Chapter 1

Mood Disorders in the Twenty-First Century

Allan Young, Marsal Sanches, Jair C. Soares, and Mario Juruena

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

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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].

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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

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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

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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.

References

1. E. Bromet, L. H. Andrade, I. Hwang, et al. Cross-national epidemiology of DSM-IV major depressive episode. *BMC Med*. 2011;**9**:90. https://doi.org/10.1186/1741-7015-9-90.
2. K. R. Merikangas, R. Jin, J.-P. He, et al. Prevalence and correlates of bipolar spectrum disorder in the World Mental Health Survey Initiative. *Arch Gen Psychiatry*. 2011;**68**:241. https://doi.org/10.1001/archgenpsychiatry.2011.12.
3. B. Gaynes. Assessing the risk factors for difficult-to-treat depression and treatment-resistant depression. *J Clin Psychiatry*. 2016;**77**(Suppl 1):4–8. https://doi.org/10.4088/JCP.14077su1c.01.
4. K. B. Wells. The functioning and well-being of depressed patients. Results from the Medical Outcomes Study. *JAMA*. 1989;**262**:914–19. https://doi.org/10.1001/jama.262.7.914.
5. A. Danese, T. E. Moffitt, H. Harrington, et al. Adverse childhood experiences and adult risk factors for age-related disease: depression, inflammation, and clustering of metabolic risk markers. *Arch Pediatr Adolesc Med*. 2009;**163**: 1135–43. https://doi.org/10.1001/archpediatrics.2009.214.
6. A. Cleare, C. M. Pariante, A. H. Young, et al.; Members of the Consensus Meeting. Evidence-based guidelines for treating depressive disorders with antidepressants: a revision of the 2008 British Association for Psychopharmacology guidelines. *J Psychopharmacol*. 2015;**29**:459–525. https://doi.org/10.1177/0269881115581093.
7. M. Fava. Diagnosis and definition of treatment-resistant depression. *Biol Psychiatry*. 2003;**53**:649–59. https://doi.org/10.1016/s0006-3223(03)00231-2.
8. D. Souery, P. Oswald, I. Massat, et al.; Group for the Study of Resistant Depression. Clinical factors associated with treatment resistance in major depressive disorder: results from a European multicenter study. *J Psychiatry*. 2007;**68**:1062–70. https://doi.org/10.4088/jcp.v68n0713.
9. A. J. Rush, M. H. Trivedi, S. R. Wisniewski, et al. Acute and longer-term outcomes in depressed outpatients requiring one or several treatment steps: a STAR* D report. *Am J Psychiatry*. 2006;**163**:1905–17.
10. A. H. Young, M. F. Juruena. The neurobiology of bipolar disorder. *Curr Top Behav Neurosci*. 2021;**48**:1–20. https://doi.org/10.1007/7854_2020_179.
11. S. R. Dube, R. F. Anda, V. J. Felitti, et al. Childhood abuse, household dysfunction, and the risk of attempted suicide throughout the life span: findings from the Adverse Childhood Experiences Study. *JAMA*. 2001;**286**:3089–96. https://doi.org/10.1001/jama.286.24.3089.
12. K. S. Kendler, K. Sheth, C. O. Gardner, C. A. Prescott. Childhood parental loss and risk for first-onset of major depression and alcohol dependence: the time-decay of risk and sex differences. *Psychol Med*. 2002;**32;**1187–94. https://doi.org/10.1017/s0033291702006219.
13. R. H. Belmaker, G. Agam, Major depressive disorder. *N Engl J Med*. 2008;**358**:55–68. https://doi.org/10.1056/NEJMra073096.
14. H. Jiang, Z. Ling, Y. Zhang, et al. Altered fecal microbiota composition in patients with major depressive disorder. *Brain Behav Immun*. 2015;**48**:186–94. https://doi.org/10.1016/j.bbi.2015.03.016.
15. V. L. Nikolova, M. R. B. Smith, L. J. Hall, et al. Perturbations in gut microbiota composition in psychiatric disorders: a review and meta-analysis. *JAMA Psychiatry*. 2021;**78**:1343–54. https://doi.org/10.1001/jamapsychiatry.2021.2573.

https://doi.org/10.1017/9781108973922.002 Published online by Cambridge University Press

16. F. Navarro-Mateu, M. J. Tormo, D. Salmerón, et al. Prevalence of mental disorders in the south-east of Spain, one of the European regions most affected by the economic crisis: the cross-sectional PEGASUS-Murcia Project. *PloS One*. 2015;**10**: e0137293. https://doi.org/10.1371/journal.pone.0137293.

