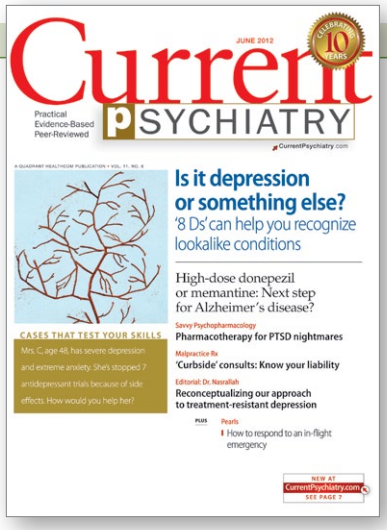

June 2012

Primum non nocere

Dr. Nasrallah's June editorial ("Innovative approaches to treatment-resistant depression," From the Editor, CURRENT PSYCHIATRY, June 2012, p. 4-5; http://bit.ly/FTE612) and the authors' response to a letter on treating resistant depression (CURRENT PSYCHIATRY, June 2012, p. 19; http://bit.ly/LBSrvD) remind us of depression's complexity and the wide range of treatments available. I question whether in our zeal to help our patients we have forgotten the bedrock principle of medicine: *Primum non nocere* (First, do no harm).

Do we as psychiatrists make this principle a staple of our daily practice? Do we ask, "Which treatment modality offers the greatest likelihood of restoring wellness with the least risk of harm?" or do we restrict such inquiry to the confines of pharmacotherapy, considering only which medicine is least harmful? Is it not common practice to prescribe atypical antipsychotics to patients who have failed antidepressants? Do we offer modalities such as transcranial magnetic stimulation (TMS) before introducing atypical antipsychotics? If we keep our oath to abstain from doing harm, should we offer TMS before atypicals?

Some have argued that the high cost of TMS is reason not to offer it. But what is the cost of developing type 2 diabetes mellitus? Should we put patients at risk for such a disorder without giving them the option to choose a modality that doesn't confer such risk?

The language used in Drs. Desseilles, Fava, Mischoulon, and Freeman's "Comments & Controversies" response suggesting TMS was in the "same vein" as vagus nerve stimulation and deep brain stimulation concerned me. Such a comment—hopefully inadvertently—suggests a failure to recognize our oath to first, do no harm. Do the authors really believe that such invasive procedures confer no greater risk of harm than TMS? Are such modalities in the same vein as TMS, or do they take us to a new level of treatment risk and complexity?

Although no evidence suggests TMS is a panacea that successfully treats all patients with treatment-resistant depression, we can say with great confidence it is the safest of all somatic treatments and confers the least risk of harm. Because no evidence demonstrates that any other somatic treatment provides greater efficacy, do our ethics not require us to offer TMS as part of informed consent, before starting atypical antipsychotics, which carry a risk of metabolic syndrome, type 2 diabetes mellitus, sexual dysfunction, parkinsonism, and a host of other potentially life-altering problems and complications?

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Dr. Nasrallah responds

Dr. Jennings is correct in reminding us that above all, physicians must do no harm. However, there are certain other principles in medicine: 1) the lack of treatment for severe illness can result in serious harm, and 2) there always is a side-effect burden with any treatment. The risk-benefit considerations are complicated when dealing with chronically suffering, disabled, or suicidal patients with refractory depression.

Bold new interventions must be developed for such desperate cases at the cost of side effects, which must not be unacceptably severe. That's why controlled studies to prove the usefulness of a new therapy are conducted in a few hundred patients so that millions of others can benefit from a new treatment mechanism. That's how medical science advances, always balancing risks and benefits. It's up to the clinician to determine which intervention is the best and least harmful for each patient. However, what may be considered an effective treatment may quickly be discarded when better and less harmful treatments are found, such as abandoning prefrontal lobotomy for aggressive psychotic patients shortly after chlorpromazine was discovered.

The authors respond

We thank Dr. Jennings for his comments and appreciate his concern to offer patients pharmacologic or nonpharmacologic treatments with the least amount of side effects. We also recognize the diversity of clinical situations, which, according to factors such as the degree of depression severity, the therapeutic choice of the patient,

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and the availability of treatments, lead the clinician to suggest an antidepressant treatment that is the most efficient and least harmful as possible.

By proposing that the Massachusetts General Hospital Antidepressant Treatment Response Questionnaire consider the diversity of antidepressant treatments that various clinical situations have necessitated, we by no means encourage the use of antidepressant treatments that are inefficient and harmful to the patient. We look to provide clinicians with tools that take into consideration the therapeutic interventions available for treatment-resistant depression. In the same manner, we have not established a hierarchy of pharmacologic options, because we hope clinicians will identify the multiple treatments that the patient needs. If it is essential to "abstain from doing harm," we must not forget that if healing is an ideal objective, we often only "treat" our patients with the best available methods.

As Dr. Jennings suggests, the least harmful treatments often are those that target depression's physiopathology with the highest degree of specificity. In the same vein, neuromodulation treatments target the different neurobiologic mechanisms underlying depression. However, response predictors of TMS include age, degrees of treatment resistance, and the absence of comorbid anxiety or psychotic symptoms.[1] Moreover, a long-term retrospective still seems necessary,[2] and the nonavailability of this retrospective certainly ensues from the most recent introduction of TMS in therapeutic arsenal, contrary to pharmacologic treatments. Varied clinical situations do not permit prediction of an optimal response with TMS only, without using pharmacologic or nonpharmacologic therapeutic options.

Furthermore, the concern to protect the patient undeniably is accompanied by a fundamental reminder: the neurobiologic model of depression is only 1 model among many, and several etiological models of depression have been suggested, many of which coexist, without completely explaining the physiopathology of depression.[3] Therefore, next to the biologic and neuropsychologic models of depression, psychoanalytical, behavioral and environmental, cognitive, systemic, and ethological models also exist. Taking these different models into account means clinicians can suggest a psychotherapeutic treatment sometimes accompanied by a pharmacologic or neuromodulation treatment.

On a neurobiologic level, the subgenual part of the anterior cingulate cortex seems to be 1 of the final common pathways of the various neurobiologic mechanisms underlying depression, and as such, the final common pathway of various antidepressant treatments, whether they involve TMS,[4] the numerous antidepressant pharmacologic treatments,[5] or even potentially the variation in attentional effort.[6]

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Ketamine for depression

Dr. Nasrallah failed to mention radical short-term memory loss as a side effect of ketamine in his June editorial ("Innovative approaches to treatment-resistant depression," From the Editor, Current Psychiatry, June 2012, p. 4-5; http://bit.ly/FTE612). This so-called side effect may be the central antidepressant effect, because short-term memory loss may be a central effect in any seizure therapy for depression.

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Dr. Nasrallah responds

Memory loss with regular and heavy ketamine use or with a course of bilateral electroconvulsive therapy (ECT) is widely regarded as an undesirable side effect, not a therapeutic effect or mechanism. The side effects of short-term ketamine use in refractory depression studies included dissociation and unusual beliefs—such as conspiracy theories—as well as full-fledged delusions.

Both ketamine and ECT increase brain-derived neurotrophic factor (BDNF), which has been found to significantly decline in depression. The BDNF deficit is emerging as the leading mechanism of antidepressant therapy, both pharmacologic and nonpharmacologic, in both animal models and clinical populations.