EDITORIAL

The Search for Treatments for Depressed Veterans—Of Paramount Importance, Yet Still Elusive

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Remission rates in patients with major depressive disorder (MDD) remain unacceptably low. From the 28% to 33% remission rate in the Sequenced Treatment Alternatives to Relieve Depression (STAR-D*) Study[1] after treatment with the selective serotonin reuptake inhibitor citalopram to the more recent Predicting Response to Depression Treatment (PReDICT) Study[2] of treatment-naïve depressed patients treated with escitalopram, duloxetine, or cognitive-behavioral therapy (CBT), with remission rates of approximately 50%, it is clear that a sizeable number of depressed patients do not achieve remission, the universally acknowledged and desired gold standard of outcome. This is of paramount importance, because depressed patients who do not achieve remission are at greatly increased risk for suicide, drug and alcohol abuse, morbidity, and mortality from several major medical disorders, including stroke, myocardial infarction, diabetes, and others.[3] One population at high risk for MDD and repeatedly documented to be relatively resistant to treatment is military veterans.[4] Suicide rates are high in this population[5] and comorbidity of MDD with other psychiatric disorders, such as posttraumatic stress disorder (PTSD), is very common.[6] A recently published multicenter Veterans Affairs (VA)-sponsored study[4] of 1522 patients that compared antidepressant switching with augmentation in patients who had failed at least 1 antidepressant medication resulted in relatively low remission rates (in the range of 22.3% to 28.9%). It is in this context that a large multicenter VA-sponsored study by Yesavage et al[7] of repetitive transcranial magnetic stimulation (rTMS), a US Food and Drug Administration–approved treatment for MDD, was undertaken in the VA population.

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The authors of the article[7] in this issue of *JAMA Psychiatry* include experienced leaders in the field who have been led or played seminal roles in many previous clinical trials in mood disorders. This double-blind, sham-controlled clinical trial of 164 veterans with treatment-resistant depression (TRD) (defined as failure of at least 2 prior adequate pharmacological treatments) was conducted at 9 VA medical centers. It is important to note that patients with comorbid PTSD and/or a history of substance use disorders were included in the trial population. In contrast to a burgeoning literature documenting the efficacy of rTMS in a broad panoply of depressed patients, including those with TRD and those receiving concomitant antidepressant treatment,[8-10] the study revealed no significant treatment effect of rTMS compared with sham treatment on the primary outcome measure (remission) or a host of secondary outcome measures. Remarkably, approximately 40% of the patients with TRD achieved remission regardless of treatment group assignment, although those with comorbid PTSD showed lower remission rates in both treatment groups. The results are puzzling for several reasons. First, the remission rates are unusually high, especially in a treatment-resistant population and especially compared with other studies in similar populations, including the Veterans Affairs Augmentation and Switching Treatments for Improving Depression Outcomes (VAST-D) Study.[4] Second, the lack of efficacy for rTMS is in sharp contrast with previous TRD studies.

What might explain these findings? First, this population is largely male, in clear contrast to most depression clinical trials, which typically are about two-thirds female, mirroring the prevalence rates of MDD in the general population. Second, one cannot underestimate the psychological benefits of participation in clinical trials. The repeated engagement of the subjects by the treatment team is not a neutral experience but tantamount to at least supportive psychotherapy, if not more. Perhaps an analysis of the frequency of mental health clinic visits prior to entry into the studies would reveal a clear effect of the treatment trial visit intensity as a major contributor to the observed effects. Finally, high placebo response rates have increasingly plagued the field of depression research.

This is an important negative study, but it does not fully answer the question of what the appropriate role for rTMS is in the treatment of TRD in veterans. As personalized medicine in psychiatry progresses, we will likely someday soon be able to accurately identify the best treatment for individual patients. This will likely involve both genomic markers as well as functional brain imaging predictors of response.

ARTICLE INFORMATION

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Pharmaceuticals Inc, TC MSO Inc, and Intra-Cellular Therapies, Inc; holding stock in Xhale, Celgene, Seattle Genetics, Abbvie, OPKO Health Inc, Antares, BI Gen Holdings Inc, Corcept Therapeutics Pharmaceuticals Company, and Gilead; acting as a member of scientific advisory boards for the American Foundation for Suicide Prevention, Brain and Behavior Research Foundation, Xhale, Anxiety Disorders Association of America, Skyland Trail, Bracket, and Laureate Institute for Brain Research, Inc; serving on the board of directors of American Foundation for Suicide Prevention, Gratitude America, and Anxiety Disorders Association of America; and having income or equity of $10 000 or more from American Psychiatric Publishing, Xhale, Bracket (Clintara), CME Outfitters, Takeda, Intra-Cellular Therapies Inc, and Magstim. He also holds patents in the Method and devices for transdermal delivery of lithium (US 6,375,990B1) and the Method of assessing antidepressant drug therapy via transport inhibition of monoamine neurotransmitters by ex vivo assay (US 7,148,027B2). No other disclosures were reported.

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