New Insights Into Major Depression and the Treatment of Bipolar Depression

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Major depression is a common and often disabling illness with significant morbidity and mortality. In 2019, the 12-month prevalence of major depression in U.S. adults was estimated to be 7.8%, and in adolescents 15.7% (1). While children can also suffer from major depression, the peak prevalence of major depression occurs during adolescence and early adulthood. Major depression is frequently accompanied by comorbid anxiety symptoms and anxiety disorders, and when significant anxiety symptoms are present during preadolescence, they often precede the development of depression. For reasons that are not understood, women during their reproductive years have an approximately twofold increase in the incidence of major depression and anxiety disorders. Major depression also occurs in the context of bipolar disorder, and patients with bipolar disorder frequently experience one or more major depressive episodes before the onset of their first hypomanic or manic symptoms. Bipolar I disorder, characterized by recurrent manic and depressive episodes, is estimated to have a 12-month prevalence of 0.6% to 2.8% (2, 3). Bipolar II disorder, characterized by a history of a hypomanic episode without mania, along with depressive episodes, has an estimated 12-month prevalence of 0.8% (2). It should be noted that due to the difficulty in defining and recalling hypomanic symptoms, the estimated prevalence rates for bipolar II disorder may be less reliable. Patients with bipolar disorder and major depression, especially those who are untreated, are at high risk for suicide. For both disorders, the estimated lifetime risk of suicide for untreated patients is around 20% (4, 5). In part related to suicide but also due to medical comorbidities and other illness-related factors that impede medical care, patients with bipolar disorder and major depression are estimated to have an 8- to 12-year reduction in longevity (6, 7). There is a critical need for developing better treatments for these disorders, as many patients have inadequate responses, fail to respond at all, or cannot tolerate the side effects of current medications. Additionally, due to access issues and various other socioeconomic and cultural factors, many patients with major depression and bipolar disorder do not receive any treatment. For example, it is estimated that in 2019, 35% of adults and 57% of adolescents with major depression went untreated (1).

This issue of the *Journal* includes papers directly relevant to the treatment of depression and bipolar depression, as well as papers that provide insights into understanding structural brain alterations and inflammatory changes that are associated with depression. We begin this issue with an informative overview on neuromodulation strategies used for the treatment of depression (8). Coauthored by Dr. Susan Conroy from Indiana University and Dr. Paul Holtzheimer from Dartmouth, this article serves as a concise review specifically focusing on modalities such as electroconvulsive therapy (ECT), deep brain stimulation, vagal nerve stimulation, and repetitive transcranial magnetic stimulation (rTMS). Continuing the theme of neuromodulation, one of the research articles in this issue addresses the impact of ECT treatments on all-cause mortality and suicide when administered to elderly psychiatric inpatients. Another reports results from a randomized controlled trial assessing the efficacy of lumateperone, an antipsychotic medication approved for the treatment of schizophrenia, in treating major depression associated with bipolar I or bipolar II disorder. Regarding factors associated with the pathophysiology of depression, we include an article that characterizes inflammatory markers, such as C-reactive protein (CRP), as they relate to depression symptom profiles. We also present an article focused on structural brain alterations that reports data from a meta-analysis using coordinate-based network mapping to understand network-related involvement of brain regions in younger and older patients with major depression.

The findings reported in this issue of the *Journal* represent steps along the path toward developing a better understanding of depression, its heterogeneous presentations, and its treatment.

Finally, we conclude with three letters to the Editor (9–11) that raise some concerns related to a paper that was published in the *Journal* earlier this year that reviewed the evidence for the use of ketamine and esketamine in treatment-resistant depression (12). These editorials, along with the response by Dr. Roger McIntyre (13), provide a lively back-and-forth on various issues relevant to the use of ketamine and esketamine. The concerns that were brought up include questioning where ketamine fits into the sequence of treatments for treatment-resistant depression,

the importance of underscoring the abuse potential of ketamine, and the relative binding affinities of ketamine to mu opioid, NMDA, and kappa opioid receptors, since this may relate to ketamine's mechanisms of action.

