Advances in Understanding and Treating Mood Disorders

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Mood disorders, primarily major depression and bipolar disorder, are among the most debilitating psychiatric illnesses. Although significant progress has been made, there is much to be learned about their pathophysiology and much to be improved upon regarding their treatment. It is important to acknowledge that considerable work in the past has enhanced our understanding and treatment of mood disorders as evidenced by currently available effective treatments, which range from specific psychotherapies to psychopharmacology to neuromodulation. Still, many of our patients fail to fully respond to treatment or stay chronically ill.

Significant advances have been made in relation to the neurobiology underlying emotion, cognition, and behavior, and multitudes of studies have been performed in clinically ill populations; however, we are still far away from applying most of these findings to the clinical setting. From neuroimaging studies, we have developed a reasonable understanding of the circuity underlying negative emotion, reward, fear, anxiety, cognition, and behavior and have characterized various abnormalities in task and "resting-state" brain function in populations of patients with depression and bipolar disorder. Replicability of many of these findings, especially those in patient populations, has become an issue. Genetic studies are identifying structural genetic variants associated with the likelihood of developing mood disorders. However, the effect size of the influence of any one single-nucleotide polymorphism is quite small, and as with most psychiatric illness, we are understanding that many genes interact to increase susceptibility or provide protection. The use of polygenic risk scores appears to be an effective way to capture the complex genetics of these disorders, and over time this approach has potential to inform clinical care. Environmental factors also play a prominent role in the expression of mood disorders: advances are being made at the molecular level in understanding how environmental events are epigenetically programmed to result in altered gene expression that is informative for understanding the gene-by-environment interactions relevant to mood disorders. Most in the field believe that new effective treatment development depends on elucidating a fundamental understanding of mood disorder–related alterations in specific neural circuits and the molecules within these circuits. In addition, the use of machine learning to capitalize on combining critical components of large data sets (i.e., genetic, epigenetic, circuit function, and environmental events) holds promise for personalized psychiatric treatment approaches.

This issue of the *Journal* is devoted to providing our readership with a better understanding of where the field is in relation to our understanding and treatment of mood disorders, as well as introducing our readers to new promising findings. The centerpiece of this issue is a broad overview on depression by Dr. Charles Nemeroff, chair of the Department of Psychiatry and Behavioral Sciences at the University of Texas Dell Medical School in Austin. In his insightful and thought-provoking overview (1), Dr. Nemeroff provides his perspective on how we can conceptualize and integrate the multitude of findings and issues relevant to understanding the heterogeneity of depression, diagnostic criteria, mechanisms associated with depression-related pathophysiology, and insights into current and future treatments. This overview is followed by a comprehensive review focused on the use of hormonal treatment strategies for major depression (2). Dysregulated hormonal systems (e.g., pituitary-adrenal, thyroid, and gonadal) have long been associated with mood alterations and have been a focus of a vast number of studies investigating the potential role of specific hormonal systems in the pathophysiology and treatment of depression. This review, a product of the APA Council of Research Task Force on Novel Biomarkers and Treatments, synthesizes findings from the existing literature to provide clinicians and researchers with a resource for the evidence underlying hormonal treatment strategies. I particularly want to acknowledge the two co-first authors of this review, Dr. Jennifer Dwyer and Dr. Awais Aftab, who at the time were trainee members on the research council. I had the privilege of working closely with Drs. Dwyer and Aftab on this review and personally thank them for their insights and considerable

Exciting findings reveal insights into alterations in reward processing in adolescents with depression, an understanding of how environmental influences affect the risk for developing stress-related psychopathology, and groundbreaking new neuromodulation strategies.

efforts, which they relate in further detail in this month's AJP Audio podcast episode.

This issue of the *Journal* also presents original research articles that address topics related to the treatment of bipolar disorder, the use of a new transcranial magnetic stimulation (TMS) strategy for treatment of refractory depression, and the effects of gender-affirming interventions on the treatment of mood and anxiety disorders in transgender individuals.

