Study Compares Antidepressant Response Rates

BY ROBERT FINN

The efficacy of antidepressant treatment over placebo for major depressive disorder "varies considerably," depending upon symptom severity, a recent meta-analysis showed.

Only patients whose depression is classified as "very severe" appear to have a greater benefit from antidepressants than from placebo pills, according to the study by Jay C. Fournier of the University of Pennsylvania, Philadelphia, and his colleagues (JAMA 2010;303:47-53) .

Most placebo-controlled studies of antidepressants specifically exclude individuals who score below 23 on the Hamilton Depression Rating Scale (HDRS). HDRS scores of 8-13 indicate mild depression, scores of 14-18 indicate moderate depression, scores of 19-22 indicate severe depression, and scores of 23 or above indicate very severe depression.

In addition, many antidepressant studies include a "placebo washout period" in which all patients receive placebo pills for several days to 2 weeks before randomization. Often, patients who improve by 20% or more in the HDRS are excluded from the trial. Removing known placebo responders at the outset is thought to enhance the statistical power of the antidepressant-placebo comparison.

"This design feature severely limits the ability to generate accurate estimates of the placebo response rate," wrote Mr. Fournier and his colleagues, noting that "the true rate of placebo response may be underestimated in trials that use this feature."

To determine the true placebo response rate across the entire range of depression severity, the investigators combed the literature for randomized, controlled studies of minor depressive disorder that did not include a placebo washout period.

Of the 2,146 randomized, controlled trials of depressants published in English from January 1980 to March 2009, only 23 studies met those criteria. But only six of those studies could provide patient-level data to the investigators. It was those six studies, comprising 434 patients in antidepressant groups and 284 patients in placebo groups, that were the subject of the meta-analysis.

Actually, most meta-analyses include only group-level data. A study such as this one that includes patient-level data is called a "mega-analysis." This approach allows investigators to conduct a more fine-grained multivariate analysis.

Three of the six studies used imipramine, a tricyclic antidepressant, and the other three used paroxetine, a selective serotonin reuptake inhibitor. The mean baseline HDRS score in the studies ranged from 14 to 24.

As expected, the higher the patient's baseline HDRS score, the more improvement was seen with both the active drug and the placebo. A difference of 3 points or more on the HDRS is considered clinically significant. It was only at HDRS baseline levels of 25 and above that active drug was both statistically and clinically better than placebo. This finding was the same for imipramine and paroxetine.

The investigators wrote that in marketing antidepressants, pharmaceutical manufacturers rarely mention that most efficacy studies specifically exclude patients who derive little benefit from their medications.

The authors concluded that "efforts should be made to clarify to clinicians and prospective patients that whereas [antidepressant medications] can have a substantial effect with more severe depressions, there is little evidence to suggest that they produce specific pharmacological benefit for the majority of patients with less severe acute depression."

Commenting on the meta-analysis, Dr. Eric G. Tangalos emphasized that conclusions based on studies published as early as 1980 might not be relevant to current medical practice.

"Papers published in the 1980s took their data from clinical practice in the 1970s, and papers in the 1990s took their information from the 1980s. SSRIs, which are the current mainstay of therapy, did not emerge until the 1990s. Prior to the advent of SSRIs, physicians were reluctant to even identify depression because the available treatments (MAO inhibitors and, later, tricyclics) carried so many serious side effects," said Dr. Tangalos, a professor of medicine at the Mayo Clinic in Rochester, Minn. He reported no relevant conflicts of interest. ■

Disclosures: *The National Institute of Mental Health funded the study. Mr. Fournier stated that he had no relevant financial conflicts of interest. Several of the other investigators did report financial relationships with several pharmaceutical companies.*

Findings Need Careful Assessment

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This is an important study for internists, but I am cautious about its message. In view of the diagnostic variability of mild depression, we need to examine the findings carefully before we implement them wholesale.

I have treated many patients with mild chronic depression or dysthymic conditions who have had excellent (family member validated) short- and long-term results with antidepressant medications—so many patients, in fact, that the responses do not seem to reflect a placebo effect.

