The Holy Grail of Psychiatry

By Charles B. Nemeroff, M.D., Ph.D.

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Editor's Note: "Holy Grail" is a well-known metaphor for the eternal spiritual pursuit for truth and wisdom. It suggests that in order for us to find what no one has found, we must search where few have looked. In 2013, a group led by Helen Mayberg published a groundbreaking paper that sought an answer to one of the most discussed conundrums in psychiatry and neuroscience: Can specific patterns of brain activity indicate how a depressed person will respond to treatment with medication or psychotherapy? Our author examines the findings and discusses their potential impact on treatment for a public health problem that affects millions of people worldwide.

The personal and societal toll of major depression is almost unfathomable. This year we will lose more than 42,000 people to suicide in the United States, the only top 10 cause of death in this country that has increased year after year. Much of this tragic outcome can be attributed to untreated, poorly treated, treatment-resistant, and undiagnosed major depression. In this regard, it is worth remembering the familiar quote, attributed to Joseph Stalin, "A single death is a tragedy, a million deaths is a statistic." Perhaps the personal misery and tragedy of major depression are best exemplified by the award-winning novelist William Styron's personal account in *Darkness Visible*:

"What I had begun to discover is that, mysteriously and in ways that are totally remote from normal experience, the gray drizzle of horror induced by depression takes on the quality of physical pain. But it is not an immediately identifiable pain, like that of a broken limb. It may be more accurate to say that despair, owing to some evil trick played upon the sick brain by the inhabiting psyche, comes to resemble the diabolical discomfort of being imprisoned in a fiercely overheated room. And because no breeze stirs this caldron, because there is no escape from this smothering confinement, it is entirely natural that the victim begins to think ceaselessly of oblivion."[1]

I had the opportunity to get to know Styron well in his later years and can attest to the severity of his depressive symptoms—the absolute inability to experience pleasure of any kind and a feeling of hopelessness.

The consequences of untreated or unremitted depression are quite dire, including an increased risk not only for suicide, but also for alcohol and substance abuse, as well as for a variety of major medical disorders (cancer, heart disease, stroke, kidney disease, and others). Perhaps of equal importance is the well-replicated observation that the longer a patient remains depressed, the less likely he or she is to achieve remission. Taken together, the linking together of findings indicates that the personal, societal, and economic consequences of undiagnosed or not well managed major depression are devastating and represent a major public health problem in the U.S. and worldwide. Indeed, the latest Global Burden of Disease study revealed major depression to represent a major cause of disability.[2] All of the aforementioned considerations serve as the major impetus for developing predictors of treatment response in depressed patients.

The Current State of Evidence-based Treatments

The U.S. Food and Drug Administration (FDA) has approved around 30 antidepressant medications for the treatment of major depression. Among them are selective serotonin reuptake inhibitors (SSRIs). These drugs change the balance of serotonin in the brain, such as fluoxetine (Prozac), paroxetine (Paxil), sertraline (Zoloft), escitalopram (Lexapro), and citalopram (Celexa). Another family of medications, selective serotonin and norepinephrine reuptake inhibitors (SNRIs), help increase serotonin and norepinephrine levels in the brain, such as venlafaxine (Effexor), duloxetine (Cymbalta), and levomilnacipran (Fetzima). Still others in this family include bupropion (Wellbutrin), vortioxetine (Brintellix), mirtazapine (Remeron) vilazodone (Viibryd), nefazodone (Serzone), and trazodone (Desyrel). In addition, tricyclics and monoamine oxidase inhibitors, which are two classes of older antidepressants that work by inhibiting the brain's reuptake of serotonin and

norepinephrine, are also approved but tend to cause more side effects than the other classes of antidepressants.

But pharmacotherapy isn't the only option; two other major classes of treatment are also available—psychotherapy and somatic nonpharmacological treatments. In randomized, controlled trials, cognitive-behavioral therapy (CBT) and interpersonal psychotherapy (IPT) repeatedly have been demonstrated to be effective in the treatment of major depressive disorder (MDD). Whether other forms of psychotherapy, such as insight-oriented, psychodynamically based therapy, are effective in major depression remains controversial. Brain stimulation therapies involve activating or touching the brain directly with electricity, magnets, or implants, and the FDA has approved three somatic nonpharmacological treatments for depression: electroconvulsive therapy (ECT), vagus nerve stimulation (VNS), and repetitive transcranial magnetic stimulation (rTMS).

ECT is generally considered the most effective of all depression treatments, although no head-to-head, randomized, controlled trial has compared it with other interventions. It generally requires inpatient hospitalization, at least initially, and general anesthesia with nine to twelve treatments over a three- to four-week period. Its cost and concerns about memory loss and the stigma associated with "shock treatment" has precluded its more widespread use. VNS and rTMS are both FDA-approved for treatment-resistant depression; the former requires an invasive surgical procedure. Researchers have conducted relatively few controlled studies of these devices compared with the vast number of pharmacotherapy and psychotherapy treatment trials.

