The Search for Knowledge: Developing the American Psychiatric Association's Practice Guideline for Major Depressive Disorder

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Working in Boston in the late 1980s, I received a telephone call from Byram Karasu, M.D. Byram was to chair the workgroup writing the American Psychiatric Association's (APA) first Practice Guideline for the Treatment of Patients With Major Depressive Disorder (MDD)[1] and honored me with an invitation to join. The first MDD Guideline was published in 1993. Byram chaired the workgroup that prepared the second edition, which was published in 2000.[2] In 2005, Laura J. Fochtmann, M.D., and I wrote an update, which APA terms a "Guideline Watch."[3]

The third edition of the MDD Guideline is now in process, and it is my privilege to chair the workgroup. (I think I'm the "last man standing" from the original team.) A draft is circulating for comments, and we hope for publication in 2009. It has been an interesting journey, and both the process and the content of this important work make a fascinating tale.

The word *epistemology* comes from the Greek *epistēmē*, meaning knowledge. Epistemology is the study or theory of the nature and grounds of knowledge, especially with reference to its limits and validity. Simply put, epistemology addresses how we know what we know. Nothing is more relevant to the practicing doctor. Critical scholars eschew practice based solely on anecdotes or uncontrolled case series. The "gold standard" of clinical science is the double-blind randomized controlled trial (RCT). But every scientific experiment represents a series of compromises that form the trial protocol. To maintain internal validity, a study typically compromises external validity or generalizability. For example, patients enrolled in a clinical trial on MDD may represent only a small sample of the universe of MDD patients. Patients with comorbid medical conditions or substance abuse, for example, are apt to be excluded but likely to represent many patients seen in practice. Knowledge becomes secure and convincing only when it is reproduced by multiple investigators employing different research techniques in diverse populations.

But how often does clinical science achieve that level of "truth" in today's clinical psychiatry? Various scientific organizations have attempted to define "levels of evidence" as a way to establish "truth." These levels range from systematic reviews with meta-analysis of RCTs to noncontrolled case series. Many patients require treatment, yet often there is insufficient hard scientific knowledge to guide treatment choices. Even if a particular treatment is supported with evidence, there may be numerous questions about its administration that are not addressed by the evidence. Thus, guidelines are just that—guidelines. They attempt to bring the best in rigorous knowledge, carefully culled from the literature by experienced scientist-clinicians and presented in a way that is relevant to practitioners.

The colleagues who have labored long and hard on the third edition are a dream team of scholars, scientists, and clinical psychiatrists. They are all dear friends: Marlene P. Freeman, M.D.; John C. Markowitz, M.D.; Jerrold F. Rosenbaum, M.D.; Michael E. Thase, M.D.; and Madhukar H. Trivedi, M.D. Richard S. Van Rhoads, M.D., has done a great job as consultant, compiling extensive literature and protecting the English language. Superb staff assistance has been provided by Laura Fochtmann, M.D., and Rob Kunkle of APA. The process begins with a literature search and the creation of evidence tables. A first draft is then prepared. The second draft of the current guidelines is now available for review. We hope to have a third draft in the hands of APA's Assembly and Board for ratification in November and December of this year, with an expected publication date in 2009.

There have been important developments since the second edition of the guideline was published in 2000. What follows are some of my own impressions and reflections. They do not reflect the position of APA or the opinions of my colleagues on the workgroup.

One of the issues we considered has received considerable media attention: the alleged association between antidepressants and "suicidality." The so-called signal of suicidality was "discovered" in retrospective analyses of data from clinical trials with serotonin-specific reuptake inhibitor (SSRI) antidepressants—initially in children and adolescents. As a result, the FDA and regulatory bodies abroad issued a "black-box" warning.[4]

It is important to understand that the concept of "suicidality" was constructed retrospectively of heterogeneous adverse effect data from diverse trials. Many of the behaviors categorized as "suicidal," especially in young people, clinicians would debate. There were no suicides in these studies, and there is no established cause-and-effect relationship between so-called suicidality and suicidal acts. Growing evidence suggests that the decreased antidepressant prescribing following the black-box warnings has led to an increased incidence in suicides.[5,6]

Without doubt, depression is associated with an increased risk of suicide. Regardless of whether antidepressant drugs might increase this vulnerability in selected patients, it is only good clinical practice to observe and monitor patients carefully during the early days and weeks of treatment. Whenever possible, family members and caregivers should be enlisted as part of the therapeutic "team," educated about the illness and treatment-emergent effects, and given information on observing patients and encouraged to report worrisome changes in behavior.

Since the 2000 MDD Guideline,[2] much research has been conducted on treating depression. In the past few years, data have emerged from several large collaborative trials. Best known among these is the Sequenced Treatment Alternatives to Relieve Depression (STAR*D).[7] To oversimplify the findings of this large, complex trial, the "bad news" is that only about 1 in 3 MDD patients can expect to achieve remission with an initial trial of a single antidepressant. The "good news" is that, when patients fail to achieve remission on an initial therapy, subsequent trials, whether involving switching treatments or augmenting the first treatment with a second, bring incremental likelihood of achieving remission. Despite decades of clinical theorizing that some patients would respond preferentially to specific antidepressants or that dual-acting agents would surpass selective antidepressants, in STAR*D no antidepressant was superior to another; all were equally effective.

