Yong-Ku Kim
*Editor*

# Understanding Depression

Volume 2

## Clinical Manifestations, Diagnosis and Treatment

Springer

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# Preface

This book, in two volumes, focuses on contemporary issues and dilemmas in relation to depression. The aim is to equip readers with an up-to-date understanding of the clinical and neurobiological underpinnings of depression, its clinical manifestations, and the development of more effective treatments. This second volume is devoted specifically to clinical and management issues. Readers will find detailed information on a wide range of frequently encountered and more complicated clinical presentations, with examination of risk factors and links to other conditions. Diagnostic aspects, including progress toward biological classification and the role of neuroimaging, are explored. Current trends in therapy are examined at length, drawing on the latest evidence and covering not only antidepressant medications but also the roles of neurostimulation, combined pharmacotherapy and psychotherapy, mindfulness-based cognitive therapy (MBCT), and complementary and alternative medicine (CAM). The companion volume is dedicated to the underlying biomedical and neurobiological basis of depression. *Understanding Depression* will be an excellent source of information for both researchers and practitioners in the field.

Part I (Chaps. 1–6) deals with diagnostic issues of depression. The perspectives on depression—past, present, and future—and issues about current changes and criticism based on the DSM-5 are discussed. Currently, the diagnosis of depression is based primarily on symptoms rather than objective biological markers. So, biological diagnostic classification for depression is also needed in biological psychiatry. The possibility of current and future biological classifications of depression in view of blood biological markers, neuroimaging, and voice analysis is addressed.

Chapter 1 highlights the changes to diagnostic criteria for depressive disorders from the DSM-IV to DSM-5. Depressive disorders have been reformulated based on a combination of categorical and dimensional approaches in the DSM-5. However, despite the transdiagnostic specifiers, severity assessments, and cross-cutting measure assessments contained in the DSM-5, depression is still defined using a symptom-based classification, and its heterogeneity is of significant concern. It is necessary to develop an etiology-based classification of depressive disorders and to consider humanistic approaches together with potential cultural and social influences.

Chapter 2 focuses on the differentiating features and contemporary treatment approaches between major depressive disorder and bipolar disorder. Major depressive disorder and bipolar disorder are distinct conditions with

differences in clinical presentation and treatment modalities. Since current treatments are palliative rather than curative in nature, there is an urgent need to foster a better understanding of the underpinning pathogenic mechanisms and discover novel therapies.

Chapter 3 discusses the potential diagnostic biomarkers for depression. Since depression is so heterogeneous and associated with different clinical presentations and symptoms, the development of a single biomarker is highly unlikely. A reliable panel or a set of biomarkers, when developed, will have significant clinical use and lead toward personalized treatment strategies.

Chapter 4 provides a detailed overview of biological markers that may serve as reliable tools for the diagnosis and treatment of depression. Some of the frequently reported findings include abnormalities in neurotransmitter systems, such as those for 5-HT, dopamine, norepinephrine, glutamate, and GABA, and alterations in the levels of growth factors, such as BDNF, VEGF, and FGF. Evidence also indicates that there are conspicuous changes in the levels of inflammatory, endocrine, and metabolic markers and the presence of structural and functional abnormalities in specific cortico-limbic regions of depressed patients. Future studies are needed to indicate whether these changes constitute a direct cause of depression or a compensatory mechanism for specific neurobiological alterations.

Chapter 5 sheds light on the application of neuroimaging in the diagnosis and treatment of depression. Accumulating neuroimaging studies suggest potential biomarkers, such as metabolic activity and structural or functional connectivity, within the cortico-limbic circuitry. The continuous progress in neuroimaging studies will help produce better consistent data, which contribute to the identification of biomarkers for personalized, prognostic, predictive, and preventive medicine.

Chapter 6 introduces the clinical application of pathophysiological voice analysis for the diagnosis and monitoring of depression. Pathophysiological analysis by voice is noninvasive, remote, and continuous, without requiring special equipment. Therefore, this technique is effective as a screen for many subjects and long-term continuous monitoring at home. In clinical settings, it is possible to give objective indicators to medical areas that previously had only subjective indicators in depression.

Part II (Chaps. 7–11) refers to clinical manifestations of depression. Anhedonia has been understood as a "loss of pleasure," but neuropsychological and neurobiological studies reveal a multifaceted reconceptualization. The current methodology to measure anhedonia and its neurobiological underpinnings and treatment are discussed. The current knowledge of neurocognitive mechanisms in depression and several psychological models that may explain how cognitive impairment works in depression are addressed. Disturbances in the sleep-wake cycle and chronobiological rhythm are very common in depression and serve as sensitive biological markers. The clinical treatment options available for sleep-wake disturbances and abnormal circadian rhythms in depression are discussed. Suicidal behavior in depression is more than just a severe form of depression, and distinct predispositions to suicide behaviors in depression should be better understood.

Chapter 7 highlights the neurobiology, measurement, and treatment of anhedonia, a core symptom of depression. Several key brain regions and connections have been identified in reward processing, particularly within the prefrontal cortex. It is possible that neural dysfunction in any aspect of reward processing could lead to the clinical symptom of anhedonia. There are various treatments that target anhedonia symptoms due to their effect on the dopaminergic and noradrenergic systems; however, further research is needed to elucidate the effects of conventional antidepressants on anhedonia. The development of new assessment tools, including self-report scales and behavioral tasks, improves our understanding of the underlying neurobiology.

Chapter 8 discusses the differential diagnosis and management of various sleep patterns in depression and the clinical treatment options available for sleep-wake disturbances that are comorbid with depression. Sleep-wake disturbances are not only prevalent symptoms of depression but also are a biological marker for depression. Primary sleep disorders, such as obstructive sleep apnea, restless leg syndrome, and REM sleep behavior disorder, are also prevalent in depression. Antidepressants can have a variety of effects on sleep, depending on their mechanism and characteristics. Cognitive behavioral therapy of insomnia (CBT-I), which is the treatment of choice for chronic insomnia, is also effective for the treatment of insomnia comorbid with depression.

Chapter 9 focuses on the mechanisms and treatment of sleep homeostasis abnormalities and circadian rhythm disruptions in depression. Chronotherapies, which synchronize and stabilize biological rhythms (including sleep-wake patterns), such as bright light therapy, melatonin and its agonists, sleep deprivation, and social rhythm therapies, may be useful treatments in depression. Four types of chronotherapies (bright light therapy, agomelatine, sleep deprivation, and phase advance) show efficacy in the treatment of depression both in unipolar or bipolar disorders and seasonal or nonseasonal subtypes.

Chapter 10 reviews the risk factors, neurobiological changes, and reconceptualization of suicidal behaviors in depression. The interplay between interconnected neural systems contributes to suicidal behaviors in depression, and these neurobiological changes underlie the psychological vulnerability of suicidal behavior. Reconceptualization of suicidal behavior as a distinct disorder improves suicide risk screening and detection in clinical practice and helps expand suicide research by using a well-defined phenotype.

Chapter 11 investigates the psychological and biological mechanisms and assessments of cognitive impairments in depression. A psychological hypothesis states that depressed patients cannot effectively distribute and utilize cognitive resources. A biological hypothesis states that weakened top-down cognitive control and enhanced bottom-up emotion activation result in cognitive impairment. To assess cognitive function in depression, typical neurocognitive function tests to assess overall cognitive function are preferred over specific examination tools. Amyloid PET is being highlighted for its usefulness in patients with depression and cognitive impairment.

Part III (Chaps. 12–15) considers complicated clinical manifestations of depression. Chronic pain and depression show shared psychological and neurobiological mechanisms. Neuroimaging studies, genetic and molecular factors in the pathophysiology, and current novel therapeutic strategy in both conditions are described. Depression with medical illness, such as cancer or diabetes, is differentiated from functional depression without medical illness. The clinical, biological, and therapeutic characteristics between depression with and without medical illness are discussed. Burnout syndrome has been defined as a combination of emotional exhaustion, depersonalization, and reduced personal accomplishment caused by chronic occupational stress. The current state of the science suggests that burnout is a form of depression rather than a differentiated type of pathology. Increasing evidence has pointed to the association between obesity and depression. The association between both conditions has been described as bidirectional and convergent, and several biological and psychosocial factors may be influencing the association.

Chapter 12 proposes several biological hypotheses regarding pathophysiology and treatments of chronic pain in depression. The role of activation of inflammatory cytokine systems and abnormal neurotransmitter systems, such as glutamine, serotonin, noradrenaline, and dopamine, explains the overlapping pathophysiology in chronic pain and depression. Neuroimaging studies show alterations in regions involved in pain perception and structures considered part of the neural bases of depression. The usefulness of tricyclic antidepressants and serotonin-noradrenaline reuptake inhibitors in neuropathic pain and functional somatic syndromes (fibromyalgia and irritable bowel syndrome) is convincingly documented, whereas the superiority of antidepressants from different classes in the treatment of painful physical symptoms in depression is still a matter of debate.