ECT Outcomes in Older Inpatients: All-Cause Mortality and Suicide

ECT is a highly effective treatment that is primarily used for severe mood disorders. The paper by Rhee et al. (14) in this issue is of particular interest as it focuses on ECT treatment-related outcomes when administered to psychiatric inpatients 65 years of age or older. Motivated by the fact that mood disorders are associated with premature mortality due to suicide and medical causes, the authors' primary focus was to understand the extent to which ECT treatment has an impact on suicide and overall mortality rates in this age group. To accomplish this, data from 10,460 patients who received inpatient ECT were compared with data from 31,160 matched psychiatric inpatients who did not receive ECT. Of the patients treated with ECT, 82.9% received a minimum of five treatments over a 30-day period. Importantly, the researchers attempted to match the non-ECT-treated comparison participants as closely as possible to those participants receiving ECT. For example, the variables that were used to match participants in both groups included gender, age, number of injurious suicide attempts in the past year, number of psychiatric hospitalizations in the past year, principal psychiatric diagnosis, and medical mortality risk. Outcomes including suicide and death from other causes were assessed up to 1 year after hospitalization. The results demonstrated that patients treated with ECT had significantly less all-cause mortality during the follow-up year as compared with non-ECT-treated patients, and this effect was strongest for those individuals who received five or more ECT treatments (hazard ratio=0.56). It is interesting that the authors found that the ECT-treated patients were less likely to die from diseases related to the circulatory system, diabetes, smoking, substance use, and cancer. In contrast to effects on all-cause mortality, ECT treatment did not appear to significantly reduce suicides at the 1-year follow-up point but did have more short-lived effects that were only apparent up to 90 days after treatment. Taken together, these data add support to the therapeutic utility of ECT in older patients, address the broader benefits of ECT treatment on longevity in psychiatrically ill patients, and can serve as an alert to practitioners regarding the ongoing risk of suicide even in patients relatively recently treated with ECT.

Lumateperone Efficacy for Major Depression in Bipolar I and II Patients

Depressive episodes are common in individuals with bipolar I and bipolar II disorder and can be particularly difficult to treat. Treatment frequently involves optimizing the patient's mood stabilizer dosage as well as using other agents, such as second-generation antipsychotics and antidepressants. Metabolic issues and other side effects are a concern with long-term second-generation antipsychotic treatment, and the use of antidepressants has been associated with an induction of hypomanic or manic states. Calabrese et al. (15) report results from a phase 3 multisite double-blind study comparing the efficacy of the antipsychotic lumateperone to placebo. Lumateperone is approved for the treatment of schizophrenia and has numerous actions, including acting as an antagonist at the 5-HT_{2A} receptor, binding to D_1, D_2, and D_4 receptors, and some serotonin transporter inhibition. Patients meeting criteria for major depression with a history of bipolar I or bipolar II disorder were randomized to receive either lumateperone 42 mg/day or placebo for 6 weeks of treatment. Approximately 80% of the patients in the trial had bipolar I disorder. With change from baseline to 6 weeks on the Montgomery-Åsberg Depression Rating Scale (MADRS) as the primary outcome, the results demonstrated that lumateperone treatment was significantly more effective than placebo, an effect that was observed as early as day 8. Lumateperone treatment was also associated with significantly greater response rates (lumateperone: 51.1%; placebo: 36.7%) and remission rates (lumateperone: 39.9%; placebo: 33.5%). However, it should be noted that while significant, the actual difference in remission rates between the lumateperone and placebo groups was small. Additional separate analyses in the bipolar I and bipolar II subgroups revealed that at the end of the study there were greater reductions in MADRS scores in the lumateperone compared with the placebo group. Overall, lumateperone treatment was well tolerated, with nausea and somnolence being the most common adverse events. During the relatively short period of drug exposure, there were minimal effects on metabolic parameters and weight. In his editorial (16), Dr. Michael Ostacher from Stanford University provides perspective on the findings from this study in relation to other clinical trials performed with lumateperone and suggests caution in interpreting the findings related to the efficacy of lumateperone in the bipolar II group. This is based on issues related to the reliability of retrospectively diagnosing bipolar II, as well as the small number of bipolar II participants in the study. His editorial also provides a nice overview of the important issues related to treating bipolar depression, including the use of antidepressants.

Inflammatory Markers and Depression Symptom Profiles

Considerable work has implicated inflammatory processes in the pathogenesis of depression, and inflammatory processes have been suggested to contribute to the heterogeneity in the presentation of depressive symptoms and in its treatment responses. Frank et al. (17) use data from 56,351 individuals obtained from 15 population-based cohorts to examine the relation between peripheral inflammatory markers—CRP and interleukin-6—and individual differences in depressive symptoms. Depression and depressive symptoms

were assessed with validated self-report measures, resulting in the determination that 14% of the sample had elevated depressive symptoms. After controlling for numerous potential confounders, including socioeconomic status and chronic illness risk factors, CRP levels were found to be associated with four physical symptoms of depression (changes in appetite, felt everything was an effort, loss of energy, and sleep problems) as well as with difficulty concentrating and lack of interest or motivation. It is noteworthy that these findings remained significant when excluding individuals with very high CRP levels and those who were chronically medically ill. In contrast to the findings related to the physical symptoms of depression, no significant associations were found between emotion-related depressive symptoms and CRP levels. These findings point to a symptom-specific inflammatory presentation of depression and are generally consistent with the concept of "sickness behavior" commonly observed in medically ill individuals with high levels of inflammation. Another recent paper by Pitharouli et al. (18) also reported that CRP levels were significantly higher in depressed subjects when assessed in participants from the UK Biobank. Also, Pitharouli et al. found a positive association between polygenic risk scores for depression and CRP levels. However, this finding was no longer significant when controlling for BMI and smoking status, suggesting the possibility that the association between genetic risk and CRP levels could be mediated by unhealthy behaviors that are accentuated in some depressed patients. In his editorial, Dr. Carmine Pariante, from King's College London, reviews the findings and discusses them in the context of earlier reports of the inflammation-depression linkage (19). He further speculates that a subgroup of patients with high levels of inflammation and high levels of somatic symptoms might be particularly responsive to treatments directly targeting inflammatory processes.