A Personalized Approach

With a plethora of drugs and psychotherapy approaches available, let us consider the problem psychiatrists encounter on a daily basis. A patient in my own practice serves as an example. A 50-year-old academic physician suffers from a classic major depressive episode associated with severe work stress. He has difficulty falling asleep, awakens several times during the night, and rises early with severe anxiety. He has reduced appetite, difficulty concentrating, and trouble enjoying any leisure activities, and he feels pessimistic about the future. He admits to passive contemplations about suicide, with recurring thoughts that if a car jumped the median and landed on his car, it would be an end to his suffering. He has no prior episodes or family history of depression. He has no underlying medical disorder that might be contributing to depression, such as hypothyroidism or drug or alcohol abuse. What treatment should I recommend for him? Antidepressants, and if so, which one? Psychotherapy, and if so, which one? One of the somatic, nonpharmacological treatments?

I want to recommend the treatment most likely to be successful in producing a complete remission of his depressive syndrome and relieving him of his considerable misery. What are the known and best-validated predictors of response? Our group has previously reviewed the scientific findings in this area.[3-6] The most reliable predictor is past response, but in this case the patient has never been treated for depression. A positive response in first-degree family relatives is also predictive of a beneficial response to antidepressants, but again, this is not applicable to this patient. Some evidence suggests that certain subtypes of depression respond best to certain treatments—monoamine oxidase inhibitors (the first type of antidepressants developed) are believed to be the most effective for patients with so-called atypical depression characterized by hypersomnia, overeating, extreme rejection sensitivity, and feeling better in the morning than later in the day.

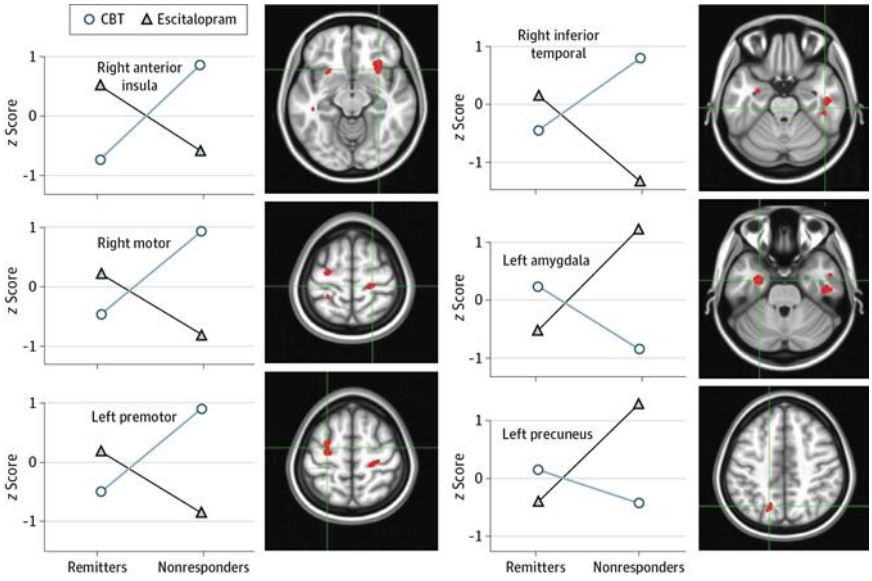
Combinations of antidepressants and antipsychotics or ECT are best for patients with major depression with psychotic features. However, neither of these subtypes are relevant to the patient I have described. What then can guide my recommendations? Surely patient choice is an important consideration, but it will likely be guided by my discussion with the patient.

In 2013, Helen Mayberg and her colleagues published groundbreaking findings that help in this case. One important caveat and disclosure: Several of the authors (Drs. Mayberg, Holtzheimer, Dunlop, and Craighead) were colleagues of mine for many years, and we continue to collaborate on various projects. However, I was not involved in the following study.

Mayberg's study sought to identify a biomarker that could predict which type of treatment would benefit a patient based on the individual's brain activity. Using regional brain glucose metabolism as measured by positron emission tomography (PET) as a proxy for neural activity, her group sought to determine whether baseline resting state activity predicted remission after twelve weeks of treatment with either the selective serotonin reuptake inhibitor escitalopram (10 to 20 mg per day) or sixteen sessions of cognitive-behavioral therapy. The study sample initially comprised eighty-two men and women who were randomized between the two treatments. Of these, sixty-five patients completed the study and thirty-eight had clear outcomes and acceptable PET data. The thirty-eight patients who comprise the analyzable data set were distributed as follows: eleven who went into remission with escitalopram (six non-responders) and twelve who did so with CBT (nine non-responders). The major finding were that hypometabolism of glucose in the insula, likely reflecting reduced activity of neurons in this brain region, was associated with remission using CBT, and with poor response to escitalopram. Contrariwise, insula hypermetabolism, reflecting increased activity

of neurons in this brain region, was associated with remission using escitalopram and with poor response to CBT.