Chapter 13 focuses on the clinical, biological, and therapeutic characteristics in depression with and without medical illness. Depressive symptoms can be easily affected by symptoms due to accompanying physical illnesses, sometimes resulting in difficulties differentiating between sole physical illness and comorbid depression, which comes from inflammatory pathways, alteration in the hypothalamic-pituitary-adrenal (HPA) axis, and dysfunctional regulation of hormones and change in neurotransmitters. Considering the significant prevalence of depression in medical illnesses and its impact on prognosis of medical illnesses expressed as morbidity or mortality, careful assessment of depressive symptom screening and severity should be completed with validated assessment tools.

Chapter 14 provides a comprehensive overview of burnout syndrome and describes the shift from an initial exploratory and qualitative approach to more systematic, quantitative research on burnout syndrome. Recent studies clarify the issue of burnout-depression overlap at theoretical and epistemological levels and provide compelling evidence that the pathogenesis of burnout is depressive in nature. Burnout syndrome highlights the need for more conceptual parsimony and theoretical integration in psychology and psychiatry and calls for enhanced transdisciplinary communication in the fields of stress and depression research.

Chapter 15 examines the biological and psychosocial associations between depression and obesity. The bidirectional association between obesity and depression is complex and affected by several common pathways. HPA axis dysfunction and leptin, insulin, and inflammatory signal disturbances are thought to bridge obesity and depression. In addition, the moderating effects of behavioral and social actors should be considered when examining the relationship between obesity and depression. Recently, several novel interventions that target metabolic or inflammatory mechanisms have been proposed for both obesity and depression.

Part IV (Chaps. 16–23) raises therapeutic issues in depression. Ketamine has received a great deal of attention over the last 20 years, due to the discovery that a single subanesthetic dose leads to a rapid antidepressant effect in individuals with treatment-resistant depression. To date, treatment strategies for depression have been devised based on the insights gained from brain pathophysiology, including alterations in the monoamine systems. Recent novel antidepressants and promising treatments related to the monoamine systems are addressed. Regarding antipsychotic agents, short-term clinical trials support their efficacy as adjuncts to antidepressants in treating major depressive disorder in individuals inadequately responsive to antidepressant treatment alone. Novel neuromodulation treatments (deep brain stimulation (DBS), vagus nerve stimulation (VNS), transcranial direct current stimulation (tDCS), electroconvulsive therapy (ECT), transcranial magnetic stimulation (TMS)) are a treatment option for treatment-resistant depression. Internet-based MBCT is considered an adjunctive therapy to depression, and CAM receives attention, given that depression is a strong predictor of CAM use.

Chapter 16 introduces ketamine, an NMDA antagonist, which produces robust and rapid antidepressant effects after just a single dose. It was originally believed that the antidepressant effects of ketamine were mediated through its antagonism of NMDA receptors and subsequent downstream effects on the enhanced expression of process and proteins leading to synaptogenesis, but more recently, preliminary evidence suggests that the behavioral effects are mediated through AMPA receptors via hydroxynorketamine, a ketamine metabolite. Given that a growing number of providers have begun offering ketamine off-label for the treatment of psychiatric disorders, future research is urgently needed to better understand long-term risks, as well as evidence-based treatment regimens.

Chapter 17 provides updates on antidepressant therapy for depression. Emerging knowledge of key pathogenic mechanisms, such as the impairment of non-monoaminergic and monoaminergic neurotransmission, HPA axis hyperactivity, alterations in neurogenesis signaling pathways, and enhanced brain oxidative stress and inflammatory activity, has led to a host of new molecular drug targets. Several of these have been validated through the preliminary use of lead compounds and therapeutic agents in animals and humans.

Chapter 18 focuses on the efficacy and effectiveness of prescribing atypical antipsychotics in depression. Each possible antipsychotic agent is useful

in the treatment of depression, particularly in cases of treatment-resistant depression and mixed states associated with depressive episodes. In the future, the therapeutic potentialities of newer atypical antipsychotics in the treatment of depression, both as monotherapy and as adjunctive therapy, should be further investigated.

Chapter 19 reviews the neurobiology and evidence for novel therapeutic strategies for treatment-resistant depression (TRD). Although numerous antidepressants are available, there are still very few alternatives for TRD. Among those, ECT emerges as an evidence-based approach. Ketamine, anti-inflammatory treatments, and DBS might be promising, but further studies are needed.

Chapter 20 addresses neurostimulation techniques, such as ECT, repeated TMS, MST, tDCS, VNS, and DBS, in the treatment of depression. Neurostimulation is a good alternative treatment for patients who do not achieve remission after several psychopharmacological treatments and psychotherapy. Currently, ECT and TMS are the most extensively studied neurostimulation methods, while MST, tDCS, VNS, and DBS must be studied thoroughly so their efficacy and safety can be evaluated. Risks and benefits of neurostimulation methods should also be weighed in each case.

Chapter 21 provides an overview of the superiority of the combination of pharmacotherapy and psychotherapy to each treatment alone in depression, from the perspective of learning theory and neuroplasticity. The synergistic effects of combined therapy can be explained by the pharmacological augmentation of memory reconstruction updating. In this regard, a different class of pharmacological agents, such as histone deacetylase (HDAC) inhibitors, has received attention in the research of combination therapy in depression.

Chapter 22 introduces Internet-based MBCT as an adjunctive treatment for depression. MBCT is developed as an 8-week face-to-face group program for relapse prevention of depression. Internet-based delivery modes for MBCT provide benefits over traditional group formats. Several challenges for the successful implementation of web-delivered MBCT programs remain and need to be addressed in the future.

Chapter 23 reviews evidence-based studies of CAM in the treatment of depression. Depression has been identified as one of the most frequent indications for CAM use. The evidence on the efficacy of CAM treatments in depression indicates that the approaches that have generated the most research interest include acupuncture, Chinese herbs, hypericum (St. John's wort), mindfulness, and omega-3 fatty acids. Based on a critical review of the evidence, it appears that the most promising evidence is for hypericum (but with concerns for adverse effects and interactions), mindfulness, relaxation, and yoga.

I wish to give my heartfelt thanks to all chapter authors for their valuable time spent in preparing manuscripts. They are leading research scientists with knowledge and expertise in their respective fields. It goes without saying that, without their support, this book would not exist. I also wish to thank Dr. Sue Lee at Springer Nature for her assistance in all aspects of this book. I believe that this book will function as a step on the path toward the ultimate goal of understanding and treating depression.

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# Part I

# Diagnostic Issues of Depression

# 1 Depression in DSM-5: Changes, Controversies, and Future Directions

Seon-Cheol Park and Yong-Ku Kim

## 1.1 Introduction

Revision of the *Diagnostic and Statistical Manual of Mental Disorders*, fifth edition (DSM-5) (American Psychiatric Association 2013), involved a paradigm shift from using a categorical approach to using a dimensional approach for psychiatric diagnoses in order to encourage research beyond our current ways of thinking and the adoption of an etiologically and pathophysiologically based diagnostic system (Adam 2013). However, the grand ambition to use a dimensional approach encountered furious resistance in the DSM-5 revision process (Whooley and Horowitz 2013). Hence, the DSM-5 development goal was changed to "bridging the gap between presumed etiologies based on symptomatology and identifiable pathophysiologic etiologies" in the context of a combined categorical and dimensional approach (Kupfer and Regier 2011). Consistent with this approach, the psychiatric taxonomy of depressive disorders has been revised in the DSM-5.

Highlights of the changes to diagnostic criteria for depressive disorders from DSM-IV to DSM-5 are as follows: (1) splitting of mood disorders into bipolar and related disorders and depressive disorders; (2) adding "hopelessness" to the subjective descriptors of depressive mood; (3) introduction of disruptive mood dysregulation disorder and premenstrual dysphoric disorder as diseases entities for the first time; (4) renaming dysthymic disorder as persistent depressive disorder; (5) removal of the bereavement exclusion in the definition of major depressive episode; and (6) changes to the specifiers for depressive disorders, including "with psychotic features," "with anxious stress," "with mixed features," and "with peripartum onset." In this chapter, detailed changes, controversies, and future directions in relation to depression in DSM-5 will be explained and discussed (American Psychiatric Association 1994, 2013).

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## 1.2 Changes in Depressive Disorders from DSM-IV to DSM-5

### 1.2.1 Splitting Mood Disorders into Bipolar and Related Disorders and Depressive Disorders

Among the changes in the description of depressive disorders from the DSM-IV to the DSM-5, splitting the chapter titled "Mood Disorders" into the chapters "Bipolar and Related Disorders" and "Depressive Disorders" might be the most notable (Uher et al. 2014). This split is in accordance with deconstruction of the Kraepelinian dichotomy, which was an important issue in terms of redefining schizophrenia and bipolar disorder using a dimensional rather than a categorical approach in the development process of the DSM-5 (Vieta and Philips 2010; Kim et al. 2017). The split into bipolar and related disorders and depressive disorders is based on findings that bipolar and depressive disorders present similar degrees of symptomatologic and genetic overlap to those between schizophrenia and depressive disorder (Lichtenstein et al. 2009; Cross-Disorder Group of the Psychiatric Genomics Consortium 2013; Rasic et al. 2013). However, this split is partly inconsistent with the fact that the switch from depressive to bipolar disorder is regarded as one of the most significant transitions in psychiatric taxonomy (Berk et al. 2006; Etain et al. 2012).