17. R. M. Post. Transduction of psychosocial stress into the neurobiology of recurrent affective disorder. *Am J Psychiatry*. 1992;**149**:999–1010. https://doi.org/10.1176/ajp.149.8.999.

18. P. W. Gold. The organization of the stress system and its dysregulation in depressive illness. *Mol Psychiatry*. 2015;**20**:32–47. https://doi.org/10.1038/mp.2014.163.

19. E. S. Brown, F. P. Varghese, B. S. McEwen. Association of depression with medical illness: does cortisol play a role? *Biol Psychiatry*. 2004;**55**:1–9. https://doi.org/10.1016/s0006-3223(03)00473-6.

20. J. F. Cryan, T. G. Dinan. Mind-altering microorganisms: the impact of the gut microbiota on brain and behaviour. *Nat Rev Neurosci*. 2012;**13**:701712. https://doi.org/10.1038/nrn3346.

21. T. Yatsunenko, F. E. Rey, M. J. Manary, et al. Human gut microbiome viewed across age and geography. *Nature*. 2012;**486**:222–7. https://doi.org/10.1038/nature11053.

22. S. S. Yarandi, D. A. Peterson, G. J. Treisman, T. H. Moran, P. J. Pasricha. Modulatory effects of gut microbiota on the central nervous system: how gut could play a role in neuropsychiatric health and diseases. *J Neurogastroenterol Motil*. 2016;**22**:201–12. https://doi.org/10.5056/jnm15146.

23. G. Clarke, S. Grenham, P. Scully, et al. The microbiome-gut-brain axis during early life regulates the hippocampal serotonergic system in a sex-dependent manner. *Mol Psychiatry*. 2013;**18**:666–73. https://doi.org/10.1038/mp.2012.77.

24. K.-A. Neufeld, J. A. Foster. Effects of gut microbiota on the brain: implications for psychiatry. *J Psychiatry Neurosci*. 2009;**34**:230–1.

25. D. J. Kupfer. Long-term treatment of depression. *J Psychiatry*. 1991;**52**(Suppl):28–34.

26. G. A. Fava, S. K. Park, N. Sonino. Treatment of recurrent depression. *Expert Rev Neurother*. 2006;**6**:1735–40. https://doi.org/10.1586/14737175.6.11.1735.

27. S. Quraishi, S. Frangou. Neuropsychology of bipolar disorder: a review. *J Affect Disord*. 2002;**72**:209–26. https://doi.org/10.1016/s0165-0327(02)00091-5.

28. P. Ay-Woan, C. P. Sarah, C. Lyinn, C. Tsyr-Jang, H. Ping-Chuan. Quality of life in depression: predictive models. *Qual Life Res*. 2006;**15**:39–48. https://doi.org/10.1007/s11136-005-0381-x.

29. M. K. Nock, I. Hwang, N. A. Sampson, R. C. Kessler. Mental disorders, comorbidity and suicidal behavior: results from the National Comorbidity Survey Replication. *Mol Psychiatry*. 2010;**15**:868–76. https://doi.org/10.1038/mp.2009.29.

30. M. F. Juruena, L. A. Jelen, A. H. Young, A. J. Cleare. New pharmacological interventions in bipolar disorder. *Curr Top Behav Neurosci*. 2021;**48**:303–24. https://doi.org/10.1007/7854_2020_181.

31. L. L. Judd, H. S. Akiskal. Depressive episodes and symptoms dominate the longitudinal course of bipolar disorder. *Curr Psychiatry Rep*. 2003;**5**:417–18. https://doi.org/10.1007/s11920-003-0077-2.

32. J. Angst, J.-M. Azorin, C. L. Bowden, et al.; BRIDGE Study Group. Prevalence and characteristics of undiagnosed bipolar disorders in patients with a major depressive episode: the BRIDGE study. *Arch Gen Psychiatry*. 2011;**68**:791–8. https://doi.org/10.1001/archgenpsychiatry.2011.87.

33. R. M. Post. The Kindling/Sensitization Model and early life stress. *Curr Top Behav Neurosci*. 2021;**48**:255–75. https://doi.org/10.1007/7854_2020_172.

34. T. Barichello, V. V. Giridharan, G. Bhatti, et al. Inflammation as a mechanism of bipolar disorder neuroprogression. *Curr Top Behav Neurosci*. 2021;**48**:215–37. https://doi.org/10.1007/7854_2020_173.

