Insights and Advances Into Treatments for Major Depression

Ned H. Kalin, M.D.

This issue of the *Journal* is broadly focused on mood disorders, with an emphasis on understanding how treatments for major depressive disorder may work and how the efficacy of current neuromodulation and antidepressant medication treatment strategies can be enhanced. The issue begins with an overview by Drs. Manish Jha and Sanjay Matthew on treatment-resistant depression (1); they focus on augmentation strategies with atypical antipsychotic medications as well as other new treatment strategies. This issue also includes 1) a study that starts to provide a genetic framework for understanding heterogeneity in bipolar disorder as characterized by the number of depressive and manic episodes an individual experiences; 2) the long-term relation, and interaction, between different degrees of alcohol use and depression; 3) a study that characterizes functional brain connectivity changes associated with treatment outcomes for cognitive behavioral therapy versus antidepressant medication; and 4) two studies aimed at optimizing treatment outcomes for depressed patients: one addressing the utility of using functionally defined dorsolateral prefrontal cortex coordinates for transcranial magnetic stimulation treatment, the other presenting clinical trial data assessing the efficacy of cariprazine as an adjunctive treatment to enhance antidepressant responses in patients with major depression.

Bipolar Illness Life Course Heterogeneity in Relation to Polygenic Risk Scores

At the individual level, there is marked heterogeneity in the life course of bipolar illness, as it is characterized by varying admixtures of depressive, manic, and mixed episodes. Hasseris et al. (2) use polygenic risk scores (PRS) for bipolar disorder, major depression, and schizophrenia to help understand the factors underlying this heterogeneity. For this analysis the investigators used data from a sample of 2,705 genotyped individuals drawn from the Integrative Psychiatric Research Case Cohort (iPSYCH2015) who were diagnosed with bipolar disorder at a hospital in Denmark. Individuals were included in the study if they had their first documented episode between 10 and 35 years of age, and the median age of follow-up was 5 years after initial diagnosis. As has been reported in other studies, PRS for bipolar disorder, major depression, and schizophrenia were significantly intercorrelated with each other. The authors also found that the bipolar and schizophrenia PRS were significantly correlated with an individual's number of affective episodes regardless of polarity. In relation to manic episodes, both bipolar and schizophrenia PRS were related to the number of episodes, whereas the depression PRS were associated with depressive and mixed episodes and negatively associated with manic episodes. The researchers also examined PRS in relation to psychotic symptoms and in these analyses found that the bipolar PRS were associated with both psychotic and nonpsychotic manic episodes, the schizophrenia PRS were only associated with psychotic manic episodes, and the major depression PRS were associated with a reduced likelihood of psychotic symptoms regardless of episode polarity. These findings are interesting because they begin to help explain the genetic differences that are related to the likelihood of experiencing depression, mania, and mixed episodes in the context of a life course of bipolar disorder. In an editorial (3), Dr. John Kelsoe from the University of California San Diego discusses the genetic findings from this paper in relation to other clinical and treatment outcome data that are associated with bipolar disorder heterogeneity. He also provides a valuable discussion on the use of PRS in psychiatry and their potential limitations.

Continued neuroscientific investigations linked with clinical translational efforts are imperative to deepen our understanding of the mechanisms underlying mood disorders with the hope of developing more effective treatments that are directly aimed at these mechanisms.

The Longitudinal Relationship Between Alcohol Use and Depressive Symptoms

Visontay et al. (4) use a large longitudinal database along with a statistical approach that allows for making assumptions related to causality to understand the association between different amounts of alcohol consumption and depressive symptoms. Data drawn from the National Longitudinal Survey of Youth 1979 came from 5,667 participants beginning at ages 29–37. Longitudinal data up until age 41–49 were

available from 3,593 of the participants. At different time points, participants' alcohol use was assessed and characterized as abstinent (no drinking), occasional consumption (less than 1 day/week; no heavy episodic drinking), moderate consumption (greater than or equal to 1 day/week with no more than seven drinks/week for women and no more than 14 drinks/week for men; no heavy episodic drinking), and consumption above guidelines (greater than or equal to 1 day/week and more than seven drinks/week for women and 14 drinks/week or more for men; and/or heavy episodic drinking). Depression symptoms were derived from the Centre for Epidemiological Studies-Depression Scale short form. Using analytic methods that incorporate marginal structural models, significant protective effects were observed for the consistent occasional and consistent moderate alcohol drinkers such that, compared with abstainers, they were likely to have lower depression scores at 50 years of age. In contrast, when compared with abstainers the consistent above-guideline drinkers were found to have nonsignificantly higher depression symptoms. Similar findings were observed when categorical analyses were performed in relation to the likelihood of individuals having syndromal depression. The authors point out that these findings are consistent with previous reports and with the statistical method used they assert that the results may provide support for a statistically based causal relation between different amounts of alcohol use and depression. Dr. Edward Nunes from Columbia University contributes an editorial (5) that further discusses the intertwined relation between depression and alcohol use and more specifically addresses the clinical relevance of the findings from this paper.