As a consequence of splitting mood disorders into bipolar and depressive disorders, the diagnostic entity "mood disorder not otherwise specified," which reflects an undefined condition between "bipolar disorder not otherwise specified" and "depressive disorder not otherwise specified," has disappeared in the DSM-5. Herein, a rigidly dichotomous view of bipolar and depressive disorders is necessarily required in the context of mood disorders in the DSM-5 and could be a challenging issue in the early course of bipolar and depressive disorders (Lish et al. 1994; Uher et al. 2014).

### 1.2.2 Adding "Hopelessness" to the Subjective Descriptors of Depressive Mood

The term "hopelessness," which was not included in the DSM-IV, has been newly added to the subjective descriptors of depressive mood in the DSM-5. The addition of hopelessness to the DSM-5 is in accordance with the "bleak and pessimistic view of the future" contained in the definition of depressive mood in the *International Classification of Disease*, tenth revision (ICD-10). Hopelessness is regarded as a psychopathological feature different from depressive mood, because it can be present in the absence of depressive mood (Greene 1993; Beck et al. 1993; Joiner et al. 2001; Marsiglia et al. 2011). Moreover, hopelessness is considered to be a cognitive attitude of pessimism rather than a specific emotional state (Moller et al. 2015). Herein, we speculate that, as a consequence of adding hopelessness to the definition of depressive mood, the diagnosis of MDD will broaden, and its reliability will be reduced (Uher et al. 2014).

### 1.2.3 Introduction of Disruptive Mood Dysregulation Disorder and Premenstrual Dysphoric Disorder

The disease entities disruptive mood dysregulation disorder (DMDD) and premenstrual dysphoric disorder (PMD) have been newly introduced in the chapter titled "Depressive Disorders" in the DSM-5. The diagnosis of DMDD initially originated from that of severe mood dysregulation (SMD) in order to include chronic irritability in children and adolescents in terms of psychiatric diagnoses (Biederman et al. 2004; Carlson et al. 2009; Leibenluft 2011; Rao 2014). Patients with SMD were characterized by high rates of attention-deficit hyperactivity disorder and oppositional defiant disorder over their lifetime, a significant rate of comorbid anxiety disorder, and higher risk of anxiety and depressive disorders rather than bipolar disorders (Brotman et al. 2007; Leibenluft 2011).

Based on the high prevalence rates of SMD in children and adolescents, temper dysregulation disorder with dysphoria (TDD) was proposed as a potential entity by the DSM-5 task force (American Psychiatric Association Taskforce DV 2010). However, since there were no significant systemic studies in the realm of TDD at the time of revision and the word "temper" had the potential to be erroneously considered only as a temperament variation (Stringaris 2011), TDD was finally renamed as DMDD in the DSM-5. Furthermore, partly due to longitudinal study findings suggesting that patients with SMD presented with high rates of depressive disorder outcomes (Stringaris and Goodman 2009a, b), DMDD was included in the chapter "Depressive Disorders." However, the stability of the DMDD entity is controversial; several studies have reported that it has low prevalence, frequently co-occurs with other psychiatric disorders, and is difficult to differentiate from oppositional defiant disorder and conduct disorder (Axelson et al. 2012; Copeland et al. 2013).

In contrast, PMD is considered a distinct independent disease entity in the DSM-5, whereas late luteal phase dysphoric disorder was an initial diagnostic entity for PMD in Appendix A of the DSM-III, renamed as PMD in the DSM-IV (Epperson et al. 2012). Both age and gender were regarded as important issues in the definition of psychiatric illnesses in the revision process of the DSM-5 (Narrow et al. 2007). Hence, diagnosis of DMDD and PMD based on the DSM-5 should be considered in the context of age and gender. The mean prevalence rate of PMD is estimated to be about 2% (Sveinsdottir and Backstrom 2000; Gehlert et al. 2009). The Mood Disorders Work Group for the DSM-5 proposed the following benefits of including PMD as a category in the DSM-5: greater feasibility of detecting women with PMD, promoting accurate collection of data regarding treatment needs and delivery of services, and facilitating the development of specific medications (Epperson et al. 2012). Moreover, the Carolina Premenstrual Assessment Scoring System (C-PASS) has been proposed as a valid and reliable method for diagnosing PMD (Eisenlohr et al. 2017).

### 1.2.4 Renaming Dysthymic Disorder as Persistent Depressive Disorder

Although dysthymic disorder (dysthymia) was firstly introduced in the DSM-III and regarded as a distinct diagnostic entity with homogenous characteristics, there was significant criticism that dysthymic patients were heterogeneous in terms of depressive, anxiety, and personality features (Klein et al. 2000; Blanco et al. 2010; Rhebergen and Graham 2014). Hence, it has been proposed that dysthymic disorder can be optimally defined as a subtype of depressive disorder and differentiated from MDD by the low level of symptoms and high level of chronicity (Judd and Akiskal 2000). In terms of temperament domains, dysthymia, compared to MDD, is more closely associated with harm avoidance (Dinya et al. 2012). Moreover, it has been suggested that dysthymia might be more closely associated with personality disorder than with Axis I disorders in the DSM-IV (Rhebergen and Graham 2014). In addition, a neuroimaging study reported that, compared with normal controls, patients with dysthymia had less activation in left frontal regions including left ventro- and dorsolateral prefrontal cortices during working memory tasks (Vilgis et al. 2014). Chronic MDD is also regarded to be a subtype of a larger group of affective disorders (Rubio et al. 2011). Finally, dysthymic disorder and chronic MDD have been integrated into persistent depressive disorder (PDD). In accordance with this change, the specifier "chronic," which denotes a major depressive episode continuing for more than 2 years, has been removed from the DSM-5.

However, there are several significant criticisms of PDD as a diagnostic entity. First, given the significant overlap in diagnostic criteria for PDD, MDD, and generalized anxiety disorder (GAD), the validity of differentiating PDD from MDD and )GAD is questionable (Rhebergen and Graham 2014). Secondly, several meta-analyses found few differences in treatment modalities between PDD and MDD (Iovieno et al. 2011; Cuijper et al. 2013; von Wolff et al. 2013). Third,

because few neuroimaging and pathophysiology studies of PDD have been performed, it is unclear whether significant conclusions can be drawn.

### 1.2.5 Elimination of Bereavement Exclusion in the Definition of MDD

The most prominent change in the area of depressive disorders from the DSM-IV to the DSM-5 is the elimination of the bereavement exclusion in the diagnosis of MDD (Pies 2014; Uher et al. 2014). The reasons for this removal are as follows. First, in the context of clinical characteristics, including sadness, sleep disturbance, and decreased appetite; course; and outcome, there are few significant differentiating features between bereavement-related and bereavement-unrelated depressive disorders (Zisook et al. 2012). Second, MDD is an important issue in global mental health, as it is closely associated with overall suicidal rate (Coryell and Young 2005). Third, individuals with bereavement-related MDD are characterized by past personal and family histories of major depressive episodes. Both bereavement-related and bereavement-unrelated MDD have been reported to be influenced by genetics and to have associations with similar personality characteristics, patterns of comorbidity, and risks of chronicity and/or recurrence (American Psychiatric Association 2013).

Purely based on symptoms, an operational diagnosis of MDD regardless of any environmental factors can be made with removal of the bereavement exclusion. Hence, study of environmental factors in the etiology of MDD could benefit from the expected decrease in confounding effects of the diagnostic procedure on outcome. However, it is unclear how to distinguish between normal grief and MDD (Uher et al. 2014). Thus, elimination of the bereavement exclusion could result in overdiagnosis and overtreatment of MDD, a potentially expanded market for pharmaceutical companies, and loss of traditional and cultural ways of grieving. In addition, appropriateness and rationality from social and medical perspectives have been proposed as key features of the medicalization of a condition or behavior (Bandini 2015; Moller et al. 2015). Herein, in relation to the removal of the bereavement exclusion, medicalization of normal grief and normalization of MDD should be avoided through the introduction of appropriate methods in the area of psychiatric nosology (Pies 2014).

### 1.2.6 Changes in Specifiers for Depressive Disorder

#### 1.2.6.1 With Psychotic Features

In the DSM-IV, coding the specifier "with psychotic features" was permitted only in severe MDD and a relatively high prevalence of the specifier "mood-congruent psychotic features" compared to "mood-incongruent psychotic features" was reported. The definition of the specifier "with psychotic features" in the DSM-IV was in accordance with the severity-psychosis hypothesis that the presence of psychotic symptoms was limited to severe MDD in patients with psychotic depression. However, this hypothesis has been rejected by several studies (Ohayon and Schatzberg 2002; Maj et al. 2007; Østergaard et al. 2012a).

Moreover, in the context of deconstructing the Kraepelinian dichotomy, the following factors have been emphasized in the definition of psychotic depression in the DSM-5 revision process: potential co-occurrence of psychotic symptoms independent of the severity of depressive disorders, more adequate definition of psychotic symptoms, and clinical relationship and overlap between unipolar psychotic depression and bipolar psychotic depression (Keller et al. 2007a, b). Thus, in the DSM-5, the specifier "with psychotic features" can be coded in PDD and mild to severe MDD, and the notion of prevalence of mood-congruent and mood-incongruent psychotic features has been removed. There is still an intuitive distinction between mood-congruent and mood-incongruent psychotic features. The revised concept of psychotic depression has been suggested as a distinct disease entity as well as a "meta-syndrome," which includes unipolar and bipolar psychotic depression in the diagnostic criteria proposal of ICD-11(Østergaard et al. 2012b).