35. K. N. Fountoulakis, E. Vieta. Treatment of bipolar disorder: a systematic review of available data and clinical perspectives. *Int J Neuropsychopharmacol*. 2008;**11**:999–1029. https://doi.org/10.1017/S1461145708009231.

36. M. Sanches, I. E. Bauer, J. F. Galvez, G. B. Zunta-Soares, J. C. Soares. The management of cognitive impairment in bipolar disorder: current status and perspectives. *Am J Ther*. 2015;**22**:477–86. https://doi.org/10.1097/MJT.0000000000000120.

37. G. Rayner, G. Jackson, S. Wilson. Cognition-related brain networks underpin the symptoms of unipolar depression: evidence from a systematic review. *Neurosci Biobehav Rev*. 2016;**61**:53–65. https://doi.org/10.1016/j.neubiorev.2015.09.022.

38. J. Savitz, W. C. Drevets. Bipolar and major depressive disorder: neuroimaging the developmental-degenerative divide. *Neurosci Biobehav Rev*. 2009;**33**:699–771. https://doi.org/10.1016/j.neubiorev.2009.01.004.

39. E. J. Nestler, M. Barrot, R. J. DiLeone, et al. Neurobiology of depression. *Neuron*. 2002;**34**:13–25. https://doi.org/10.1016/s0896-6273(02)00653-0.

40. M. P. Richardson, B. A. Strange, R. J. Dolan. Encoding of emotional memories depends on amygdala and

hippocampus and their interactions. *Nat Neurosci*. 2004;**7**:278–85. https://doi.org/10.1038/nn1190.

41. H. S. Mayberg. Limbic-cortical dysregulation: a proposed model of depression. *J Neuropsychiatry Clin Neurosci*. 1997;**9**:471–81. https://doi.org/10.1176/jnp.9.3.471.

42. H. S. Mayberg. Targeted electrode-based modulation of neural circuits for depression. *J Clin Invest*. 2009;**119**:717–25. https://doi.org/10.1172/JCI38454.

43. A. K. Afifi, R. A. Bergman. *Functional Neuroanatomy: Text and Atlas*. International ed. New York: McGraw-Hill, Health Professions Division, 1998.

44. S. Vogel, G. Fernández, M. Joëls, L. Schwabe. Cognitive adaptation under stress: a case for the mineralocorticoid receptor. *Trends Cogn Sci*. 2016;**20**:192–203. https://doi.org/10.1016/j.tics.2015.12.003.

45. T. Beblo, G. Sinnamon, B. T. Baune. Specifying the neuropsychology of affective disorders: clinical, demographic and neurobiological factors. *Neuropsychol Rev*. 2011;**21**:337–59. https://doi.org/10.1007/s11065-011-9171-0.

46. J. V. Taylor Tavares, W. C. Drevets, B. J. Sahakian. Cognition in mania and depression. *Psychol Med*. 2003;**33**:959–67. https://doi.org/10.1017/s0033291703008432.

47. M. M. Loman, K. L. Wiik, K. A. Frenn, S. D. Pollak, M. R. Gunnar. Postinstitutionalized children's development: growth, cognitive, and language outcomes. *J Dev Behav Pediatr*. 2009;**30**:426–34. https://doi.org/10.1097/DBP.0b013e3181b1fd08.

48. M. Rutter, T. G. O'Connor, English and Romanian Adoptees (ERA) Study Team. Are there biological programming effects for psychological development? Findings from a study of Romanian adoptees. *Dev Psychol*. 2004;**40**:81–94. https://doi.org/10.1037/0012-1649.40.1.81.

49. S. D. Pollak, C. A. Nelson, M. F. Schlaak, et al. Neurodevelopmental effects of early deprivation in postinstitutionalized children. *Child Dev*. 2010;**81**:224–36. https://doi.org/10.1111/j.1467-8624.2009.01391.x.

50. E. Colvert, M. Rutter, J. Kreppner, et al. Do theory of mind and executive function deficits underlie the adverse outcomes associated with profound early deprivation?: findings from the English and Romanian adoptees study. *J Abnorm Child Psychol*. 2008;**36**:1057–68. https://doi.org/10.1007/s10802-008-9232-x.

51. A. H. Young, P. Gallagher, S. Watson, et al. Improvements in neurocognitive function and mood following adjunctive treatment with mifepristone (RU-486) in bipolar disorder. *Neuropsychopharmacology*. 2004;**29**:1538–45. https://doi.org/10.1038/sj.npp.1300471.

