria should be applied to research findings in judging their readiness for clinic use? Should we withhold from patients access to genetic information that could help prevent bad outcomes?

Questions such as these will arise with increasing frequency and urgency in the near future (5). We submit that it is now time for the field of psychiatry to begin an active debate on the issue of clinical genetic testing. Criteria will probably differ for tests intended to predict severe adverse outcomes, tests intended to identify patients most likely to improve with treatment, and tests intended to support a clinical diagnosis. In any case, we as a profession need to develop some guidelines as to what clinical genetic tests should be used, when psychiatrists should offer them, and how they should be interpreted in the context of diagnosis and treatment. If we fail to act promptly, then the marketplace will fill the vacuum, which has already begun to occur in other fields of medicine, and psychiatrists may lose the initiative in a debate in which the outcome could have real consequences for our patients and their families.

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NIH has filed a patent based on the diagnostic technology described in the article by Dr. Laje et al. While the article was in press, NeuroMark of Boulder, Colorado, negotiated a non-exclusive license with NIH to develop this technology commercially. The license was signed on September 27, 2007. Federal law prohibits the inventors from any involvement in the negotiation and execution of this license but requires NIH to pay them a portion of any royalties received. The inventors (Drs. McMahon, Laje, Paddock, Manji, and Rush) may not and have not endorsed any commercial use of the patent. Disclosures for each individual author accompany the original article.

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Adjunctive Versus Monotherapeutic Treatment for Schizophrenia: Addressing Antipsychotic Side Effects

TO THE EDITOR: In the article by Joo-Cheol Shim, M.D., Ph.D., et al., published in the September 2007 issue of the *Journal,* aripiprazole was added to haloperidol to evaluate the beneficial effects on haloperidol-induced hyperprolactinemia. The authors pointed out that switching is "not always possible in clinical practice, especially if the patient has responded well to the antipsychotic that produced the hyperprolactinemia" (1, p. 1404). The addition of aripiprazole significantly decreased prolactin levels and improved negative symptoms, sleep, and extrapyramidal side effects. The authors attributed these effects to aripiprazole's unique mechanism(s) of action (2). We do not take issue with the scientific merit of this study but are concerned with the clinical implications, specifically the apparent promotion and justification of the adjunctive use of aripiprazole.

Well-controlled clinical studies have not supported the use of antipsychotic polypharmacy, and this practice has been associated with increased adverse effects (3, 4), premature death (5), and unnecessary economic demands (6). Good clinical practice argues for the fewest medications possible and, in the case of treatment with antipsychotics, advocates for the adjunctive use of antipsychotics as a last resort (7). As a class, the newer antipsychotics have afforded us advantages in decreasing extrapyramidal symptoms, lowering prolactin