However, the specifier "with psychotic features" might still be associated with depressive subtyping models (Harald and Gordon 2012).

#### 1.2.6.2 With Anxious Distress

The specifier "with anxious distress" was introduced in the DSM-5. This specifier can be coded in MDD in the presence of two or more of five symptoms (feeling keyed up or tense, feeling unusually restless, difficulty concentrating due to worry, fear that something awful will happen, and fear of losing control of oneself) most days. Grading of the specifier "with anxious distress" is as follows: mild, moderate, and moderate-severe levels involve the presence of two, three, and four or more of the five symptoms, respectively (Uher et al. 2014). A large cohort study reported that individuals with MDD "with anxious distress" showed poorer clinical outcomes than those with MDD "without anxious distress," and the specifier "anxious distress" was found to have significant discriminant performance and convergent validity (Gaspesz et al. 2017).

The symptoms feeling tense, feeling restless, difficulty concentrating, and fear that something awful will happen overlap with and/or share diagnostic criteria for both the specifier "with anxious distress" and GAD. In the development process of the DSM-5, the problem of differentially diagnosing MDD and GAD was considered an important issue. Introduction of the specifier "with anxious distress" is in accordance with the significant overlap between MDD and GAD in terms of familial/genetic factors, childhood environment, personality traits, and demographic characteristics (Hettema 2010). In contrast, due to insufficient evidence from clinical research, the entity "mixed anxiety and depressive disorder," which denotes a combination of subthreshold anxiety and subthreshold depression, is regarded to be a useless category in clinical psychiatry and is not included in the section for further research in the DSM-5 (Moller et al. 2015). To determine the diagnostic boundary between MDD and GAD, sharing and separation of depressive and anxious symptoms should be systematically analyzed in appropriate epidemiological hypotheses and pharmacological treatment studies (Kendler et al. 1992; First 2014; Flint and Kendler 2014).

#### 1.2.6.3 With Mixed Features

"With mixed features" is also a new coding specifier in the depressive disorder section of the DSM-5. In the DSM-IV, a mixed episode is defined as a condition that simultaneously meets the criteria for manic episode and depressive episode; in the DSM-5, this has been removed and replaced with the specifier "with mixed features," which can be coded in manic, hypomanic, and depressive episodes. Herein, a definite distinction between episodes being predominantly depressive or predominantly manic is needed given the removal of mixed episodes in the DSM-5. The specifier "mixed features" for depressive disorder can be coded for subthreshold bipolar features during the predominantly depressive episode, and subthreshold bipolarity denotes a condition that does not meet the threshold of manic or hypomanic episodes. Coding the specifier "mixed features" is permitted with the presence of three or more of seven symptoms, namely, elevated mood, inflated self-esteem, pressure of speech, racing thoughts, goal-directed activity, involvement in risky activities, and decreased need for sleep (Uher et al. 2014; Moller et al. 2015). A large-sample study has reported that individuals with MDD "with mixed features" had significantly more severely depressive phenotypes than individuals with MDD without mixed features (McIntyre et al. 2015). Another study found an association between the presence of mixed features and complex clinical course/reduced treatment response in individuals with comorbid MDD and borderline personality disorder (Pergi et al. 2015). Furthermore, it has been proposed that additional medications beyond antidepressants or lurasidone monotherapy might be efficacious for individuals with MDD "with mixed features" (Rosenblat et al. 2016; Targum et al. 2016). The Clinically Useful Depression Outcome Scale supplemented with questions regarding the DSM-5 "mixed features" (CUDOS-M) has been developed and showed high reliability and validity for measuring the specifier "mixed features" in the Rhode Island

Methods to Improve Diagnostic Assessment and Services project (Zimmerman et al. 2014).

The specifier "with mixed features" can be criticized in terms of difficulties in reliably identifying subsyndromal hypomanic presentations, operationalizing subthreshold bipolarity, differentiating subthreshold bipolarity from borderline personality disorder, overdiagnosing bipolar spectrum disorders, and uncertainties about optimal interventions for subthreshold bipolarity (Nusslock and Frank 2011). Specifically, agitation and irritability have been excluded from the definition of the specifier "with mixed features" in the DSM-5 due to potential diagnostic nonspecificity, whereas agitation and irritability are regarded as hallmarks of mixed mood states in the DSM-IV (Koulopoulos et al. 2013). While the frequency rate of mixed mood states according to the DSM-5 definition (depressive episode with euphoric mood excluding agitation) ranges from 0 to 12% in empirical studies (Koukopoulos and Sani 2014), the frequency rate using the definition including agitation and irritability ranges from 33 to 47% (Koukopoulos et al. 2007; Angst et al. 2011). Psychomotor agitation and fatigue/loss of energy were identified as factors that could differentiate between predominantly depressive and predominantly manic episodes in an empirical study. Based on these findings, Malhi et al. (2015) proposed splitting mixed mood states into mixed mania and mixed depression. Moreover, agitated depression, which denotes depressive syndromes with psychomotor agitation and which was initially included in the original research diagnostic criteria, was proposed as an alternative diagnostic entity by Koulopoulos et al. (2013).

#### 1.2.6.4 With Peripartum Onset

The specifier "with postpartum onset" in the DSM-IV has been expanded to "with peripartum onset" in the DSM-5 and can be coded not only within 4 weeks after delivery but also during the entire pregnancy. Expansion of the specifier "with peripartum onset" accepts the finding that postpartum depressive episodes can start during pregnancy and worsen after delivery and rejects the belief that pregnancy has a protective effect against development of a major depressive episode. In addition, the specifier "with peripartum onset" emphasizes the clinical significance of the management of depressive disorders both during pregnancy and after delivery (di Florio et al. 2013; Uher et al. 2014).

However, there are several controversies about the specifier "with peripartum onset." A study of a nationally representative sample from the United States reported that the clinical presentation of depressive symptoms in women of childbearing age was not significantly different during pregnancy, after delivery, and outside the period of peripartum (Hoertel et al. 2015). The recurrence of MDD was also shown to be closely associated with the discontinuation of antidepressant treatments during the period of planning pregnancy or pregnancy (Cohen et al. 2006; Yonkers et al. 2011). In addition, postpartum onset depressive episodes have been associated with obsessive-compulsive and psychotic disorder, whereas depressive episodes during pregnancy have been associated with the recurrence of MDD (Altemus et al. 2012). Furthermore, it has not been established if there are differential responses to treatment in depressive episodes during pregnancy and after delivery (Uher et al. 2014).

#### 1.2.6.5 With Catatonia

"Catatonia associated with another mental disorder" has been newly conceptualized as a semi-independent category in the chapter "Schizophrenia Spectrum and Other Psychotic Disorders" in the DSM-5. Hence, the specifier "with catatonia" is coded for a condition that has three or more of the following symptoms: stupor, catalepsy, waxy flexibility, mutism, negativism, posturing, mannerism, stereotypy, agitation, grimacing, echolalia, and echopraxia. As a consequence of this revision, the definition of catatonia has been broadened, and validation through response to specific treatments including benzodiazepines and electroconvulsive therapy is needed (Moller et al. 2015; Uher et al. 2014).

## 1.3 Controversies

### 1.3.1 Categorical Versus Dimensional Approaches

In the development process of the DSM-5, combination of categorical and dimensional approaches to express the main distinction between affective psychosis (e.g., bipolar disorder and psychotic depression) and non-affective psychosis (e.g., schizophrenia and schizophreniform disorder) was proposed to deconstruct the Kraepelinian dichotomy (Adam 2013; Moller et al. 2015). However, symptom-based classification of schizophrenia and bipolar disorder remains, and dimensional approaches were abandoned in the DSM-5, although the Clinician-Rated Dimensions of Psychosis Symptom Severity in the emerging measures and models of the DSM-5 contain psychometric properties of dimensional approaches for hallucinations, delusions, disorganized speech, abnormal psychomotor behavior, negative symptoms, impaired cognition, depression, and mania domains (Heckers et al. 2013; Moller et al. 2015). In accordance with the distinction between schizophrenia and bipolar disorder, differentiating between MDD and GAD was regarded as a significant issue in the DSM-5 revision process (Hettema 2010). In addition, symptom-based classification of MDD and GAD is still present, and the specifier "with anxious distress" was introduced to express comorbid anxiety symptoms, whereas dimensional grading is used for both MDD (mild, moderate, and severe) and the specifier "with anxious distress" (mild, moderate, moderate-severe, and severe).