I would hope that formulary committees would not jump to blunt conclusions about the value of antidepressants without nuanced review of the study and substantiation of its findings.

WILLIAM E. GOLDEN, M.D., *is professor of medicine and public health at the University of Arkansas, Little Rock. He reports no conflicts of interest.*

More Soldiers Receiving Treatment for Depression, PTSD

BY DIANA MAHONEY

NEW YORK — A systems-level collaborative care model for the screening, referral, and treatment of depression and posttraumatic stress disorder in U.S. soldiers has led to an increase in the number of soldiers receiving mental health care, Col. Charles C. Engel, MC, USA, said at the American Psychiatric Association's Institute on Psychiatric Services.

A feasibility study of the Re-Engineering Systems for the Primary Care Treatment of Depression and PTSD in the Military (RESPECT-Mil) model shows that the intervention often leads to clinical improvements, Dr. Engel reported.

Since its 2007 rollout, the model has been implemented in 35 of a planned 43 primary care clinics on 15 military bases in the United States, Germany, and Italy. Preliminary data from the participating clinics indicate that screening for depression and PTSD has occurred in two-thirds of primary care visits, with a positive screen rate of 14%, said Dr. Engel, director of the Department of Defense Deployment Health Clinical Center at Walter Reed Army Medical Center, Washington, and associate professor in the department of psychiatry at the Uniformed Services University of the Health Sciences.

Since its 2007 rollout, the RESPECT-Mil model has been implemented in 35 of a planned 43 primary care clinics on 15 military bases in the United States, Germany, and Italy.

Of the 14% who screened positive, 60% received a diagnosis of depression or PTSD and started treatment, noted Dr. Engel, a psychiatric epidemiologist who has been instrumental in helping the departments of Veterans Affairs and Defense develop guidelines for depression, PTSD, and medically unexplained symptoms.

The RESPECT-Mil program, based on a three-component model that has been used extensively in civilian populations, addresses some of the challenges that have kept soldiers from receiving needed mental health services, including reluctance to seek behavioral health services, insufficient mental health workforce, lack of competency in evidence-based mental health practice, and inadequate access to care, Dr. Engel said.

It achieves those goals by integrating the efforts of primary care physicians, nurse care facilitators, and psychiatrists, starting with a mandate for universal screening for depression and PTSD for soldiers during routine primary care visits, he said.

Patients who screen positive on the two-question depression screen (PHQ-2) or the four-item PTSD screen undergo a diagnosis and severity assessment using the Patient Health Questionnaire-9 (PHQ-9) and the 17-item PTSD Check List, as well as a suicide and violence risk assessment, Dr. Engel said. "We've modified the assessment tools so that it's easy for clinicians to look at and determine whether patients are high or low probability for suffering from a trauma reaction or suicidal ideation."

When there is a presumptive diagnosis of depression or PTSD, the primary care clinician will initiate treatment and offer follow-up monitoring with a psychiatrist-supervised care facilitator and, when necessary, a behavioral health specialist.

"The care facilitators are the single most important ingredient in the [RESPECT-Mil] model," Dr. Engel said. After the initial primary care visit, the care facilitators serve as the liaisons between the primary care providers and the consulting psychiatrists. The care facilitators provide follow-up via telephone and consult weekly with the supervising psychiatrist to evaluate patient progress. Patients with significant mental health issues may be referred from primary care to specialty care. Patients' initial treatment response is evaluated at 6-8 weeks for those on antidepressants and 4-6 weeks for those undergoing psychological counseling, and the treatment plan is adjusted if necessary, he said.

The early data are promising, but "the real challenge is going to come during the course of [2010], because we're going to be doubling the size of the program by getting it into almost all of the Army's approximately 100 primary care clinics," Dr. Engel said. As this happens, "it's going to be a great platform for studying systems solutions approaches." ■

Disclosures: *Dr. Engel has no relevant conflicts of interest.*