Using data from the National Ambulatory Medical Care Survey from 1997 to 2016, Rhee et al. (3) statistically characterize 20-year trends in the pharmacological treatment of bipolar disorder. Although it is probably not a surprise to somewhat older practitioners who have lived these changes, an important finding from this study is documenting the dramatic increase in the use of second-generation antipsychotics with the co-occurrence of a large reduction in the use of traditional mood stabilizers, such as lithium or valproic acid. The authors also report a considerable decrease in the use of psychotherapy, which may be problematic given the considerable psychosocial issues faced by patients with bipolar disorder. Dr. Michael Thase, from the University of Pennsylvania and an expert in the development and evaluation of new treatments for mood disorders, contributes an editorial that provides further historical context for these changes in treatment as well as the implications of these changes (4).

In another article, the Stanford group presents extremely promising data toward improving TMS methods for treatment-resistant depression (5). Capitalizing on intermittent theta-burst stimulation (iTBS), which is approved for the treatment of depression, Cole and coworkers report findings from an open-label trial of 22 patients who underwent an intensive iTBS treatment over the course of 5 consecutive days. Importantly, this early study used resting-state functional connectivity MRI to individualize the treatment target region within the left dorsolateral prefrontal cortex, such that stimulation was placed over the area that was most negatively correlated with the functional MRI signal in the subgenual anterior cingulate cortex (sgACC). This targeting strategy was used as the sgACC is a neural hub that receives the confluence of prefrontal cortical and subcortical information that is relevant to emotion and mood regulation, as well as to depression. One important outcome of the study is the demonstration that this intensive theta-burst treatment protocol was safe for patients. Treatment efficacy was rapid, with a remarkable remission rate of approximately 90%. Drs. Carpenter and Philip, from the Brown Department of Psychiatry and Human Behavior and experts in TMS neuromodulation, provide an editorial emphasizing the exciting treatment prospects supported by the data from this study (6). They also discuss these findings in relation to existing TMS treatment strategies and study design issues, including the small sample size and open-label nature of the study.

Also in this issue, along with an accompanying editorial by Dr. Sven Mueller from Ghent University (7), is an article that addresses the very important concern regarding the mental well-being of transgender individuals, specifically the effects of gender-affirming treatments on their mental health (8). In their article, Bränström and Pachankis use Swedish registries to assess mental health visits and outcomes after hormonal and surgical gender-affirming interventions. Compared with the general population, the results demonstrate that transgender individuals had higher numbers of clinical visits for the treatment of depression and anxiety prior to the interventions. The authors initially concluded, and presented in their article, that gender-affirming surgery, and not hormonal treatment, was associated with a subsequent reduction in the need for mental health intervention. However, when the article was initially available online, concerns were raised by some of our readers regarding the conclusions. Based on these concerns, we solicited secondary reviews of the article, including statistical consultation that recommended additional analyses. Among these analyses, the authors compared matched groups of gender identity patients who did and did not receive gender-affirming surgery, which resulted in the revised conclusion that gender-affirming surgery did not provide an advantage in relation to mental health outcomes. A robust discussion of this issue, and other methodologic and interpretive concerns, can be found in the numerous accompanying letters to the editor (9–15), published along with Bränström and Pachankis' response to these letters (16) and a note from myself regarding the corrections and the process the *Journal* followed to vet the concerns that were raised (17). In addition to a published erratum notice, the Bränström and Pachankis article now includes an addendum referring to this postpublication discussion.

Two articles in this issue address environmental influences on mental health and depression, though in very different ways. One article examines the effects of air pollution on increasing hospital admissions for depression in China, and another article focuses on mechanisms involved in the intergenerational transmission of the effects of trauma. In their article, Gu et al. (18) present information building on earlier work that draws an association between short-term ambient air pollutant concentration and hospital admissions for depression. Using daily assessments of air pollutant concentrations across 75 cities and admission data from more than 111,000 hospitals, the authors found that from 2013 to 2017, increasing exposure to fine particles (<2.5 μm) and inhalable particles (<10 μm) was associated with increased rates of hospitalization. This association was demonstrated to be present within 7 days of increasing pollutant exposure, and the effects appeared to be particularly strong for nitrogen dioxide. It should be emphasized that in interpreting these findings, there are important methodologic issues that the authors discuss in the limitations paragraph of the article's Discussion section. Furthermore, these findings represent associational data, which do not address causality. Nonetheless, the authors speculate on the possibility that pollutant-induced oxidative stress and inflammation may be

underlying factors that could mediate this interesting and troubling association with depression.