Functional Brain Changes Associated With the Successful Treatment of Depression With CBT or Antidepressants

Both antidepressants and cognitive behavioral therapy (CBT) are effective treatments for major depression and evidence supports that they are most effective when combined. While the specific mechanisms underlying the efficacy of these treatments are not understood, they are hypothesized to, in part, be due to the modification of different neural pathways. In this regard, Dunlop and colleagues (6) use resting-state functional MRI to assess brain changes associated with remission from major depression. A primary goal of the study was to compare changes in brain activity between psychotherapeutic and psychopharmacologic interventions. The study used resting-state functional connectivity (RSFC) data from 131 individuals collected at the beginning and end of a randomized clinical trial in which treatment-naive depressed patients received either 16 weeks of CBT, duloxetine 30–60 mg/day, or escitalopram 10–20 mg/day. Seed-based analyses were performed to assess RSFC using a posterior cingulate cortex seed for the default mode network, dorsolateral prefrontal cortex seed for the executive control network, anterior insular cortex seed for the salience network, and subgenual cingulate cortex seed for the affective network. Data from the two antidepressant medication treatment groups were combined in the analysis. First, shared brain changes in remitters were assessed across all treatment groups (N=64 of 131), and next data from antidepressant remitters (N=45 of 91) were compared with data from CBT remitters (N=19 of 40). Across both treatments, remitters (Hamilton Depression Score [HAM-D] $\leq$ 7), and nonresponders ($\geq$50% reduction HAM-D) demonstrated significantly decreased RSFC between the subgenual anterior cingulate and motor cortices. Numerous differential changes in RSFC were detected when comparing CBT with antidepressant medication remitters involving connectivity patterns of the executive control network, the affective network, and the salience network. For example, when using the dorsolateral prefrontal cortex as a seed, its connectivity with the left inferior parietal lobule increased in CBT remitters and decreased in antidepressant remitters. Likewise, when using the subgenual cingulate cortex seed, increased connectivity with the posterior insula was observed in the CBT responders, whereas decreased connectivity occurred in the antidepressant responders. In the discussion section, the authors emphasize the finding that CBT remitters, and not antidepressant remitters, showed increased connectivity between the executive control network and attention-related regions. In an editorial (7), Dr. Stephen Strakowski from Indiana University discusses the difficulties in replicating findings in studies of this nature and cautions the reader to consider the findings as preliminary. He also highlights the potential importance and veracity of the findings defining the functional brain changes that are associated with successful CBT treatment.

Assessing the Utility of Functional Connectivity Measures in Directing rTMS Targeting for Treating Depression

The subgenual anterior cingulate cortex (sgACC) serves as an integrative hub between regulatory prefrontal cortical regions and emotion-related limbic structures, such as the amygdala, and altered sgACC function has often been associated with depression. Furthermore, this region has also been used as a deep brain stimulation target for the treatment of refractory depression. In relation to repetitive transcranial magnetic stimulation (rTMS), a number of studies, yielding somewhat mixed results, have assessed the value of using negative functional connectivity measures between the left dorsolateral prefrontal cortex (dlPFC) stimulation site and sgACC as a means to improve rTMS targeting. Elbau et al. (8) present data from a large sample, 295 participants, with the goal of further understanding the extent to which individualized functional connectivity measures between the left dlPFC stimulation site and sgACC predict treatment outcomes. The resting functional MRI data used for the analyses came from a sample of individuals with treatment-resistant depression that previously participated in a noninferiority

clinical trial designed to compare 10Hz rTMS to theta burst TMS (9). It is important to note that the same neuroanatomical coordinates for the left dlPFC TMS stimulation site were used across all the subjects, and this was based on neuroanatomical coordinates from an earlier study that linked functional connectivity measures to optimal outcomes. In other treatment studies, individualized dlPFC stimulation sites are selected based on the dlPFC region that is most negatively functionally coupled to sgACC (10). The current study is distinguished by its large sample, and the thorough analytic approach that was used, which included electric field modeling to estimate the actual subregions of dlPFC in which electrical changes were induced. The authors found that pretreatment individual differences in negative functional coupling between the dlPFC stimulation site and sgACC accounted for 3% of the variance in treatment outcomes. While this is a considerably smaller effect than previously reported, it is important to consider that the method used here did not prospectively select the dlPFC site that was most functionally connected with sgACC. It is interesting that the strongest effects for the predictive value of the functional coupling between the stimulation site and sgACC were found to be in a subgroup of patients that had a distinct breathing pattern characterized as "burst breathing." Burst breathing, which is associated with a pattern of BOLD signal fluctuations across the brain, also has distinct impacts on resting connectivity that differ from individuals that typically engage in other forms of breathing such as deep breathing (11). In their editorial (12), Dr. Noah Phillips from Brown University and Dr. Shan Siddiqi from Harvard Medical School discuss this finding in relation to earlier work and comment on important methodological issues as they relate to the small but significant predictive effect that was observed.

