The Holy Grail of Psychiatry

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

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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 ten 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.

I had the opportunity to determine...
"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 unremitting 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. 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 12 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 problems 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 he would be better off in a car, it would be an end to his long history of depression. He has a history of contributing to depression—child abuse. What treatment should we try? If so, which one? Psychotherapy or somatic nonpharmacological treatments?

I want to recommend producing a complete remission and him of his considerable mis-suspects as predictors of response? Our groupings of findings in this area. The most case the patient has never been diagnosed in first-degree family relatives. Antidepressants, but again, the evidence suggests that certain subtypes of treatments—monoamine oxidase (MAO) (developed) are believed to be effective in atypical depression characterized by projection sensitivity, and feeling.

Combinations of antidepressants in patients with major depression, if these subtypes are relevant to guide my recommendations? Otherwise, but it will likely be greater.

In 2013, Helen Mayberg and her findings that help in this case. All of the authors (Drs. Mayberg and colleagues of mine for many years on various projects. However, I was not

Mayberg’s study sought which type of treatment would alter brain activity. Using regional brain positron emission tomography (PET)
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 of 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. 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 12 weeks of treatment with either the selective serotonin reuptake inhibitor escitalopram (10 to 20 mg per day) or 16 sessions of cognitive-behavioral therapy. The study sample initially comprised 82 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 38 patients who comprise the analyzable data set were distributed as follows: 11 who went into remission with escitalopram (six nonresponders) and 12 who did so with CBT (nine nonresponders). The major findings 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.

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 replicate these results, it suggests that a simple brain imaging test could reliably predict whether a given patient will respond to a particular depressant medication. It also suggests that MDD patients may exhibit unique brain imaging differences that distinguish responders from nonresponders and that these differences may be related to the pathophysiology of depression.

- A wealth of data, now surmountable, suggests that MDD patients with a poor treatment response to pharmacotherapy exhibit unique brain imaging differences that may be related to this critical clinical characteristic.
- It is somewhat unclear how these imaging differences are related and why several regions exhibit a significant effect, including these with others.

Potential Treatment-Specific Biomarkers and nonresponders segregated based on a significant treatment x outcome interaction. Activity values are displayed as regression splines matched those shown in Table 2. Escitalopram indicates cognitive-behavioral therapy.
staging state activity predicted remission of the selective serotonin reuptake inhibitor (SSRI) or 16 sessions of cognitive-behavioral therapy: comprised 82 men and women with MDD. Of these, sixty-five patients had clear outcomes and accounted for the analyzable data set. The study compared remission with escitalopram (nine nonresponders) or cognitive-behavioral therapy (CBT) (nine nonresponders). Increased activity of glucose in the insula, like other brain regions, was associated with a better response to escitalopram. Conversely, increased activity of neurons in the posterior cingulate cortex was associated with a better response to CBT.

The right insula metabolism is the first objective marker of response in depression. Closer scrutiny of this region eliminated those who did not go into remission, those who went on to escitalopram or CBT were segregated into responders and nonresponders, matched for age and sex, and the results revealed a significant difference in activity in the right anterior insula and the right inferior temporal cortex among responders and nonresponders.

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.

dict 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. 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 the significance of 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, or biomarkers also need to be part of the ongoing and the marriage of neuroscience will be judged as crucial in a predictor of individual treatment in psychiatry research.
findings that only the right anterior motor cortex, left amygdala, left region show dramatic differences in remission versus nonresponder especially the left anterior insula, left right amygdala, right precuneus, composite of the left and right sides of the study comprises a relatively small number, 10, with pilot study findings that, larger trials.

The more often used functional magnetic resonance imaging. As Mayberg and her colleagues in the paper, fMRI studies have examined resting state connectivity, but neither type of imaging has been shown to be among antidepressants or be-

The general, and pharmacogenetics in the sequencing database documents the heritability to mood disorders and, treatment response to different depressive traits collected in Mayberg's study is interesting in view of recent findings in the identification of the MDD patients as variants of the serotonin transporter, with clear alterations in relation to the results.

Based on these groundbreaking findings, not being to take great leaps forward, subsequent studies will reveal if the 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.