Similar results emerged from 2 other large trials, one sponsored by the National Institute of Mental Health, the other by a pharmaceutical company. The Research Evaluating the Value of Augmenting Medication With Psychotherapy (REVAMP) trial was designed based on evidence that a psychotherapy for patients with chronic depression (Cognitive Behavioral

Analysis System of Psychotherapy [CBASP], created by James P. McCullough, Ph.D.), when combined with antidepressants, was superior to medication alone (J. H. Kocsis, M.D.; A.J.G.; B. Rothman, Ph.D.; et al., manuscript submitted). Patients with chronic depression who did not achieve remission with an algorithm-based medication intervention were randomly assigned to either continue further with a medication algorithm or have medication supplemented with one of 2 forms of psychotherapy. CBASP was compared to Brief Supportive Psychotherapy, created by John Markowitz, M.D., based on a Rogerian model. Echoing the STAR*D results, REVAMP failed to show that either psychotherapy was superior to continuing medications alone.

A third large trial was called Prevention of Recurrent Episodes of Depression With Venlafaxine XR for Two Years (PREVENT).[8] Sponsored by Wyeth Pharmaceuticals, PREVENT was predicated on the assumption that an antidepressant which inhibits the uptake of both norepinephrine and serotonin would be superior to an SSRI alone. In this $2^{3}/_{4}$-year study, over 1000 patients were treated with either venlafaxine or fluoxetine. Once again, few meaningful differences between drugs emerged. Once again, a reasonable hypothesis failed the test of prospective science.

After a half century of modern antidepressant medications, and several decades of systematic studies of psychotherapy for MDD, we do not yet have a means to tailor or "personalize" interventions. As a result, today's best strategy is to empirically test each treatment trial. To accomplish this, clinicians need to carefully assess and monitor patient symptoms in what has come to be called measurement-based care. Whether using clinician or patient ratings, captured via paper and pencil or electronically, systematic assessment is valuable in guiding care. A second part of today's strategy is to use strategic decision points to guide changes in treatment. For example, if after a specified number of weeks the patient has failed to achieve sufficient improvement, the clinician should consider, in collaboration with patient and family, whether to raise the dose, add another agent, or switch to another intervention.

Since the second MDD Guideline was published in 2000, several additional biological treatments have received the FDA's imprimatur for MDD. Medications include escitalopram, duloxetine, the fluoxetine-olanzapine combination, the selegiline transdermal patch, desvenlafaxine, and the first medication to be approved for adjunctive treatment of resistant depression, aripiprazole. None is viewed as a "blockbuster" breakthrough. Rather, each offers incremental benefits and expands therapeutic options.

There are effective biological interventions beyond medicines. Electroconvulsive therapy has been a mainstay in depression treatment since 1938. Evidence for its efficacy has grown even stronger since the last guideline. In 2005, the FDA approved vagus-nerve stimulation for treatment-resistant depression. Ironically, it is difficult to get third-party payors to pay doctors and hospitals for this treatment. Deep brain stimulation is still in the research phase but holds promise. Repeated transcranial magnetic stimulation may be approved in the near future to treat depression.

So-called complementary and alternative treatments often are used for patients suffering from MDD.[9] St. John's wort is probably best known among these. Data are mixed. Data on acupuncture are far from robust. Some treatments, such as omega-3 fatty acids and exercise, have obvious benefits for general physical health and can be recommended as relatively benign. It is unclear whether light therapy is effective beyond the treatment of seasonal affective disorder.

Among psychotherapies, cognitive behavioral therapy is the best studied for MDD, and its efficacy is well established. There is good evidence for interpersonal psychotherapy, and other approaches, such as problem-solving treatment, are being studied and seem beneficial.

The 2000 Guideline recommended that during the 16 to 20 weeks following remission from MDD, patients treated with antidepressants should be maintained on these agents to prevent relapse. Following this "continuation phase" of treatment, maintenance treatment should be considered based on the risk of recurrence, severity of episodes, tolerability of treatment, and patient preference. Most of the data that informed these recommendations came from studies with tricyclic antidepressants. But the same advice on continuation and maintenance therapy seems to apply as well to modern antidepressants. A meta-analysis of relapse prevention studies[10] has shown impressive differences between antidepressants and placebo, suggesting that the best evidence for efficacy of these drugs is in the maintenance phase of depression.

An instructor in my medical school encouraged students to be therapeutic skeptics but not nihilists. This admonition holds true today in the treatment of MDD. We have many and varied treatments. Careful attention to diagnosis, use of measurement-based care, vigorous attention to timeframe and next-step options, collaboration with patient and family, and the knowledgeable use of the wide array of available treatments—both biological and psychosocial—can pave the way to remission for most patients. As in other medical specialties, personalized medicine will find its way into psychiatry and the treatment of patients with the heterogeneous syndrome we call MDD. Someday, neuroscientists will divide MDD into biologically homogeneous diseases, presumably at the level of the genome. At that time, we will truly be able to personalize interventions. Until then, knowledge and optimism are our best allies.

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