

Mood Disorders in the Twenty-First Century

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Introduction

Mood disorders are among the most prevalent and potentially severe psychiatric disorders. In the case of major depressive disorder (MDD), despite great geographical variations, data from the World Health Organization point to approximately a 6% 12-month prevalence and a 20% lifetime prevalence [1]. With regard to bipolar disorders (BD), epidemiological findings indicate a lifetime prevalence of 0.6% for bipolar type I and 0.4% for bipolar type II, with a 2.4% prevalence when all bipolar spectrum conditions are considered [2]. In addition to their significant impact on functional status and quality of life, mood disorders are associated with considerable psychological suffering and elevated rates of suicide [3]. Moreover, available evidence shows association between mood disorders and an increased risk for different medical conditions, including cardiovascular disease, diabetes, metabolic disorders, obesity, dyslipidemia, hypertension, and dementia [4,5].

Considering all these potential implications of mood disorders for individuals, families, and communities, their early diagnosis and effective management are essential. Researchers have strived to better understand the pathophysiology of these conditions and to identify predictive factors related to response to treatment and outcome [6]. Nevertheless, despite important advances in the management of mood disorders, studies estimate that the currently available antidepressant treatments may be ineffective in 30–50% of patients with MDD [7–9].

In light of these limitations, as well as the complexity of society in the twenty-first century, which can make the management of mental disorders particularly challenging, a personalized approach for the treatment of mood disorders is highly desirable [10]. Multidisciplinary collaborations, including the combination of pharmacotherapy with different psychosocial interventions, are strongly recommended.

Diagnostic Aspects

A fundamental limitation of the currently adopted diagnostic systems is related to the inexistence of established biological markers for the different psychiatric conditions. Consequently, the diagnosis of mood disorders is based mostly on the presence of certain criteria, usually comprised by certain core symptoms and specific history data. The *Diagnostic and Statistical Manual of Mental Disorders* (DSM), currently in its fifth edition (DSM-5), is the best example of such approach.

While these systems usually offer a good degree of diagnostic reliability, they may face problems in contemplating the considerable phenotypical overlap found across different types of mood disorders. Alternative diagnostic formulations, utilizing a dimensional approach in contrast to the standard categorical diagnostic systems, try to take these limitations into consideration. These approaches are based on the idea of a continuum across different mood disorders, being aware of not only clinical but also biological factors shared by different mood disorders.

It is expected that these diagnostic and nosological limitations will be overcome by the identification of validated biomarkers for mood disorders. Based on neurobiological and genetic findings, biomarkers will allow the integration of neuroscience into psychiatric diagnostic practice. By routinely incorporating data on biomarkers, future diagnostic systems should allow the integration of clinical, etiological, and pathophysiological factors, improving our diagnostic accuracy and having the potential to revolutionize the practice of psychiatry.

Depressive Disorders

The impact of depression on individuals' lives results from a combination of genetic vulnerability and

environmental risk factors [11,12]. While the biological mechanisms behind depressive disorders are not yet completely understood, they seem to involve the hypothalamic–pituitary–adrenal (HPA) axis, genetic and neurodevelopmental factors, monoaminergic deficiencies, and other possible mechanisms [13], such as alteration of the intestinal microbiota [14,15].

The influence of stress on the pathophysiology of depression is well known [16,17]. Many depressive patients experience disturbances in the regulation of the HPA axis, and these dysfunctions are often reflected in changes in cortisol concentrations in blood and saliva [18,19].

Similarly, abnormalities involving the gut microbiota and the bidirectional communication of the intestine–brain axis [20] have been found to be involved in the pathophysiology of depression. Changes in the composition of the intestinal microbiota, due to factors such as age, diet, stress, use of antibiotics, prebiotics and probiotics, immune status, and intestinal transit [15,21] may result in intestinal dysbiosis, which shows important correlations with depression and other mental disorders [15,22]. Numerous authors recognize this bidirectional gut–brain communication via the autonomic nervous system (ANS), enteric nervous system (ENS), and neuroendocrine and immune systems [23,24].