### 1.3.2 Heterogeneity of MDD in the Context of Polythetic Diagnostic Criteria

In both the DSM-IV and DSM-5, the diagnostic criteria for MDD are the presence of five or more of nine specific depressive symptoms (necessity of the presence of depressive mood or loss of interest) (Uher et al. 2014). Hence, 227 depressive symptom combinations can meet the diagnostic criteria of MDD. In real situations, Zimmerman et al. (2014) reported 170 symptom combinations in more than 1500 MDD patients diagnosed using the DSM-IV, while Park et al. (2017) reported 119 different combinations in 853 MDD patients diagnosed using the DSM-IV who scored $\geq 8$ on the Hamilton Depression Rating Scale. Moreover, several of the diagnostic criteria for MDD consist of multiple or alternative symptoms, including psychomotor agitation or retardation, impaired concentration or indecisiveness, worthlessness or guilt, insomnia or hypersomnia, decreased or increased appetite, and death wish or suicidal ideation. Separation of each component symptom of the six compound criteria means that 14,528 symptom combinations can meet the diagnostic criteria of MDD. Thus, Zimmerman et al. (2010) proposed defining MDD in a simpler way through the elimination of four somatic symptoms in the DSM-IV definition in order to overcome the epistemological restriction associated with the heterogeneity of MDD. In addition, a high concordance rate between the simpler definition and the DSM-IV definition of MDD was reported in 2907 psychiatric outpatients (Zimmerman et al. 2011). However, the simplification proposal was abandoned in the DSM-5 revision process (Uher et al. 2014). The heterogeneity of MDD in terms of its polythetic diagnostic criteria has often been criticized (Østergaard et al. 2011; Olbert et al. 2014; Fried and Nesse 2015; Zimmerman et al. 2015) and regarded as a concept corresponding to a language game in Wittgensteinian philosophy, because a single or "essential" characteristic of MDD cannot be identified, and cases of MDD comprise a set of "family resemblances" (Rosenman and Nasti 2012). Moreover, one study reported that the heterogeneity of depressive syndromes likely contributes to the limited knowledge and understanding of depression among nursing personnel in general hospitals (Park et al. 2015).

Moreover, because each of the symptoms in the DSM depression criteria is etiologically

heterogeneous, individual symptoms rather than symptom sum-scores should be considered to gain a holistic understanding of MDD (Fried et al. 2014). For example, the symptom combination of helplessness and hopelessness has been proposed as the most important distinguishing feature between depressed patients and healthy controls (McGlinchey et al. 2006). In addition, weight gain rather than weight loss is more closely associated with chronic stressors (Keller et al. 2007a, b). Moreover, the co-occurrence of disturbed sleep and appetite was shown to be more closely associated with bipolar than with unipolar depressive episodes (Papadimitriou et al. 2002). The interest-activity symptom dimension, including low interest, reduced activity, indecisiveness, and lack of enjoyment, was identified as a predictor of poor outcomes after treatment of 811 adults with moderate to severe depression with flexibly dosed escitalopram or nortriptyline (Uher et al. 2012). A network analysis of data from the Sequenced Treatment Alternatives to Relieve Depression (STAR*D) study rejected the assumptions that depression symptoms equivalently indicate MDD and that DSM symptoms of depression have greater clinical relevance than non-DSM depression symptoms (Fried et al. 2016).

## 1.4 Future Directions

Although transnosological specifiers as well as severity and cross-cutting assessments enable us to individualize treatments and differentially describe treatment outcomes (Moller et al. 2015), the grand ambition of the paradigm shift from categorical to dimensional approaches in the realm of depressive disorders was frustrated in the DSM-5 revision process, and symptom-based classification of depressive disorders remains in the DSM-5 (Whooley and Horowitz 2013). Although the Research Domain Criteria project has been suggested as an alternative research-related methodology (Insel et al. 2010), it does not provide routine framework conditions for clinical psychiatry (Moller et al. 2015). To achieve a better neurobiological understanding in the area of psychiatry, the diagnostic classification of depressive disorders should take into account the following comments of Thomas Insel (2013): "Unlike definitions of ischemic heart disease, lymphoma, or AIDS, the DSM diagnoses are based on a consensus about clusters of clinical symptoms, not any objective laboratory measure. In the rest of medicine, this would be equivalent to creating diagnostic systems based on the nature of chest pain or the quality of fever. Indeed, symptom-based diagnosis, once common in other areas of medicine, has been largely replaced in the past half century as we have understood that symptoms alone rarely indicated the best choice of medicine."

In addition, Kato et al. (2016) proposed that modern-type depression in Japanese younger generations is characterized by fatigue, feelings of worthlessness, blaming others, impulsive suicidal action, and occasional depressive symptoms mainly during work/school and is a distinctive entity associated with Japanese cultural and social influences. Diagnostic criteria for modern-type depression should consider depressive syndromes in the context of specific cultural and social backgrounds. Moreover, a humanistic approach that considers subjectivity and interpersonal context needs to be emphasized in future etiologically based classification systems (Castiglioni and Laudisa 2015).

**Conclusions**

Depressive disorders have been reformulated based on a combination of categorical and dimensional approaches in the DSM-5. However, despite the transdiagnostic specifiers, severity assessments, and cross-cutting measure assessments contained in the DSM-5, MDD is still defined using a symptom-based classification, and its heterogeneity is of significant concern. Moreover, it is necessary to develop an etiology-based classification of depressive disorders and to consider humanistic approaches together with potential cultural and social influences.

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# 2 Major Depressive Disorder and Bipolar Disorder: Differentiating Features and Contemporary Treatment Approaches

Ather Muneer

## 2.1 Introduction

Primary mood disorders, including major depressive disorder (MDD) and bipolar disorder (BD), are among the most prevalent psychiatric conditions. In a relatively recent international survey of 18 countries, the average lifetime prevalence of major depressive episodes (MDE) was 14.6% in 10 high-income countries and 11.1% in 8 low- to middle-income nations (Bromet et al. 2011). The population studied was not stratified according to the type of affective disorder, so that it can be assumed that the patients comprised of both MDD and BD as long as they fulfilled DSM-IV criteria for a major depressive episode. The current nosological classifications do not differentiate between these disorders as far as the diagnostic features of MDE are concerned, but prevailing viewpoint dictates that MDD and BD have fundamental neurobiological distinctions with therapeutic and prognostic implications. In this vein it must be appreciated that these disorders are discrete conditions, with differences that encompass genetic and pathophysiologic aspects impacting on illness trajectory and longitudinal course (Duman and Monteggia 2006). Such emerging insights are reflected in the Diagnostic and Statistical Manual's 5th edition in which a necessary shift has been implemented by segregating the two conditions into separate chapters, whereas previously these were described under the common rubric of "mood disorders."

Affective disorders are complex gene x environment diseases and are heterogeneous in phenotypic expression. Current knowledge assumes that these disorders lie on a spectrum with depression and mania being opposite poles of a disturbance that has myriad presentations confounded by such factors as personality characteristics, neuropsychiatric comorbidities, and psychosocial incumbencies (Becker and Grilo 2015). In the early phase of the illness, stress factors are identified as precipitating events, but with advancement of the diathesis, mood episodes recur spontaneously. Further, asymptomatic periods become progressively shorter and an unrelenting disease state ensues with impairments in cognitive and functional domains (Moylan et al. 2013). These phenomena are epitomized by such negative attributes as rapid cycling, residual affective states and subthreshold symptoms. The overall consequence of this process which has been aptly termed as "neuroprogression" is a decline in autonomy, impairment in role functioning, and loss of personal independence. In this regard the later stages of mood disorders are typified by severe psychosocial and biological disturbances, with incremental damage to all body systems because of the derangement of the homeostatic balance caused by increased "allostatic load"

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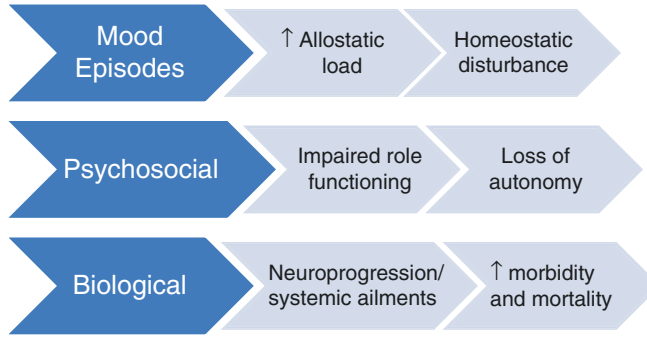


**Fig. 2.1** The pernicious nature of mood disorders. Mood disorders, whether MDD or BD, are conceptualized as very serious conditions with profound consequences in the biopsychosocial realm. Repeated affective episodes increase "wear and tear" in the body with increased allostatic load. The resulting homeostatic imbalance has a pervasive negative effect with such consequences as cognitive impairment, physical comorbidities, persistent affective symptoms, and role impairment leading to eventual loss of autonomy

(McEwen 2003). Figure 2.1 gives a schematic representation of the pernicious nature of mood disorders with ensuing profound negative consequences for all bodily systems (Fig. 2.1).

