Introduction

Diego A. Pizzagalli, PhD
Special Issue Editor

Emerging from a tumultuous breakup from her long-term partner, Jane has been having increasing difficulty sleeping, which has led to substantial fatigue during the day and difficulty concentrating at work. Facing financial pressures (including the need to pay rent without her partner's co-payment), she has been driving for a rideshare service after work and over the weekends, leaving no time for exercise and pursuing hobbies. With a compressed schedule, she often finds herself eating fast food between rides. When Jane's mood begins to deteriorate and rumination dominates her thinking, she contacts her primary care provider, who recommends that she starts the same selective serotonin reuptake inhibitor (SSRI) that she took when she experienced two prior major depressive episodes (including a first episode in adolescence, after a period of prolonged sexual harassment). As it happens, however, Jane's current depressive episode is markedly different from her prior ones. Over several weeks, she feels no pleasure, and her motivation to see friends and pursue hobbies is virtually absent. Her sleep continues to be disrupted, leading to extreme physical and mental fatigue throughout the day; unable to get up from bed, she has started to call in sick at work, which causes additional tension with her supervisor. Jane's asthma symptoms, which had been in check for years, reemerge, and she constantly feels sick. Exercising is all but impossible. Jane feels hopeless and ashamed that, despite her college degree, she is losing her financial independence; her parents ultimately have to step in to pay her rent. Alarmed by her apathy, her lack of engagement with the environment, and her increasingly significant weight loss, Jane's parents urge her to discuss different treatment options with a psychiatrist: the SSRI she has been taking over the past 12 weeks is clearly not working. Reluctantly, Jane makes an appointment to see a psychiatrist.

Jane is a fictive patient, but her case and presentation are all too familiar. An individual with a putative vulnerability to depression, as manifested by two prior episodes of major depressive disorder (MDD), starts to reexperience symptoms following several life stressors. Financial hardships compound the problem, leading to additional changes in daily activities—prominently including the ability to concentrate and perform at work, to exercise, and to maintain a healthy diet. Signs of increased inflammation (asthma and sickness syndrome) emerge; profound anhedonia (loss of pleasure) and amotivation dominate her current episode. How should Jane be treated? What advances in understanding the etiology, pathophysiology, and treatment of MDD can we bring to bear when trying to select a better treatment for her? More broadly, can advances in technology and neuroscience make a difference for the many depressed patients seeking help?

The current special issue of the *Harvard Review of Psychiatry* focuses on efforts to harness biology and technology to develop the next generation of treatments for depression. The issue is specifically designed to provide some answers to these challenging questions, to evaluate cross-disciplinary trends in depression research, and to highlight major gaps in our understanding of this common disorder.

The special issue starts with a wide-ranging review by Hyde and Mezulis,[1] "Gender Differences in Depression: Biological, Affective, Cognitive, and Sociocultural Factors," which summarizes epidemiological evidence indicating that, by age 12, the prevalence of MDD starts to diverge between the sexes, with MDD being twice as prevalent in girls as in boys. Within the conceptual framework of the affective, biological, cognitive (ABC) model of gender differences in depression, these authors discuss key factors contributing to this marked difference in prevalence. Among biological factors, pubertal hormones and early pubertal timing have emerged as important contributors, whereas genetic markers of sex differences have not been consistently replicated; however, Hyde and Mezulis correctly note that the effect of "sex" has not been formally integrated in genome-wide association studies of depression, highlighting an important future direction. Among affective vulnerabilities, negative emotionality has attracted significant attention. Finally, a negative cognitive style, including negative cognitions about the body and (as in Jane's case) rumination, has emerged as an important contributor to sex differences in MDD. A particularly clear set of points to emerge from this review is that each risk factor explains a relatively small amount of variance but that the effects of these risk factors are amplified by stressors, both distal (e.g., childhood sexual abuse) and proximal (e.g., ongoing peer sexual harassment). Sex differences in prevalence require our full attention, and a critical deliverable for this line of research is to foster the development of evidence-based treatments optimized for girls and women.

As in our fictive case study, many individuals receiving evidence-based treatments for MDD do not respond to them.[2] Moreover, as in Jane's case, loss of pleasure (anhedonia) or

DOI: 10.1097/HRP.0000000000000244

motivation is often poorly addressed by current first-line interventions. This deficiency is highly problematic because anhedonia has been linked to poor disease course and increased risk of suicide.[3] In "Using Neuroscience to Augment Behavioral Interventions for Depression," Vinograd and Craske[4] provide an integrative review of emerging "neuroscience-based augmentation strategies" designed to target anhedonia as well as attentional, interpretative, and cognitive biases. With respect to anhedonia, these treatment modules reflect modern, neuroscientific conceptualizations of reward-processing subcomponents. For example, the *positive affect treatment* developed by these authors aims to increase positive affect by targeting deficits in motivation, reward attainment, and reward learning—three key subdomains in the *positive valence system* described in the National Institute of Mental Health Research Domain Criteria (RDoC) initiative.[5] Notably, in the first randomized clinical trial, individuals who received the positive affect treatment (vs. a treatment targeting negative affect) showed greater improvements in positive (and negative) affect post-treatment, as well as weaker depressive symptoms, less suicidal ideation, and reduced stress at six-month follow-up.[6] A key priority for future studies will be to identify moderators and mediators of treatment response, which could help identify individuals who might preferentially benefit from this type of intervention.