52. M. D. De Bellis, S. R. Hooper, D. P. Woolley, C. E. Shenk. Demographic, maltreatment, and neurobiological correlates of PTSD symptoms in children and adolescents. *J Pediatr Psychol*. 2010;**35**:570–7. https://doi.org/10.1093/jpepsy/jsp116.

53. R. F. Anda, V. J. Felitti, J. D. Bremner, et al. The enduring effects of abuse and related adverse experiences in childhood. A convergence of evidence from neurobiology and epidemiology. *Eur Arch Psychiatry Clin Neurosci*. 2006;**256**:174–86. https://doi.org/10.1007/s00406-005-0624-4.

54. C. P. Navalta, A. Polcari, D. M. Webster, A. Boghossian, M. H. Teicher. Effects of childhood sexual abuse on neuropsychological and cognitive function in college women. *J Neuropsychiatry Clin Neurosci*. 2006;**18**:45–53. https://doi.org/10.1176/jnp.18.1.45.

55. P. Pechtel, D. A. Pizzagalli. Effects of early life stress on cognitive and affective function: an integrated review of human literature. *Psychopharmacology*. 2011;**214**:55–70. https://doi.org/10.1007/s00213-010-2009-2.

56. S. U. Kaymak, B. Demir, S. Sentürk, et al. Hippocampus, glucocorticoids and neurocognitive functions in patients with first-episode major depressive disorders. *Eur Arch Psychiatry Clin Neurosci*. 2010;**260**:217–23. https://doi.org/10.1007/s00406-009-0045-x.

57. P. Neu, M. Bajbouj, A. Schilling, et al. Cognitive function over the treatment course of depression in middle-aged patients: correlation with brain MRI signal hyperintensities. *J Psychiatr Res*. 2005;**39**:129–35. https://doi.org/10.1016/j.jpsychires.2004.06.004.

58. S. Reppermund, M. Ising, S. Lucae, J. Zihl. Cognitive impairment in unipolar depression is persistent and non-specific: further evidence for the final common pathway disorder hypothesis. *Psychol Med*. 2009;**39**:603–14. https://doi.org/10.1017/S003329170800411X.

59. R. Grassi-Oliveira, C. F. de Azevedo Gomes, L. M. Stein. False recognition in women with a history of childhood emotional neglect and diagnose of recurrent major depression. *Conscious Cogn*. 2011;**20**:1127–34. https://doi.org/10.1016/j.concog.2011.03.005.

60. D. N. Cagney, J. Sul, R. Y. Huang, et al. The FDA NIH Biomarkers, EndpointS, and other Tools (BEST) resource in neuro-oncology. *Neuro Oncol*. 2018;**20**:1162–72. https://doi.org/10.1093/neuonc/nox242.

61. R. M. Califf. Biomarker definitions and their applications. *Exp Biol Med (Maywood)*. 2018;**243**:213–21. https://doi.org/10.1177/1535370217750088.

62. S. Watson, P. Gallagher, J. C. Ritchie, I. N. Ferrier, A. H. Young. Hypothalamic-pituitary-adrenal axis function in patients with bipolar disorder. *Br J Psychiatry*. 2004;**184**:496–502. https://doi.org/10.1192/bjp.184.6.496.

63. M. F. Juruena, B. Agustini, A. J. Cleare, A. H. Young. A translational approach to clinical practice via stress-responsive glucocorticoid receptor signaling. *Stem Cell Investig*. 2017;**4**:13. https://doi.org/10.21037/sci.2017.02.01.

64. J. R. Geddes, D. J. Miklowitz. Treatment of bipolar disorder. *Lancet*. 2013;**381**:1672–82. https://doi.org/10.1016/S0140-6736(13)60857-0.

65. A. C. Andreazza, M. Kauer-Sant'anna, B. N. Frey, et al. Oxidative stress markers in bipolar disorder: a meta-analysis. *J Affect Disord*. 2008;**111**:135–44. https://doi.org/10.1016/j.jad.2008.04.013.

66. M. Berk, H. Plein, B. Belsham. The specificity of platelet glutamate receptor supersensitivity in psychotic disorders. *Life Sci*. 2000;**66**:2427–32. https://doi.org/10.1016/s0024-3205(00)80002-8.

67. A. Pascual-Leone, M. J. Taylor. A developmental framework of brain and cognition from infancy to old age. *Brain Topogr*. 2011;**24**:183–6. https://doi.org/10.1007/s10548-011-0197-7.