The burden imposed by these ailments in the biopsychosocial realm is immense, as subjects of both sexes are initially afflicted in youth or early adulthood and suffer from relapses and recurrences throughout their lifetimes. Modern perspective states that these are in essence multisystem disorders, affecting essentially all parts of the body and leading to increased morbidity and mortality from such conditions as diabetes mellitus, cardiovascular diseases, and immunological disorders (Mansur et al. 2015). Further, the neurobiology of mood disorders is incompletely understood, and presently available treatments are of palliative rather than curative value. Despite continued research efforts, gaps in knowledge are significant which translate into less than optimal therapeutic measures with adverse consequences for the sufferers, their families, and the society as a whole (Muneer 2016a). In this scenario it is crucial to inculcate a better understanding of these ailments so that the patients are managed more effectively and their disease burden is reduced. With this preamble, the manuscript is dedicated to discussing the most relevant issues in the etiology, pathogenesis, and treatment of mood disorders. However, first clinical features are mentioned followed by a description of the genetic aspects and pathophysiologic implications; lastly, therapeutic measures are considered.

## 2.2 Clinical Considerations

The sine qua non of BD is a manic episode, but in actual practice depression is its most frequent clinical presentation (Muneer 2016b). Longitudinal naturalistic studies show that bipolar patients spend the majority of their time in the depressed state, rather than being manic or hypomanic (De Dios et al. 2012). The former can manifest as major depressive episodes or as subthreshold symptoms. Additionally, depressive manifestations can intermingle with manic or hypomanic symptoms and give rise to mixed states, which are more severe and lead to adverse psychosocial sequelae (Valenti et al. 2015). Whereas in MDD, depressive episodes occur in the mid-20s onward, bipolar depression has a much earlier onset in early teenage years, is often the index episode, and usually has melancholic features (Muneer 2016c). BD is notorious in masquerading in myriad forms, and the presenting illness can be in the way of anxiety spectrum disorders, conduct disorders, and substance use disorders. Because of these reasons, the condition is misidentified, and the lag period in diagnosis is of the magnitude of several years (Nasrallah 2015).

The major depressive episodes in MDD can be single or recurrent but tend to be discrete, with well-characterized periods of remission. In the case of BD, patients are symptomatic for longer periods; they may have full blown severe mood episodes or subsyndromal symptoms in the inter-episode which has a pervasive negative effect on the overall prognosis. Rapid cycling is a phenomenon in which bipolar patients have four or more affective episodes in a 12-month period. This is regarded as an extreme form of the disorder with harmful consequences in the functional and psychological domains (Carvalho et al. 2014). With repeated mood episodes, there is deterioration in all aspects of living and neuroprogression, which in essence implies the persistence of a deficit state with eventual loss of autonomy (da Costa et al. 2016). The suicide rate is very high in BD, and this may be attributable to many factors, chief among which are greater number and severity of episodes, existence of mixed states, and presence of such comorbidities as anxiety spectrum and substance use disorders (Rajewska-Rager et al. 2015).

In this situation, a primary question for the treating psychiatrist is the correct identification of the mood disorder when a patient presents with a major depressive episode. Although there are no validated criteria for such a distinction, certain features should alert the clinician in this regard. This is important because treatment of bipolar disorder is primarily with mood stabilizers, whereas unipolar depression is best managed with standard antidepressant medications (Karanti et al. 2016). Administration of antidepressants without adjunctive mood stabilizers to bipolar subjects can result in manic/hypomanic switch, induction of mixed states, and rapid cycling (Muneer 2015).

When a patient first presents with an MDE, the presence of family history of bipolar disorder is a cautionary sign. Age of onset is also significant, with the index episode occurring in adolescence or teenage years in BD, while in the case of major depression, this is usually in the mid-20s. Furthermore, bipolar subjects tend to suffer from recurrent episodes which are of greater severity, so that there may be a history of psychiatric hospitalizations (Shapiro et al. 2014). Of note, major depression which is treatment resistant to two or more first-line antidepressant medications should raise the suspicion of a masquerading bipolar diathesis. Unipolar patients who shift to mania or hypomania when treated with antidepressants, ECT, or chronobiological measures are considered to lie on the bipolar spectrum. In this regard seasonal variation may be marked in BD, with patients experiencing repeated depressive episodes during fall and winter months (Akhter et al. 2013).

With respect to clinical presentation, patients with bipolar depression often experience mixed features such as racing thoughts, irritability, grandiose ideation, and increased energy. Moreover, they are prone to having recurrent suicidal ideation, and a history of repeated self-injurious behavior in unipolar depression should raise the specter of underlying bipolar illness (Musliner et al. 2016). Neuropsychiatric and physical comorbidities are frequently associated with BD including panic disorder, posttraumatic stress disorder, alcohol and other substance use disorders, borderline personality disorder, and eating disorders (Simhandl et al. 2016). Neurological conditions found more often in bipolar patients comprise of migraine, idiopathic neuropathic pain, vertigo, and restless legs syndrome (Fornaro and Stubbs 2015). An important caveat with respect to the bipolar diathesis is its association with the metabolic syndrome, obesity, and diabetes mellitus so that cardiovascular diseases are considered as the foremost cause of premature mortality in this group of subjects (Grover et al. 2014). In conclusion, it can be construed that among mood disorders BD is a much more severe condition than MDD and is challenging to manage because of the facts mentioned above. Table 2.1 gives a summary of clinical features that should alert clinicians for the possible presence of bipolar spectrum disorders in patients presenting with major depressive episodes (Table 2.1).

**Table 2.1** Likely indicators of bipolarity in patients presenting with major depressive episodes

| Onset in adolescence or early teenage years |
|---|
| 1. Family history of bipolar disorder |
| 2. Comorbid anxiety, substance use or conduct disorders |
| 3. Major depressive episode with melancholic features |
| 4. Psychotic depression |
| 5. Repeated mood episodes |
| 6. Increased severity of episodes, with history of hospitalization |
| 7. Treatment-resistant depression |
| 8. Mixed states |
| 9. Seasonal affective disorder |
| 10. Suicidal behavior/repeated attempts at self-harm |
| 11. Switching on antidepressants |

## 2.3 Etiology of Mood Disorders

### 2.3.1 Genetic Aspects

Depression is a prevalent mental illness that is projected to be among the most common causes of morbidity by 2020. Research efforts have shown that the share of genetic factors in the causation of depression is 30–40%, and there is a growing literature that is linking this vulnerability to biological substrates (Lohoff 2010). The methodology adopted for research purposes is greatly varied, ranging from candidate gene approaches to genome-wide association studies. In this regard, the serotonergic system is a principal target due to its involvement in the regulation of mood and anxiety. Of particular significance is the serotonin transporter protein responsible for 5HT synaptic reuptake, which is also the key target of monoaminergic antidepressants. The gene coding for this protein is SLC6A4, and in humans the s (short) allele of the 5-HTTLPR polymorphism of the serotonin transporter gene is incriminated in anxiety related attributes and neuroticism (Daniele et al. 2011). This variation conveys increased attention and sensitivity to environmental stressors, and carriers of the genotype have a tendency to experience neutral stimuli as negative and threatening. Accompanied by less efficient coping strategies in the face of stress, these individuals are more liable to developing depressive disorders (Kuzelova et al. 2010). In human studies, an immense range of methodologically diverse approaches including the exploration of different stressors, self-report questionnaires, imaging techniques, investigation of the HPA axis, and postmortem brain examination have given credence to an association between the s allele and stress-induced reactivity (Hildebrandt et al. 2016).

s allele carriers are discovered to exhibit increased and rapid activation in the amygdala, a structure implicated in regulating homeostatic and behavioral responses to outside stressors and fearful stimuli. Further, alterations in the functional and microstructural connectivity of the amygdala and the medial prefrontal cortex are also described in s allele carriers (Savitz and Drevets 2009). The gene for the serotonin transporter protein, 5-HTTLPR, is involved in other possible mood disorder antecedents such as subthreshold depression and affective temperaments. In an important prospective study, Caspi et al. showed the effect of s allele of the 5-HTTLPR polymorphism on the development of depressive symptoms in the presence of stressful events (Caspi et al. 2003). This finding was afterward substantiated by a very large meta-analysis, which included 54 studies on overall 41,000 subjects. In some of the earlier studies, conflicting findings regarding the link between different types of stressors, 5-HTTLPR genotype, and depression were related to distinctions concerning the definition, evaluation, inclusion of and delineation between diverse stressors, and life events. However, the said meta-analysis clarified these issues and further demonstrated that childhood and adolescent maltreatment, proximal life events, and serious medical conditions were all liable to cause depression in those carrying the s allele or the ss genotype of the 5HT transporter gene (Karg et al. 2011). In a European study comprising of a large population sample, comparable and statistically significant associations were observed in subjects carrying the ss genotype and a moderately significant association in sl cases when they were investigated for a relationship between threatening life events and mood symptoms as assessed by the Zung Self-Rating Depression Scale. Whereas extreme

stressors individually explained 2.4% of the variance in affective manifestations, this proportion increased approximately twofold to 4.2% upon including the intermediary effect of 5-HTTLPR genotype and climbed to 5.9% when genotype data of other polymorphisms of the serotonin transporter gene were incorporated in the model (Lazary et al. 2008). These statistics clearly show that genetic variability and environmental influences act together in regulating mood.

