cidual 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 clinical 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.

References

FRANCIS J. McMAHON, M.D.
Bethesda, Md.

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
levels, and reducing the risk of tardive dyskinesia (2, 7, 8). Furthermore, contrary to what is stated in the article by Drs. Joocheol Shim et al., switching antipsychotic drugs, including a switch from haloperidol to aripiprazole, has previously been shown to be safe and effective (9).

References

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Drs. Shim and Kelly Reply

To The Editor: We agree with Drs. Hazra, Mamo, and Remington that antipsychotic monotherapy is the standard of care for treating schizophrenia. Polypharmacy should only be considered as a last resort because of the potential for adverse effects and economic burden. When metabolic or extrapyramidal side effects or clinical consequences of hyperprolactinemia develop during antipsychotic treatment, strategies to eliminate or reduce these side effects should involve lowering the dose or switching to other agents.

For many chronic patients with multiple relapses, however, lowering the dose and switching treatments are not always effective and not always feasible in clinical practice. In our study, subjects with hyperprolactinemia, stabilized on high-dose haloperidol, were chronic with a history of multiple relapses. We recognize that some studies have demonstrated equivalent efficacy of aripiprazole and haloperidol in the treatment of schizophrenia symptoms (1) and that switching to aripiprazole from haloperidol has been found to be safe and effective (2); however, other studies have shown worsening of psychotic symptoms after switching to aripiprazole in some patients who were chronic and appeared only partially responsive to previous antipsychotics (3, 4).

There is a growing need to consider new and different treatment strategies, whether they are adjunctive or monotherapeutic, for schizophrenia symptoms that continue to be resistant or only partially responsive to treatment. Recently, some studies have reported that the combination of aripiprazole with other antipsychotics improved refractory schizophrenia symptoms (5, 6).

Our study was not intended to encourage or advocate the blanket use of antipsychotic polypharmacy, and empirical evidence suggests that there are beneficial effects of polypharmacy for schizophrenia, the smallest number of medications possible should be used to treat our patients with this illness. While we share the concerns expressed by Drs. Hazra, Mamo, and Remington, we also feel that clinicians should not underestimate the importance and significance of addressing and treating antipsychotic side effects such as the clinical consequences of hyperprolactinemia.

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GARY REMINGTON, M.D., PH.D., F.R.C.P.C.
DEANNA L. KELLY, PHARM.D., B.C.P.P.
Toronto, Ontario, Canada

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