Brain Structural Alterations in Major Depression in Young and Older Adults

Numerous studies have reported structural alterations that are associated with major depression. Zhukovsky et al. (20) use a meta-analytic mapping approach not only to identify structural alterations that are associated with major depressive disorder (MDD) but also to understand the extent to which there are differences between MDD in younger individuals compared with those with late-life depression (LLD). The term LLD is somewhat problematic because it can denote recurrent MDD beginning earlier in life and extending into later years, or it can refer to depression that initially presents as a first episode late in life. Presumably, this distinction is important when thinking about underlying pathophysiology, with late-onset depression hypothesized to be more related to age-related cerebrovascular changes. Therefore, the authors of this article attempted to understand differences in structural brain alterations that may be associated with these different presentations of LLD. In their meta-analyses, the authors included voxel-based and surface-based morphometry studies that compared MDD or LLD to control subjects. As their analytic strategy, they performed activation likelihood estimation (ALE) analyses, in which the likelihood of the convergence of regional cluster findings is assessed across different studies. They also performed coordinate-based network mapping, which moves away from specific regions, aiming to understand convergence across individuals in relation to involvement of known functional networks. In total, the data consisted of three groups: MDD (N=6,362 participants), LLD (N=535 participants), and control subjects (N=7,421 participants). Findings in MDD patients using the ALE analysis approach revealed structural differences in left and right medial temporal lobe regions and the ventral anterior cingulate cortex, including the subgenual anterior cingulate as well as regions of the striatum and insular cortex. In the LLD group, regions of the anterior cingulate and medial prefrontal cortex were found to significantly differ from control subjects. It is important to note that results from the coordinate-based network mapping analyses revealed findings that were not evident from the more traditional analysis. For example, the researchers found that MDD and LLD participants differed from control subjects in the connectivity of depression-related coordinates to various networks defined by functional connectivity, which included the frontoparietal control and dorsal attention networks. It also appeared that individuals with late-life-onset LLD had more extensive structural alterations in these networks when compared with participants with earlier onset, regardless of whether they went on to experience late-life depression. Taken together, the work presented in this paper confirms and extends previous findings pointing to regionally specific structural alterations associated with major depression and highlights the importance of using a network mapping approach as a more integrative analytic strategy. An important contribution of this study is the examination of structural alterations into late adulthood, providing some insights into differences in brain abnormalities associated with late versus earlier onset of depression. In their editorial, Drs. Joseph Taylor, Shan Siddiqi, and Michael Fox from Brigham and Women's Hospital at Harvard Medical School further explain the value of coordinate-based network analyses and discuss the potential for using these methods to understand symptom heterogeneity and in predicting effective treatment strategies (21).

Conclusions

While there are effective treatments for depression from which many individuals benefit, numerous patients fail to get better with our current treatments. The ultimate goal is to develop new neuroscientifically informed treatments that target underlying neurobiological processes linked to the pathophysiology of depression. In this regard, this issue of the *Journal* presents new research findings related to the treatment and understanding of major depression and

bipolar depression, as well as an overview of neuromodulation strategies currently in use, and in development, for the treatment of depression. Take-home points from the articles in this issue include 1) an appreciation for the various neuromodulation strategies—including accelerated rTMS and theta burst protocols—that can benefit depressed patients; 2) that in elderly patients followed for 1 year, ECT decreases all-cause mortality but only appears to reduce suicide risk for a briefer period (3 months) posttreatment; 3) how the antipsychotic medication lumateperone appears to be promising as an agent to treat major depression in patients with bipolar I and bipolar II disorder; 4) that inflammatory markers such as CRP are associated with the physical symptoms of depression, suggesting a depression subphenotype that may be characterized by high levels of inflammation; and 5) that network-related brain structural changes appear to be accentuated in depressed individuals with a late-life onset of their illness. Taken together, the findings reported in this issue of the *Journal* represent steps along the path toward developing a better understanding of depression, its heterogeneous presentations, and its treatment. Continued research focused on understanding mechanisms underlying the risk of developing depression as well as on mechanisms underlying antidepressant responses is critical for the development of novel treatment strategies.

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