### 2.3.2 New Understanding of Depression

In the case of depression, the interaction between the environment and genetic factors is complex. Previous models posit that in the existence of inherited predisposition, adversities experienced during childhood or adolescence contribute to enhanced susceptibility to depressive illnesses in adult life in the face of stressful life events. In this regard carriers of the s allele are at a greater risk of affective illnesses when encountering severe stressors; however, recent research underscores the importance of other DNA regions in this gene x environment model. For example, one study showed no association between seasonal affective disorder and 5-HTTLPR s allele (Molnar et al. 2010), while in another paper specific linkage between rumination, a trait-like cognitive style, and depression was mapped to CREB1 and BDNF genes (Juhasz et al. 2011). These instances allude to the fact that everyday stressors are diverse including among others childhood maltreatment, losses, health problems, hormonal changes, and seasonal variations and each person has a discrete liability profile toward adverse and protective events and occurrences. Therefore, different genes may have distinct contributory or ameliorative effects in the development of a complex phenotype, namely, depression.

In an emerging synthesis of the depression model, several other genes besides 5HT transporter play a role in the causation of the diathesis. These include genes involved in serotonergic neurotransmission (HTR1A, HTR2A, TPH1), dopaminergic neurotransmission (DRD2, DRD4), monoamine metabolism (MAOA, COMT), neurotrophins (BDNF), endocannabinoids (CNR1), transport, and other proteins (SLC1A1, SLC6A2, CREB1, KCNJ6, CACNA1, GLUR7). In many studies CNR1, the gene of the cannabinoid CB1 receptor has been strongly implicated in depression besides the SERT gene and has been further associated with trait anxiety and neuroticism. An SNP (rs2180619) in the CNR1 gene interacts with ss 5-HTTLPR genotype to increase trait anxiety manifold (Lazary et al. 2009). The substrate of this interaction is purportedly a sustained high 5HT concentration following activation of the serotonergic neurons in response to stress, resulting from a low expression of the inhibitory CB1 receptors and high synaptic serotonin concentration because of low SERT levels. Comparable observation was reported in fMRI studies where heightened amygdala activation was seen in ss carriers and this correlated with increased neuroticism scores. These findings suggest that SERT and CB1 receptor genes are the most strongly implicated among the candidate genes and further point out that depressed mood manifests on the basis of diverse DNA regions mediating the effects of varied environmental influences. Additionally, the depressive phenotype arises from an interaction of these genes at the substrate level (Bagdy et al. 2012).

The genes incriminated in depression can be classified into seven groups or sets, some of which confer resiliency while others induce vulnerability. Varied gene sets have a role in the development of personality, mediation of the effects of environmental influences, and interplay of diverse aspects of temperament with external factors. Environmental dynamics comprise of internal and external factors; several of the early influences directly affect the formation of personality traits and temperaments. While some of the genes, for example, tryptophan hydroxylase 2, are included in one set, others (5-HTTLPR and CB1) are constituents of several groups. Intriguingly, even without one gene set, discrete genes may have separate roles, and not all genes are engaged in every function. As an example, 5-HTTLPR has a profound influence in mediating the effects of particular aggravating life

events, but has no significant role in seasonal depression (Mushtaq et al. 2016). Table 2.2 delineates candidate genes grouped in sets and identified in large-scale population studies, conferring resiliency or predisposing to mood disorders in the wake of environmental stressors (Table 2.2). Figure 2.2 is an illustrative rendition of a new model of depression that emphasizes the interaction between gene sets, personality, and environment in the development of mood disturbance (Fig. 2.2).

The s allele of 5-HTTLPR has a significant but weak association with depression provoking effects of stress so that it cannot be utilized for direct screening of the susceptibility to this disease. Further, in the absence of multiple severe stressors, s allele carriers may not show more depressive symptomatology than those carrying other genotypes. Nonetheless, in the presence of extreme and manifold life stresses, s allele carriers are more prone to dysthymic mood, poor coping, and full-blown depressive illness. Additionally, these subjects show worse therapeutic response to SSRIs, the most commonly used antidepressants. They show slower onset of action, lower rates of response, poor tolerability, and frequent side effects with this group of medications, while drugs with different pharmacodynamics (e.g., norepinephrine-selective agents) are more effective in s allele carriers. When vulnerability and resiliency factors are viewed together, it can be surmised that screening for 5-HTTLPR genotype can be part of a working assumption in better understanding the evolving etiopathology of depression. Further, this could be instrumental in identifying those individuals who are at increased risk for mood disorders and be of assistance in choosing appropriate treatment for the patients (Fabbri et al. 2013).

### 2.3.3 Epigenetic Influences

In the case of neuropsychiatric disorders, the contribution of hereditary factors is estimated to exceed 30%, but even with state of the art methods, only a fraction of this variance can be mapped to specific genes and DNA base sequence alterations. In this scenario, epigenetic effects have become the focus of attention as these play a role in regulating protein synthesis, are only partially heritable, but subject to modification by environmental influences. Two chief epigenetic mechanisms can adapt the function of genes:

1. Acetylation or methylation of histones that direct the availability of DNA for biological processes
2. Methylation of the DNA itself, which inhibits the transcriptional activity of the CpG-rich regions of the genome

Since these alterations are allele specific, genetic polymorphisms are linked to different probability and type of epigenetic changes upon environmental exposure, and consequently considerable variance occurs in sensitivity to such

**Table 2.2** Gene sets responsible for heritable traits that interact with environmental factors in the causation of mood disorders

| Factors linked to mood disorders | Gene products (proteins) | Involved genes |
|---|---|---|
| Neuroticism, trait anxiety | SERT, CB1 | SLC6A4, CNR1 |
| Stress/negative life events | SERT, CB1 | SLC6A4, CNR1 |
| Depressogenic/anxiogenic effect of medications | SERT, CB1 | SLC6A4, CNR1 |
| Stress coping (resiliency versus vulnerability) | 5-$HT_{1A}$, 5-$HT_{1B}$ | HTR1A, HTR1B |
| Rumination | CREB1, GIRK, BDNF | CREB1, KCNJ6, BDNF |
| Hopelessness | TPH2 | TPH2 |
| Impulsiveness | 5-$HT_{1A}$, COMT | HTR1A, COMT |
| Seasonal variations | 5-$HT_{2A}$ | HTR2A |

*BDNF* brain-derived neurotrophic factor, *CB1* endocannabinoid receptor 1, *COMT* catechol-*O*-methyltransferase, *CREB* cyclic AMP response element-binding protein, *GIRK* G protein-coupled inwardly rectifying potassium channel, *SERT* serotonin transporter protein, *TPH* tyrosine hydroxylase, *5-HT* serotonin

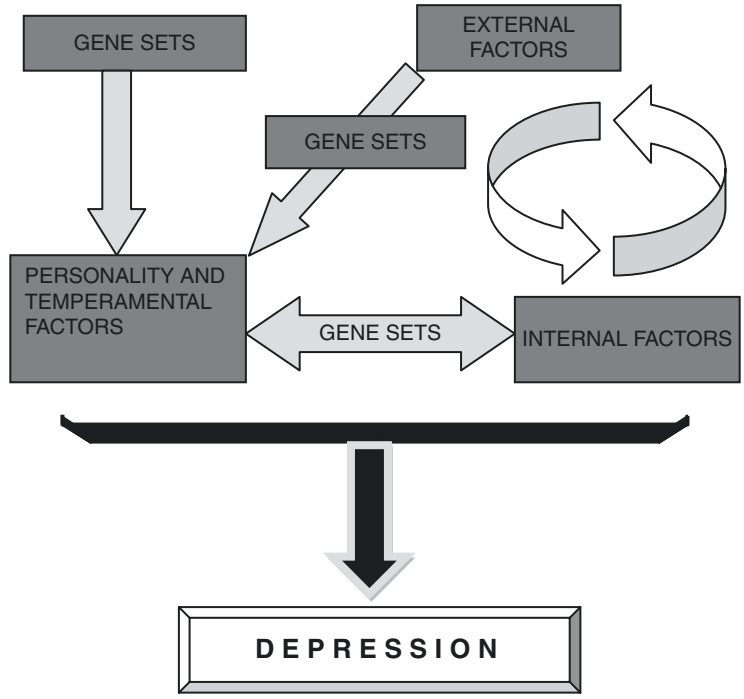


**Fig. 2.2** New gene x environment model of depression. *Candidate genes comprising gene sets*: 5-HTTLPR, CB1, TPH2, CREB1, BDNF, COMT, GIRK, HTR1A, HTR2A. *Personality/temperamental factors (predisposing)*: neuroticism, rumination, stress vulnerability, impulsivity, negative cognitive style. *Personality/temperamental factors (protective)*: openness, trust, acceptance, stress coping. *External factors*: early life events, provoking life events, seasonal changes, social support. *Internal factors*: hormones, biological rhythm generators, comorbid disorders. The new gene x environment model of depression is based on diverse gene sets that acting through personality, internal and external factors lead to the development of depression. Some genes are part of more than one set, for example 5-HTTLPR and CB1, while others like HTR2A belong to only one set. These gene sets act with intermediaries like temperamental traits or environmental factors, for example seasonal variation to cause the depressive diathesis