Approximately 50% of individuals who receive treatment for a depressive episode will experience a second episode over their lifetime, usually within 5 years, with a lifetime average of four depressive episodes [25,26]. Moreover, it is estimated that 30 to 50% of depressed patients do not achieve full remission [9,27], and patients with depression may have persistent and severe psychosocial and occupational impairments, even after recovery from an acute episode [28].

Last, as previously mentioned, suicide rates are elevated among individuals with depression. In the National Comorbidity Survey Replication, the risk of suicide attempts in MDD was found to be fivefold higher than in the general population in the United States [29].

Bipolar Disorders

Despite numerous advances observed in the last several decades with regards to the understanding of bipolar disorder (BD), its underlying neurobiological mechanisms remain far from being fully elucidated [30]. This results in several limitations involving its

diagnosis and treatment, especially with regard to depressive symptoms or episodes.

That is complicated by the fact that approximately 35% of patients with bipolar disorder experience a delay of up to 10 years between symptom onset and the correct diagnosis. Even though BD is typically characterized by alternating periods of depression with symptoms of mania or hypomania, depression is usually the main reason patients with BD seek treatment [31]. Thus, the misdiagnosis of BD as MDD is common, causing delays in the implementation of the most appropriate therapeutic measures [32].

Currently available treatment options for bipolar disorder are often insufficient to help patients achieve full remission and restore their premorbid functioning. However, in the past few years, we have witnessed a more wide-ranging understanding of the neural circuits and the various mechanisms of synaptic and neural plasticity, the molecular mechanisms of receptors, and the process by which genes code for specific functional proteins [33,34]. It is expected that these advances will help in the identification of novel therapeutic targets.

Moreover, while pharmacological treatment is considered essential for the management of this condition, a growing amount of evidence has emphasized the importance of nonpharmacological interventions, such as psychoeducation and different psychotherapy modalities, in improving patients' understanding of their illness and their treatment adherence, as well as helping with the identification of prodromal symptoms and early signs of relapse, providing family support, and offering psychosocial rehabilitation [35].

Mood Disorders, Neuroimaging, and Cognition

Cognitive deficits in patients with depression and BD have been the object of great interest, given their importance from a functional and psychopathological perspective [36]. Neuroimaging studies point to the involvement of dysfunctions in neural networks connecting the limbic system and cortical regions in the pathophysiology of mood symptoms and cognitive impairment [37,38]. Areas involved in the pathophysiology of cognitive dysfunction in depression include regions of the prefrontal cortex, cingulate cortex, hippocampus, striatum, amygdala, and thalamus [39].

For example, the neocortex and hippocampus collaborate by mediating cognitive aspects of depression, such as guilt, impaired working memory, feelings of worthlessness, and suicidal ideation. On the other hand, interactions between the amygdala and the hippocampus can mediate anhedonia, anxiety, and loss of motivation, in addition to mnemonic changes [40]. Naturally, these identified regions act in coordination with other parallel circuits, possibly forming a neural network underlying depression [39,41–43].

Within this perspective, cognitive impairments in depression may result from high levels of cortisol resulting from stressful situations or dysfunctions in the HPA axis. In response to the prolonged action of stress, the organism passes from a slower conscious control of the top-down type regulated by cognitive processes and memory to an emotional control of the bottom-up type, which is faster and reflexive and related to the amygdala and subcortical structures [44].

Depression has been linked to deficits in a wide variety of cognitive domains. During depressive episodes, the most well-known cognitive deficits are a decrease in performance in tasks involving a change of attention focus, memory impairment, and problems related to executive function [45,46]. In addition, studies have demonstrated the effects of mood disorders and stress on global cognitive performance [47,48], executive functioning [49,50], and memory [51–54], in addition to reward processing, processing of social and affective stimuli, and emotional regulation [55].