68. S. L. Andersen. Trajectories of brain development: point of vulnerability or window of opportunity? *Neurosci Biobehav Rev*. 2003;**27**:3–18. https://doi.org/10.1016/s0149-7634(03)00005-8.

69. M. Sanches, M. S. Keshavan, P. Brambilla, J. C. Soares. Neurodevelopmental basis of bipolar disorder: a critical appraisal. *Prog Neuropsychopharmacol Biol Psychiatry*. 2008;**32**:1617–27. https://doi.org/10.1016/j.pnpbp.2008.04.017.

70. M. H. Teicher, S. L. Andersen, A. Polcari, C. M. Anderson, C. P. Navalta. Developmental neurobiology of childhood stress and trauma. *Psychiatr Clin North Am*. 2002;**25**:397–426, vii–viii. https://doi.org/10.1016/s0193-953x(01)00003-x.

71. S. J. Lupien, B. S. McEwen, M. R. Gunnar, C. Heim. Effects of stress throughout the lifespan on the brain, behaviour and cognition. *Nat Rev Neurosci*. 2009;**10**:434–45. https://doi.org/10.1038/nrn2639.

72. S. Weich, I. Nazareth, L. Morgan, M. King. Treatment of depression in primary care. Socio-economic status, clinical need and receipt of treatment. *Br J Psychiatry*. 2007;**191**:164–9. https://doi.org/10.1192/bjp.bp.106.032219.

73. K. S. Al-Harbi. Treatment-resistant depression: therapeutic trends, challenges, and future directions. *Patient Prefer Adherence*. 2012;**6**:369–88. https://doi.org/10.2147/PPA.S29716.

74. R. van Westrhenen, K. J. Aitchison, M. Ingelman-Sundberg, M. M. Jukić. Pharmacogenomics of antidepressant and antipsychotic treatment: how far have we got and where are we going? *Front Psychiatry*. 2020;**11**:94. https://doi.org/10.3389/fpsyt.2020.00094.

75. M. J. Gitlin, J. Swendsen, T. L. Heller, C. Hammen. Relapse and impairment in bipolar disorder. *Am J Psychiatry*. 1995;**152**:1635–40. https://doi.org/10.1176/ajp.152.11.1635.

76. J. A. Lieberman, T. S. Stroup, J. P. McEvoy, et al.; Clinical Antipsychotic Trials of Intervention Effectiveness (CATIE) Investigators. Effectiveness of antipsychotic drugs in patients with chronic schizophrenia. *N Engl J Med*. 2005;**353**:1209–23. https://doi.org/10.1056/NEJMoa051688.

77. M. E. Thase. STEP-BD and bipolar depression: what have we learned? *Curr Psychiatry Rep*. 2007;**9**:497–503. https://doi.org/10.1007/s11920-007-0068-9.

78. R. H. McAllister-Williams, C. Arango, P. Blier, et al. The identification, assessment and management of difficult-to-treat depression: an international consensus statement. *J Affect Disord*. 2020;**267**:264–82. https://doi.org/10.1016/j.jad.2020.02.023.

79. N. Buley, E. Copland, S. Hodge, R. Chaplin. A further decrease in the rates of administration of electroconvulsive therapy in England. *J ECT*. 2017;**33**:198–202. https://doi.org/10.1097/YCT.0000000000000374.

80. A. U. Haq, A. F. Sitzmann, M. L. Goldman, D. F. Maixner, B. J. Mickey. Response of depression to electroconvulsive therapy: a meta-analysis of clinical predictors. *J Psychiatry*. 2015;**76**:1374–84. https://doi.org/10.4088/JCP.14r09528.

81. N. Ghaziuddin, G. Walter, editors. *Electroconvulsive Therapy in Children and Adolescents*. New York: Oxford University Press, 2014.

82. J.-J. Chen, L.-B. Zhao, Y.-Y. Liu, S.-H. Fan, P. Xie. Comparative efficacy and acceptability of electroconvulsive therapy versus repetitive transcranial magnetic stimulation for major depression: a systematic review and multiple-treatments meta-analysis. *Behav Brain Res*. 2017;**320**:30–6. https://doi.org/10.1016/j.bbr.2016.11.028.

83. R. S. McIntyre, J. D. Rosenblat, C. B. Nemeroff, et al. Synthesizing the evidence for ketamine and esketamine in treatment-resistant depression: an international expert opinion on the available evidence and implementation. *Am J Psychiatry*. 2021;**178**:383–99. https://doi.org/10.1176/appi.ajp.2020.20081251.