A Double-Blind Randomized Clinical Trial Assessing the Efficacy of Cariprazine as an Adjunctive Treatment for Major Depression

Sachs and colleagues (13) report data from a Phase III study that is aimed at assessing the extent to which cariprazine is an effective add-on treatment for individuals with major depression that have not responded to their current treatment. This study builds on earlier studies with cariprazine and on studies demonstrating the efficacy of other atypical antipsychotic medications as adjunctive treatments for major depressive disorder, some of which have received FDA approval (i.e., aripiprazole, quetiapine, and brexpiprazole). Cariprazine was also recently approved by the FDA as an adjunctive treatment for major depression and is also approved for treating schizophrenia and bipolar disorder (mania, depression, and mixed). Cariprazine has multiple neurochemical effects, including acting as a partial agonist at the D_3, D_2, and 5-$HT1_A$ receptors with highest selectivity for D_3. It also acts as a 5-HT_{2B} and 5-HT_{2A} partial antagonist. In this 6-week, double-blind study, patients with major depression remained on their antidepressant treatment and also received either placebo, cariprazine 1.5 mg/day, or cariprazine 1.5 mg for 2 weeks and then increased to 3 mg/day. A total of 751 patients were included in the modified intention-to-treat analysis. In relation to the primary outcome measure, change in Montgomery-Asberg Depression Rating Scale (MADRS), cariprazine 1.5mg/d resulted in significantly greater decreases when compared with placebo; however the effects of the 3.0 mg/day dose were not statistically significant. The effect of the 1.5 mg/day dose was found to be significant after 2 weeks of drug administration. Change in the Clinical Global Inventory scale was used as the secondary outcome measure and while both doses of cariprazine were associated with greater reductions than placebo, neither reached statistical significance. Regarding response and remission rates, the 1.5-mg dose of cariprazine demonstrated significantly greater response rates compared with placebo (≥50% MADRS reduction: cariprazine=44.0%, placebo=34.9%) whereas no significant differences were found for remission rates (MADRS≤10: 25.2% versus 23.3%, respectively. Among the side effects, the cariprazine-treated patients experienced more akathisia (3mg group– 7.9%, 1.5mg group −5.2% compared to placebo group-0.8%). In an editorial (14), Dr. Michael Thase from the University of Pennsylvania discusses the specific findings related to cariprazine as well as the overall utility of second-generation antipsychotics in treating depression.

Conclusions

Major depression is very common with profound deleterious consequences at individual and societal levels in terms of suffering, disability, increased medical morbidity and mortality, and suicide. We clearly need better treatments for major depression as our current treatments are ineffective or intolerable for numerous individuals. This issue of the *Journal* brings together papers that are focused on how we can better understand mood disorders and improve the efficacy of our treatments. From these papers we learn: 1) by using polygenic risks scores we can begin to understand the heterogeneity in the course of bipolar disorder; 2) that moderate alcohol intake may be associated with a decreased risk of depression whereas the opposite may be the case with excessive alcohol use; 3) that remission in depressed patients treated with CBT or antidepressants is associated with shared and distinct patterns of treatment-associated change in functional connectivity between specific brain networks; 4) the value of using functional connectivity measures between the dlPFC and sgACC to predict and enhance rTMS treatment outcomes; and 5) the potential efficacy of adjunctive cariprazine treatment, in addition to other atypical antipsychotic medications, for patients not responding to their antidepressant treatment.

The papers in this issue of the *Journal* are helping to move us in the direction of improving our interventions for depression by building on and attempting to optimize existing

treatment strategies. Continued neuroscientific investigations linked with clinical translational efforts are imperative to deepen our understanding of the mechanisms underlying mood disorders with the hope of developing more effective treatments that are directly aimed at these mechanisms.

AUTHOR AND ARTICLE INFORMATION

Department of Psychiatry, University of Wisconsin School of Medicine and Public Health, Madison.

Send correspondence to Dr. Kalin (nkalin@wisc.edu).

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