Poor sleep and eating patterns, excessive stress, and insufficient exercise likely contribute to the pervasive fatigue and anhedonia that affected Jane, as well as to the increased inflammation that exacerbated her asthma. This suggests a possible interplay between the gut and brain in the etiopathology of illnesses. Indeed, growing preclinical and clinical data reflect an increasing appreciation of the role of the microbiome–gut–brain axis in the emergence and maintenance of MDD. In their cross-disciplinary review, "Gutted! Unravelling the Role of the Microbiome in Major Depressive Disorder" Bastiaanssen, Cryan, and colleagues[7] examine bidirectional gut–brain interactions, including mounting evidence of an abnormal microbiome in MDD and the potential role of the microbiome in treatments. Although much remains unclear, the available evidence suggests that an abnormal microbiome increases risk for MDD through various mechanisms, including negative effects on immune responses, the reactivity of stress-sensitive brain circuities (e.g., the hypothalamic–pituitary–adrenal axis), and the synthesis and metabolism of neurotransmitters. Many of the hypotheses in this field are ripe for testing. For example, diets characterized by high consumption of anti-inflammatory foods, such as a Mediterranean diet involving high consumption of fibers and fish, may help shorten depressive episodes.[8,9] As cogently discussed by Bastiaanssen and colleagues, an exciting and important goal for future work is to determine whether targeting the microbiome can improve responses to first-line treatments.

In their comprehensive review, "Novel Targets to Treat Depression: Opioid-Based Therapeutics," Browne, Jacobson, and Lucki[10] present compelling preclinical and clinical evidence pointing to abnormal opioid signaling in the pathophysiology of MDD. These emerging findings are important since, as in Jane's case, a disturbingly high number of individuals with MDD do not respond to the currently available, evidence-based pharmacological treatments for MDD (e.g., SSRIs). Equally important, initial evidence indicates that opioid mechanisms are implicated in rapid antidepressant responses, which would be an additional benefit considering that two to three weeks are needed to evaluate whether "traditional" antidepressants will bring benefits. Collectively, the burgeoning literature integrated by Browne and colleagues suggests that targeting opioid receptors—including delta, kappa, and mu receptors, as well as the incompletely understood nociceptin/orphanin FQ receptor—might yield new avenues for treating MDD and other stress-related disorders.

Finally, in their column, "Technology in the Assessment, Treatment and Management of Depression," Bader, Skurla, and Vahia[11] make a compelling case for harnessing technology—wearables, natural language processing, global positioning systems, and ecological momentary assessment, to name a few—to provide a deeper phenotypic understanding of MDD. In their commentary, they highlight how each symptom of MDD can be objectively quantified by specific technology. In Jane's case, GPS data might have revealed that, when not working, she was exclusively at home, perhaps a sign of loss of engagement in social activities. A wearable with actigraphy would have highlighted disrupted sleep but also constricted movement during the day—a possible sign of psychomotor retardation and fatigue. Most importantly, Bader and colleagues discuss how this approach could profoundly affect diagnosis and treatment of MDD by providing precise assessments of abnormalities in real time and at the level of individual patients.

MDD is a prevalent and recurrent disorder that often emerges during adolescence and that carries profound personal and societal costs. Available evidence-based treatments—including pharmacology and psychotherapy—are tremendously helpful for many depressed individuals. However, since an unacceptably high proportion of patients receiving these treatments experience no benefits, there remains an acute need for novel conceptualizations of depressive pathophysiology and for new, better treatments. The articles in this special issue indicate that by embracing a multifactorial understanding of MDD, by attending carefully to the sex difference in its prevalence and manifestation, and by harnessing new technology, we should be increasingly able to prevent and treat depression. Jane and other patients like her need such breakthroughs, and it is our responsibility as researchers and clinicians to do our utmost to deliver them.

REFERENCES

1. Hyde JS, Mezulis AH. Gender differences in depression: biological, affective, cognitive, and sociocultural factors. Harv Rev Psychiatry 2020;28:4–13.
2. Cuijpers P, Karyotaki E, Weitz E, Andersson G, Hollon SD, Van Straten A. The effects of psychotherapies for major depression in adults on remission, recovery and improvement: a meta-analysis. J Affect Disord 2014;159:118–26.
3. Pizzagalli DA. Depression, stress, and anhedonia: toward a synthesis and integrated model. Annu Rev Clin Psychol 2014;10:393–423.
4. Vinograd M, Craske MG. Using neuroscience to augment behavioral interventions for depression. Harv Rev Psychiatry 2020;28:14–25.
5. Insel T, Cuthbert B, Garvey M, et al. Research domain criteria (RDoC): toward a new classification framework for research on mental disorders. Am J Psychiatry 2010;167:748–51.
6. Craske MG, Meuret AE, Ritz T, Treanor M, Dour H, Rosenfield D. Positive affect treatment for depression and anxiety: a randomized clinical trial for a core feature of anhedonia. J Consult Clin Psychol 2019;87:457–71.
7. Bastiaanssen TFS, MSc, Cussotto S, Claesson MJ, et al. Gutted! Unravelling the role of the microbiome in major depressive disorder. Harv Rev Psychiatry 2020;28:26-39.
8. Garcia-Mantrana I, Selma-Royo M, Alcantara C, Collado MC. Shifts on gut microbiota associated to Mediterranean diet adherence and specific dietary intakes on general adult population. Front Microbiol 2018;9:890.
9. Lassale C, Batty GD, Baghdadli A, et al. Healthy dietary indices and risk of depressive outcomes: a systematic review and meta-analysis of observational studies. Mol Psychiatry 2019;24:965–86.
10. Browne DA, Jacobson JL, Lucki I. Novel targets to treat depression: opioid-based therapeutics. Harv Rev Psychiatry 2020;28:40–59.
11. Bader CS, MD, Skurla M, Vahia IV. Technology in the assessment, treatment, and management of depression. Harv Rev Psychiatry 2020;28:60–66.