84. C. Morris, A. Perris, J. Klein, P. Mahoney. Anaesthesia in haemodynamically compromised emergency patients: does ketamine represent the best choice of induction agent? *Anaesthesia*.

https://doi.org/10.1017/9781108973922.002 Published online by Cambridge University Press

2009;**64**:532–9. https://doi.org/10.1111/j.1365-2044.2008.05835.x.

85. S. T. Wilkinson, E. D. Ballard, M. H. Bloch, et al. The effect of a single dose of intravenous ketamine on suicidal ideation: a systematic review and individual participant data meta-analysis. *Am J Psychiatry*. 2018;**175**:150–8. https://doi.org/10.1176/appi.ajp.2017.17040472.

86. N. Diazgranados, L. Ibrahim, N. E. Brutsche, et al. A randomized add-on trial of an N-methyl-D-aspartate antagonist in treatment-resistant bipolar depression. *Arch Gen Psychiatry*. 2010;**67**:793–802. https://doi.org/10.1001/archgenpsychiatry.2010.90.

87. R. S. Duman, G. K. Aghajanian. Synaptic dysfunction in depression: potential therapeutic targets. *Science*. 2012;**338**:68–72. https://doi.org/10.1126/science.1222939.

88. B. Kadriu, L. Musazzi, I. D. Henter, et al. Glutamatergic neurotransmission: pathway to developing novel rapid-acting antidepressant treatments. *Int J Neuropsychopharmacol*. 2019;**22**:119–35. https://doi.org/10.1093/ijnp/pyy094.

89. T. L. Smith, C. B. Nemeroff. Pharmacogenomic testing and antidepressant response: problems and promises. *Braz J Psychiatry*. 2020;**42**:116–17. https://doi.org/10.1590/1516-4446-2019-0799.

90. A. Tornio, J. T. Backman. Cytochrome P450 in pharmacogenetics: an update. *Adv Pharmacol*. 2018;**83**:32. https://doi.org/10.1016/bs.apha.2018.04.007.

91. M. Veldic, A. T. Ahmed, C. J. Blacker, et al. Cytochrome P450 2C19 poor metabolizer phenotype in treatment resistant depression: treatment and diagnostic implications. *Front Pharmacol*. 2019;**10**:83. https://doi.org/10.3389/fphar.2019.00083.

92. C. Han, S.-M. Wang, W.-M. Bahk, et al. A pharmacogenomic-based antidepressant treatment for patients with major depressive disorder: results from an 8-week, randomized, single-blinded clinical trial. *Clin Psychopharmacol Neurosci*. 2018;**16**:469–80. https://doi.org/10.9758/cpn.2018.16.4.469.

93. F. Corponi, C. Fabbri, A. Serretti. Pharmacogenetics and depression: a critical perspective. *Psychiatry Investig*. 2019;**16**:645–53. https://doi.org/10.30773/pi.2019.06.16.

94. J. F. Greden, S. V. Parikh, A. J. Rothschild, et al. Impact of pharmacogenomics on clinical outcomes in major depressive disorder in the GUIDED trial: a large, patient- and rater-blinded, randomized, controlled study. *J Psychiatr Res*. 2019;**111**:59–67. https://doi.org/10.1016/j.jpsychires.2019.01.003.

95. J. G. Winner, J. M. Carhart, C. A. Altar, et al. Combinatorial pharmacogenomic guidance for psychiatric medications reduces overall pharmacy costs in a 1 year prospective evaluation. *Curr Med Res Opin*. 2015;**31**:1633–43. https://doi.org/10.1185/03007995.2015.1063483.

96. M. Hewett, D. E. Oliver, D. L. Rubin, et al. PharmGKB: the pharmacogenetics knowledge base. *Nucleic Acids Res*. 2002;**30**:163–5. https://doi.org/10.1093/nar/30.1.163.

97. M. V. Relling, T. E. Klein, R. S. Gammal, et al. The Clinical Pharmacogenetics Implementation Consortium: 10 years later. *Clin Pharmacol Ther*. 2020;**107**:171–5. https://doi.org/10.1002/cpt.1651.

98. C. F. Thorn, T. E. Klein, R. B. Altman. PharmGKB: the pharmacogenetics and pharmacogenomics knowledge base. *Methods Mol Biol*. 2005;**311**:179–91. https://doi.org/10.1385/1-59259-957-5:179.