Moving from an epidemiological level of analysis toward a molecular one, the article in this issue by Bierer et al. (19) characterizes epigenetic changes associated with the intergenerational transfer of traumatic experiences. This article focuses on the *FKBP5* gene, which makes a protein that regulates glucocorticoid receptor responsivity. In addition, variation in the *FKBP5* gene has been shown to be associated with posttraumatic stress disorder. This article speaks to how traumatic experiences in parents prior to conception may influence the biology and behavior of their offspring. Specifically, the authors replicate and extend an earlier finding in which they demonstrated reduced methylation at a specific site of the *FKBP5* gene when measured in blood from the offspring of mothers who survived the Holocaust. The authors show that this effect was strongest in the offspring of mothers who were exposed to the Holocaust at younger ages and that reduced methylation of this site on the *FKBP5* gene was associated with lower levels of anxiety and higher levels of basal cortisol levels. Because of the association between reduced anxiety and decreased *FKBP5* methylation, the authors speculate that this epigenetic alteration may serve to protect offspring from the influences of stress exposure. The article also provides a helpful, in-depth discussion of the function of the *FKBP5* gene and its protein and how this gene may be causally related to the effects of trauma and to pituitary-adrenal function. The present finding, which is an important replication of earlier work, along with other numerous relevant discoveries involving the *FKBP5* gene, supports further serious attention to *FKBP5* as a risk factor and mediator of stress-related psychopathology.

The disruption of hedonic processes is a cardinal feature of depression, and it is well established that depression is associated with alterations in the activation of reward-related circuits. The article by Rappaport and coauthors (20) addresses depression at a neural systems level of analysis by focusing on reward-related circuitry and development. This circuitry is complex and brain-wide, including regions such as brainstem dopaminergic nuclei, the ventral and dorsal striatum (i.e., the nucleus accumbens and caudate, respectively), the prefrontal cortex, and limbic structures (e.g., the amygdala, hypothalamus, and hippocampus). In the study presented here, the researchers used a monetary reward task to examine activation of reward-related neural circuitry in adolescents in relation to current symptoms of depression as well as in relation to their lifetime history of depression. The sample used is unique in that prospective assessments of symptoms began at between 3 and 5 years of age. The findings demonstrate the importance of examining both the state and "trait-like" aspects of depression, as the data revealed different patterns of neural alterations in relation to current symptoms compared with an individual's life history of depression. Specifically, current depression was characterized by blunted activation of the nucleus accumbens when anticipating reward, whereas a cumulative history of depression involved a blunted response across a broader network of cortical and striatal regions. These findings are intriguing and potentially very important. Above and beyond the specific findings, the analytic strategy used in this study emphasizes the value of parsing current symptoms from illness history when characterizing the biology of our patients. The findings suggest that different mechanisms, even within the same general circuitry, may be at play in relation to understanding current symptoms in contrast to longer-term vulnerabilities. The developmental nature of this study is also highly important, as the findings shed light on the earliest manifestations of depression and its potential cumulative effects over development on neural circuit dysfunction. In her accompanying editorial (21), Dr. Erika Forbes, an expert in mechanisms underlying adolescent depression, highlights the importance of neurodevelopmental research while reviewing and discussing the relevance of these new findings.

In conclusion, this issue presents an in-depth view into important clinical and research issues relevant to mood disorders. The overview on depression presents our readership with where we are in the field and the challenges we face in improving outcomes for patients with depression. The review on the use of hormonal treatments and the articles on treatment trends in bipolar disorder and on gender-affirming interventions in transgender individuals provide information that is immediately applicable to clinical practice. Other exciting findings reveal insights into alterations in reward processing in adolescents with depression, an understanding of how environmental influences affect the risk for developing stress-related psychopathology, and groundbreaking new neuromodulation strategies that may significantly impact treatment outcomes in patients with treatment-resistant depression. It is my hope that this issue of the *Journal* will enthuse, and provide optimism to, readers about the potential for further advances that will benefit our patients suffering from mood disorders.