Studies investigating cognitive deficits in depressive patients have reported results similar to those with participants who suffered early stress, either in global cognitive performance [45], in executive functions [56–57], and memory [58]. Thus, the cognitive impairments that result from depression may overlap with deficits related to early stress. Therefore, authors must be aware of depression as a factor to be included in the analysis of the effects of early stress on cognition [59].

Biomarkers and Pathophysiology

The search for biological markers in psychiatry has proved arduous and somewhat thankless. According to the FDA-NIH Biomarker Working Group, a biological marker is “a defining characteristic that is measured as an indicator of normal biological processes, pathogenic processes or responses to an exposure or intervention” [60]; however, in clinical practice, a good biomarker must have high reproducibility, that

is, be present in the vast majority of patients with the same disease, and ideally be dynamically and reliably modified as the clinical picture progresses [61]. Unfortunately, these definitions determine biological markers for psychiatric diseases to be almost unobtainable, given the high rates of comorbidity between different conditions and the fact that dysfunctions in the same neural circuits seem to be involved in the pathophysiology of different mental disorders. Moreover, when discussing biomarkers, it is necessary to consider the importance of genetic polymorphisms and the fact that gene expression can be influenced by different factors and regulatory processes. Therefore, not only gene–gene but also gene–stress interactions are likely to play a cumulative role in the predisposition to mood disorders.

For example, evidence suggests that changes in the hormonal system from stress can induce distortions of thinking and memory and worsen depressive symptoms and bipolar disorder [62]. These abnormalities appear to be related to changes in the ability of circulating glucocorticoids to exert their negative feedback on the secretion of HPA axis hormones by binding to mineralocorticoid (MR) and glucocorticoid (GR) receptors in HPA tissues [63]. MR receptors in the brain are involved in regulating stress hormone secretion and complex behaviors such as emotion, memory, and sleep. In humans, the role of MR and GR receptors in the pathophysiology of stress-related psychiatric disorders has not yet been sufficiently characterized. However, studies indicate possibilities for new pharmacotherapies via modulation of the function of these receptors [64].

Furthermore, a growing body of evidence suggests that chronic inflammation and oxidative stress are involved in both the pathogenesis and progression of mood disorders, especially bipolar disorders [65], bringing about cellular dysfunction and, eventually, neuronal death. Changes in glutamatergic neurotransmission might represent the downstream effects of these processes, given the prominent role of glutamate in excitotoxicity – overstimulation of neurons via increased intracellular calcium, resulting in cell death [66].

Last, changes in brain maturation follow a trajectory of development throughout life [67]. Any environmental events generating inappropriate stimulation could alter neurotransmitters, neuroendocrine hormones, and neurotrophic factors crucial for normal brain development and precipitate affective conditions such as depression and bipolar disorder [68,69]. Early

stress may impact the development of brain structures [70]. Among the neural systems most frequently implicated in the relationship between early stress and depression, those whose development is completed during childhood and adolescence, such as the amygdala, prefrontal cortex, and hippocampus, are of particular relevance [71].

In summary, pathophysiological research in mood disorders has moved from the classic monoaminergic theory of depression to more dynamic pathophysiological models emphasizing different levels of disruptions (genetic, neurodevelopmental, physiological, neuroanatomical/neurofunctional, and biochemical). Nonetheless, despite the strong evidence supporting the role of neurobiological abnormalities in the pathophysiology of mood disorders, a unified understanding of how these different abnormalities lead to the development of clinical mood symptoms is still missing.

Treatment

Given the complexity of mood disorders, the variability of characteristics of their clinical forms, and their course among patients, no single treatment or combination of treatments is ideal for all patients. However, appropriate treatment can drastically reduce the functional disability and high mortality associated with the disorder [35].