The authors conclude that baseline insula metabolism is the first objective marker to guide initial treatment selection in depression. Closer scrutiny of their data is worthwhile. First they eliminated from their primary analysis the responders to CBT or to escitalopram who did not go into remission. More specifically, partial responders to escitalopram or CBT were excluded from the analysis. They did so in order to accentuate the differences between the extremes in the depressed population; the results revealed clear differences in glucose metabolism in six regions: the right anterior insula, right motor cortex, left premotor cortex, right inferior temporal cortex, left amygdala, and precuneus.



Potential Treatment-Specific Biomarker Candidates. Mean regional activity values for remitters and nonresponders segregated by treatment arm are plotted for the six regions showing a significant treatment × outcome analysis of variance interaction effect. Regional metabolic activity values are displayed as region/whole-brain metabolism converted to z scores. Regions match those shown in Table 2. Escitalopram was given as escitalopram oxalate. CBT indicates cognitive-behavioral therapy.[7]

When all six regions were compared, the right insula exhibited the greatest effect as a discriminator of treatment response, followed by the precuneus. When the whole sample was studied, right insular activity was positively correlated with the depression symptom severity scale, and with the Hamilton Depression Rating Scale (HRSD) score in the CBT treatment group while right insular activity was negatively correlated with the HRSD in the escitalopram treatment group.

This finding is quite provocative. If additional research can replicates these results, it suggests that a simple brain imaging test could reliably predict whether a given patient should be treated with psychotherapy or antidepressant medication. It also raises a plethora of additional questions:

- A wealth of data, now summarized in a research meta-analysis, indicate that MDD patients with a history of child abuse and neglect exhibit a poorer response to pharmacotherapy and psychotherapy and exhibit unique brain imaging differences.[8] Mayberg's research does not address this critical clinical characteristic in this population.
- It is somewhat unclear how the six brain regions of interest were identified and why several regions repeatedly identified to be implicated in the pathophysiology of depression either were not selected or exhibited no significant effect, including the hippocampus, subgenual cingulate, and others.
- It is hard to know what to make of the findings that only the right anterior insula, right motor cortex, left premotor cortex, left amygdala, left precuneus, and right inferior temporal region show dramatic differences in the CBT versus escitalopram induced remission versus nonresponder groups whereas their counterparts, namely the left anterior insula, left motor cortex, right premotor cortex, right amygdala, right precuneus, and left

inferior cortex did not. Was a composite of the left and right sides of these structures informative?

- As the authors themselves point out, the study comprises a relatively small number of patients and our field is replete with pilot study findings that, unfortunately, have not been replicated in larger trials.
- This study utilized PET instead of the more often used functional magnetic resonance imaging (fMRI) technology. As Mayberg and her colleagues appropriately point out in their paper, fMRI studies have examined regional brain activity and, more recently, resting state connectivity to identify MDD or MDD subtypes, but neither type of imaging has been used to discriminate response either among antidepressants or between antidepressants and psychotherapy.[9]

The expanding area of genetics in general, and pharmacogenetics in particular, is also of vital importance. A burgeoning database documents the role of certain genetic variations in vulnerability to mood disorders, and more recently how variations may affect treatment response to different antidepressants. Whether genetic material was collected in Mayberg's study is unclear, but this focus is crucial, particularly in view of recent findings in imaging genomics. The lack of random assignment of the MDD patients as regards, for example, the vulnerability gene variants of the serotonin transporter or others, now shown to be associated with clear alterations in regional brain activity, could have confounded the results.

Such possibilities should not detract from the groundbreaking findings. This research group has always been willing to take great leaps forward, and they should be applauded for it. Subsequent

studies will reveal if the insula is truly "the region" that predicts response to CBT versus a selective serotonin reuptake inhibitor such as escitalopram or whether other regions or biomarkers also need to be a component of the ultimate formula. This is part of the ongoing and exciting scientific process that is emblematic of the marriage of neuroscience and psychiatry. Ultimately, I believe this work will be judged as crucial in eventually attaining the goal all of us seek: a valid predictor of individual treatment response in depression, still the Holy Grail in psychiatry research.

Bio

Charles B. Nemeroff, M.D., Ph.D., is the Leonard M. Miller Professor and chairman of the Department of Psychiatry and Behavioral Sciences, and director of the Center on Aging, at the University of Miami School of Medicine. His research has focused on the pathophysiology of mood and anxiety disorders and the role of mood disorders as a risk factor for major medical disorders. He received his M.D. and Ph.D. degrees in neurobiology from the University of North Carolina (UNC) School of Medicine. After psychiatry residency training at UNC and Duke University, he held faculty positions at Duke and at Emory University before relocating to the University of Miami in 2009. He has served as president of the American College of Psychiatrists (ACP) and the American College of Neuropsychopharmacology. He has received the Kempf Fund Award for Research Development in Psychobiological Psychiatry; the Samuel Hibbs Award, Research Mentorship Award, Judd Marmor Award and Vestermark Psychiatry Educator Award from the American Psychiatric Association (APA); and the Mood Disorders Award, Bowis Award and Dean Award from the ACP. He is the co-editor-in-chief of the *Textbook of Psychopharmacology*, published by the APA. He is a member of the National Academy of Medicine.

Link to financial disclosure.

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