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REFERENCES

1. Nemeroff CB: The state of our understanding of the pathophysiology and optimal treatment of depression: glass half full or half empty? Am J Psychiatry 2020; 177:671–685
2. Dwyer JB, Aftab A, Widge A, et al: Hormonal treatments for major depressive disorder: state of the art. Am J Psychiatry 2020; 177: 686–705
3. Rhee TG, Olfson M, Nierenberg AA, et al: 20-year trends in the pharmacologic treatment of bipolar disorder by psychiatrists in outpatient care settings. Am J Psychiatry 2020; 177:706–715
4. Thase ME: Charting sea changes in outpatient pharmacotherapy of bipolar disorder (editorial). Am J Psychiatry 2020; 177:651–653

5. Cole EJ, Stimpson KH, Bentzley BS, et al: Stanford Accelerated Intelligent Neuromodulation Therapy for treatment-resistant depression. Am J Psychiatry 2020; 177:716–726
6. Carpenter LL, Philip NS: The future is now? Rapid advances by brain stimulation innovation (editorial). Am J Psychiatry 2020; 177:654–656
7. Mueller SC: Mental health treatment utilization in transgender persons: what we know and what we don't know (editorial). Am J Psychiatry 2020; 177:657–659
8. Bränström R, Pachankis JE: Reduction in mental health treatment utilization among transgender individuals after gender-affirming surgeries: a total population study. Am J Psychiatry 2020; 177: 727–734
9. Anckarsäter H, Gillberg C: Methodological shortcomings undercut statement in support of gender-affirming surgery (letter). Am J Psychiatry 2020; 177:764–765
10. Van Mol A, Laidlaw MK, Grossman M, et al: Gender-affirmation surgery conclusion lacks evidence (letter). Am J Psychiatry 2020; 177:765–766
11. Curtis D: Study of transgender patients: conclusions are not supported by findings (letter). Am J Psychiatry 2020; 177:766
12. Malone WJ, Roman S: Calling into question whether gender-affirming surgery relieves psychological distress (letter). Am J Psychiatry 2020; 177:766–767
13. Landén M: The effect of gender-affirming treatment on psychiatric morbidity is still undecided (letter). Am J Psychiatry 2020; 177: 767–768
14. Wold A: Gender-corrective surgery promoting mental health in persons with gender dysphoria not supported by data presented in article (letter). Am J Psychiatry 2020; 177:768
15. Ring A, Malone WJ: Confounding effects on mental health observations after sex reassignment surgery (letter). Am J Psychiatry 2020; 177:768–769
16. Bränström R, Pachankis JE: Toward rigorous methodologies for strengthening causal inference in the association between gender-affirming care and transgender individuals' mental health: response to letters (letter). Am J Psychiatry 2020; 177:769–772
17. Kalin NH: Reassessing mental health treatment utilization reduction in transgender individuals after gender-affirming surgeries: a comment by the editor on the process (letter). Am J Psychiatry 2020; 177:764
18. Gu X, Guo T, Si Y, et al: Association between ambient air pollution and daily hospital admissions for depression in 75 Chinese cities. Am J Psychiatry 2020; 177:735–743
19. Bierer LM, Bader HN, Daskalakis NP, et al: Intergenerational effects of maternal Holocaust exposure on *FKBP5* methylation. Am J Psychiatry 2020; 177:744–753
20. Rappaport BI, Kandala S, Luby JL, et al: Brain reward system dysfunction in adolescence: current, cumulative, and developmental periods of depression. Am J Psychiatry 2020; 177:754–763
21. Forbes EE: Chasing the Holy Grail: developmentally informed research on frontostriatal reward circuitry in depression (editorial). Am J Psychiatry 2020; 177:660–662