Diverse therapeutic approaches have been used to treat mood disorders, including medications, neurostimulation treatments, and different psychotherapy modalities [72]. While the selection of suitable pharmacological treatment is decisive for reaching a therapeutic response [73,74], the effectiveness of psychopharmacology is also considered modest in parts due to the low adherence rate (30%) to psychopharmacological agents [72]. Although contemporary pharmacological agents have revolutionized the treatment of mood disorders, long-term outcomes for many patients remain modest [9,75–77]. Therefore, exploring new therapeutic targets for mood disorders is a priority for translational research, with an urgent need for the identification of more effective treatments and the better characterization of treatment guidelines for the management of MDD and BD.

In the case of depression, although the concept of difficult-to-treat depression (DTD) helps to reframe binary definitions of treatment-resistant depression (TRD) and assess response to other treatment modalities [78], therapeutic options remain limited for

individuals who do not respond to conventional biopsychosocial interventions. Traditionally, neurostimulation has been considered an effective strategy for those with DTD. The estimated response rate to electroconvulsive therapy (ECT) in DTD surpasses 50%, making it one of the most effective treatments in psychiatry [79,80]. Nevertheless, there is a trend toward decreasing the use of this effective treatment. That may be explained by the public stigma around ECT, given its historical misuse and concerns about cognitive complications [81]. Although better accepted, other neurostimulation options, such as transcranial magnetic stimulation (TMS), lack the comparative efficacy and require more prolonged treatment courses [82].

Furthermore, over the past 20 years, a large body of evidence has demonstrated the effects of ketamine as a rapid-acting and effective antidepressant, even in those who have failed to respond to previous treatments [83]. Despite being a novel treatment within psychiatry, ketamine has long been used in medical settings as an anesthetic due to its ability to provide conscious sedation with lower risks of hypotension and respiratory depression compared to other induction agents [84]. Sharp declines in suicidal ideation have been reported in association with quick improvements in mood among acutely depressed patients receiving ketamine, corroborating its potential as a valuable acute psychiatric treatment [85]. As the clinical response from ketamine continues to be clarified, research exploring its underlying neurobiological mechanisms has provided new perspectives on the pathophysiology of depression. Ketamine's antidepressant functions are largely explained through its actions as a noncompetitive antagonist of *N*-methyl-D-aspartate (NMDA) receptors. NMDA receptors have multiple neuronal loci, and thus, many mutually inclusive molecular pathways have been implicated [86–88].

Considering the variable response to available treatments, a more personalized approach to the management of mood disorders is of great interest. Thus, pharmacogenetics represents a promising tool for the individualization of pharmacological treatment [89]. Therapeutic response, tolerability, and recurrence are some of the outcomes that can be affected by genetic differences between individuals [74,90,91]. Genetic variants account for 42% of individual differences in antidepressant response [92]. The incorporation of pharmacogenetic tests in clinical practice might increase remission rates and response in TRD patients [93,94], in addition to decreasing healthcare costs and

polypharmacy [94,95]. In the UK, the promising results obtained in several studies are compiled by the Clinical Pharmacogenetics Implementation Consortium (CPIC) and Pharmacogenomics Knowledge Base (PharmGKB), which resulted in the development of pharmacogenetic-informed antidepressant guidelines [96–98].

Conclusion

The beginning of the twenty-first century seems to be an era likely to see an essential integration of concepts and knowledge. The full understanding of the pathophysiological pathways involved in the development of mood disorders is of pivotal importance for the development of more precise, biomarker-based diagnostic systems and more effective biological treatments. The concept of neuroprogression in mood disorders supports the need for neuroprotection with biological properties. On the other hand, psychosocial interventions for the treatment of mood disorders are of great importance and a better characterization of their therapeutic role, alone and in combination with biological treatments, is essential. By better understanding, these interactions and their relevance to mood disorders, better treatments and, ultimately, better outcomes for individuals with depression and bipolar affective disorder will be achieved.

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