This issue:
A Paradigm Shift in Depression Treatment
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Guest Editor

The articles in this issue of *Psychiatric Annals* fully elaborate a shift in thinking regarding the etiology and treatment of depression, and I hope readers agree that the enthusiasm is more than justified.

The basic principles of treating depression with medication have not changed in 60 years. Since the synthesis of the first tricyclic antidepressants (TCAs), and the first trial of imipramine in the late 1950s, we have been discussing and refining the blockage of monoamine transport into neurons. It is the consensus in our field that depression is caused by low levels of serotonin and norepinephrine, and have treated the illness accordingly—with agents that allow the brain to make maximal use of these neurotransmitters in short supply. Numerous medications block the reuptake of these monoamines, and we hope that, over time, this action coaxes the neuron into synthesizing more of them—or perhaps, simply time itself will result in continued euthymia once the agent is tapered and discontinued.

The genetic vulnerability associated with depression has also been accepted to reside in the code for the serotonin transporter protein. This concept fit neatly into the traditional paradigm, as nearly all of our medications, even TCAs, held some activity at this transporter.

There is no debate that antidepressants have helped millions of people worldwide, have been lifesaving for many, and remain the standard of care. Yet, in the past two decades it has become clear that a paradigm shift is necessary. The basic efficacy of antidepressants has faced scrutiny, as the literature has highlighted symptom relief versus the rarer, but more desirable outcome of illness remission. It is generally accepted that most patients need a combination of antidepressants and adjunctive therapy to achieve a full remission. In a quest for remission, professionals in the mental health community widely adopted the standard of using antipsychotics as adjunctive therapy without first answering the most important question: are the benefits worth the risks of movement disorders (acute and latent), metabolic syndrome, and neuroleptic malignant syndrome?

The recent discovery of the plasma membrane monoamine transporter may provide some answers when examining the limits of antidepressant therapy. This high-capacity, low-specificity transporter of all monoamines is widespread throughout the central nervous system (CNS), and is not affected by serotonin reuptake inhibitors (SRIs) or serotonin-norepinephrine reuptake inhibitors (SNRIs) unless levels consistent with an overdose are reached. Perhaps modern monoamine reuptake blockers are akin to shutting a few windows, although all the doors remain wide open.

Further challenging our conventional understanding of depression, two recent meta-analyses found that the genetic vulnerability for depression after stressful events did not, in fact, reside in the genome coding for the serotonin transporter. Although the debate continues, more plausible genetic vulnerabilities have surfaced; the difference between people who experience similar stressors but have vastly different neurochemical responses is more likely related to polymorphisms of the genes critical for homocysteine (HCY) metabolism, not monoamine reuptake.

Fortunately, as these concerns regarding the etiology and treatment of depression are surfacing, the literature has also begun elaborating on the role of HCY in neuropsychiatric
pathology. HCY metabolism is not only necessary for monoamine synthesis, but also allows for methylation of DNA, ie, turning genes on or off for expression. We can now target methylation with newer, natural agents. Thus, epigenetics—the study of genetic-environment interaction that results in clinical pathology through impaired methylation of DNA, is now a focus of treatment, not simply a theory of disease etiology. The HCY hypothesis of depression and neurotoxicity elaborates exactly how numerous pathologies begin and progress, and further, provides a roadmap for how to address them.

Our first article, by Drs. Neil Mori, Laura Lockwood, and W. Vaughn McCall, presents currently available antidepressant therapies, particularly the use of SRIs and SNRIs, and the addition of adjunctive agents with the goal of achieving remission. They explore the issues of response versus remission, tolerability, compliance, and the numerous barriers preventing effective treatment. They conclude by recommending newer approaches to help battle the complex and life-threatening illness of major depressive disorder. Next, Dr. Angela Pan elaborates on the destructive role of elevated HCY in the CNS, and the importance of addressing it, not only in acute treatment but also for neuroprotection. The HCY theory of depression is fully detailed in the next article that I contributed, which also addresses the role of folates and other B vitamins in the CNS and, in particular, their critical roles in monoamine synthesis. Putting this theory into practice is the topic of discussion for the final article. In this article, I address the HCY theory clinically; with this approach, the method is to supply the patients’ neurons with “missing” materials to synthesize monoamine, which is a departure from simply blocking their reuptake into the cells. In my view, lowering HCY in the CNS will no doubt have immeasurable neuroprotective value, and no discussion of preventive neuropsychiatry can be complete without an understanding of HCY reduction. Battleships turn slowly. Hopefully, these articles will inspire clinicians to think beyond symptom relief and remission, as well as understanding their unique role in preventive care.

It has been an honor to serve as guest editor for this issue, and I am grateful to the Editor-in-Chief Jan Fawcett for the opportunity. I thank all of the contributing authors for their dedication and passion.

REFERENCES


doi: 10.3928/00485713-20150901-03

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