factors. A pertinent example is the catechol-O-methyltransferase gene in which the existence of $Val^{158}$ allele in the rs4680 SNP creates a CpG site for methylation, the repressive effect of which can compensate for the enhanced dopamine elimination in the prefrontal cortex in the high-activity Val allele carriers. However, life stressors diminish the methylation of this area of the gene, leading to increased activity of COMT with resultant impaired working memory due to decreased dopamine availability in this key brain region (Ursini et al. 2011). In a study investigating the effect of COMT gene on depressed mood, it was discovered that variations in the said gene were associated with depressive symptom scores in those who had not been depressed previously in contrast to those who had already suffered from depression, probably because epigenetic modifications altered the gene function in patients (Pap et al. 2012). This mechanism might clarify why childhood abuse amplifies the risk for later depressive disorders. In a rodent study, maternal maltreatment evoked long-lasting methylation of the BDNF gene in the prefrontal cortex, and these animals showed impaired rearing behavior toward their offspring (Roth et al. 2009). In line with this observation, the BDNF gene in a human population study was associated with increased risk of depression exceptionally in the presence of childhood trauma (Juhasz et al. 2011). In this vein it must be understood that the salient attribute of epigenetic imprint is its tissue and cell specificity, so that different parts of the brain show discrete methylation and acetylation patterns, severely

hampering the ability to investigate this in vivo human brain. There is no method yet to study epigenetic changes in the living brain, but gathering in-depth knowledge concerning genetic base sequence and its interaction with environmental factors is crucial to understanding the pathophysiology of mood disorders, as well as predicting medication beneficial and adverse effects.

## 2.4 Pathogenesis of Mood Disorders

Mood disorders afflict innumerable people every year and cause a great deal of morbidity and mortality, but their neurobiology is only partially elucidated. In this situation, a growing body of evidence points to the involvement of the immune-inflammatory system in their inception and progression. During acute affective episodes, patients have elevated levels of inflammatory proteins, i.e., cytokines and chemokines in the peripheral circulation (Rosenblat et al. 2014). It is now known that repeated and severe stressors, in the absence of pathogenic disease, can induce an inflammatory response and this has been aptly called "sterile inflammation." Recently, in the last decade or so, it has become clear that psychological stress, in the nonexistence of overt tissue damage, can trigger systemic and CNS sterile inflammation with homeostatic imbalance that can have profound effects and damage all organ systems in the body (Fleshner 2013). This has been substantiated in laboratory experiments on animals with such paradigms as social conflict, threat, isolation, and rejection which cause increase in C-reactive protein, proinflammatory cytokines (IL-6, IL-1β, TNF-α), and elevated expression of NF-κB (Aschbacher et al. 2012). The behavioral effect of this raised inflammatory status is manifested as an overt expression of the depressive phenotype in the research animals.

In human subjects parallel findings have been described, for example, a study reported that the death of a spouse increased IL-1β and IL-6 activity in older adults (Schultz-Florey et al. 2012). Intriguingly, increases in inflammatory indicators following exposure to an acute traumatic event are linked to the development, symptom severity, and duration of affective disturbances like depression, anxiety, and posttraumatic stress disorder (Mills et al. 2013). Severe and persistent stress can by itself induce a low-grade inflammatory state which can precipitate mood perturbation reminiscent of major depressive disorder. The inflammatory receptor-ligand interaction invoked in this process has been termed danger-associated molecular patterns (DAMPs), mediated by inflammasome-dependent signaling which appears to play an overarching role in the pathogenesis of mood disorders (Iwata et al. 2013).

### 2.4.1 Inflammatory Molecular Patterns

The main effectors of the inflammatory response are the innate immune cells, while adaptive immune cells are important partners. The former are found throughout the body and CNS and respond to pathogenic challenges, cellular stress, and tissue damage. Receptor-ligand recognition schema is a notable and fundamental differentiating attribute between innate and adaptive immune cells. The former use germline-encoded receptors intended to identify conserved molecular patterns and have been named pattern recognition receptors (PRRs). A huge number of ligands are capable of binding PRRs and include both pathogenic and commensal microbes, termed microbe-associated molecular patterns or MAMPs, whereas typically pathogenic patterns are labeled pathogen-associated molecular patterns or PAMPs (Sirisinha 2011). Examples of MAMPs and PAMPs include lipopolysaccharide (LPS), a membrane incorporated component of many gram-negative pathogenic bacteria or CpG DNA, a common viral motif. Of note, a strong inflammatory reaction is the result of PRR-PAMP binding. In contrast to these prototypes, DAMPs are endogenous molecules which are increased after cellular stress and tissue damage, and PRR-DAMP binding leads to sterile inflammation (Ibrahim et al. 2013). Newly recognized DAMPs are increasingly being reported and include extracellular heat shock proteins (Hsp),

adenosine triphosphate (ATP), high mobility group box 1 (HMGB1), etc. (Frank et al. 2015). There is extensive overlap in a broad array of inflammatory proteins that are mediated after either LPS (PAMP) or stressor exposure (DAMP). These are detectable in the blood and peripheral tissues and include cytokines, chemokines, and mRNA transcripts. In this vein, it needs to be recognized that brain tissue and microglia also respond to PAMPs and DAMPs by increasing the secretion of inflammatory mediators (Frank et al. 2016).

### 2.4.2 Sterile Inflammation and the Inflammasome

It has been recently reported that acute and intense psychological stress in the lack of obvious tissue damage can provoke a demonstrable local and systemic sterile inflammatory response, with DAMPs playing an inciting role. In this respect, tail shock in rodents increases tissue and blood concentration of many cytokines and chemokines, and both MAMP (derived from the gut bacteria) and DAMP signals are involved in the inflammatory response. Significantly, in the said experiments, this was attributed to the inflammasome, more specifically the NLRP3 inflammasome known as nucleotide-binding oligomerization domain, leucine-rich repeat, and pyrin domain protein 3 (Maslanik et al. 2013). Inflammasomes are intracellular multiprotein complexes that act as sensors of DAMPs and PAMPs, causing activation of catalytic caspases and the cleavage and release of proinflammatory cytokines.

For cytokines that are inflammasome independent, the process begins with NF-κB activation after MAMPs or DAMPs binding to toll-like receptor-4 (TLR-4), CD14, and other potential PRRs. The subsequent signaling cascade comprises of inflammatory gene transcription, translation, protein synthesis, and release. In contradistinction, inflammasome-dependent cytokine synthesis and release is a two-step process that is started after ligation of TLRs and other PRRs leading to NLRP3 gene transcription, translation, and protein production. Once primed in this way, a second activation signal is required for mature caspase-1 to cleave pro-IL1β into functional IL-1β (Kang et al. 2014). The NLRP3 inflammasome appears to react to a wide array of signals (ATP, $K^+$ efflux, β-amyloid, reactive oxygen species, etc.) to get activated and binds to these stimuli as it expresses several PRRs including TLRs, RAGE, and CD91. As such it has been incriminated in a wide range of sterile inflammatory diseases including ischemia-reperfusion injury, autoimmune disorders, DM II, obesity, atherosclerosis, and Alzheimer's disease, conditions which have high comorbidity rates with mood disorders (Li et al. 2014). More specifically, patients with depression had increased expression of NLRP3 and caspase-1 in peripheral blood mononuclear cells, suggesting that sterile inflammation mediated by DAMPs and the inflammasome and induced by exposure to psychological stress is implicated in the pathogenesis of MDD and other psychopathologies (Alcocer-Gomez et al. 2014).

### 2.4.3 Neuroinflammation and Mood Disorders

Peripheral inflammatory processes are liable to incite neuroinflammatory changes through well-described humoral and neural pathways of immune-to-brain signaling. For instance, the humoral pathway may involve blood-borne cytokines provoking neuroinflammatory processes through active transport across the blood-brain barrier, entry into the brain at the circumventricular organs, or binding of cognate receptors on brain endothelial cells with transduction of cytokine signaling into the CNS. In addition, cytokines as well as PAMPs (e.g., LPS) are capable of stimulating afferent vagal fibers in the periphery, which cause activation of neural pathways in brain regions involved in motivation and mood regulation (Marquette et al. 2003). Once a peripheral inflammatory signal reaches the brain, microglia the chief innate immune cells of the CNS play a pivotal role in mediating the neuroinflammatory response.

Microglia perform several crucial functions in the brain including immunosurveillance for pathogens, cellular debris, apoptotic cells, and neuronal phenotypic alterations. Upon activation microglia enter a primed position and when stimulated in this state secrete increased amounts of inflammatory mediators, including IL-1β (Nakagawa and Chiba 2015). As these specialized macrophages express pattern recognition receptors including TLR2 and TLR4, TLR ligation by danger-associated molecular patterns (ATP, Hsp, HMGB1, etc.) strongly triggers microglia (Weber et al. 2015). Furthermore, several inflammasomes have been described in the microglia including NLRP1, NLRP3, and NLRC4. The NLRP3 inflammasome has been most widely studied in the CNS and is also the focus of the preponderance of studies in animal models of depression. Recent investigations also suggest that NLRP3 may be exquisitely sensitive to the homeostatic perturbations induced by psychobiological stress, with a mechanistic role for the inflammasome-mediated processing and maturation of IL-1β in the generation of mood disorders (Li et al. 2016). While space limitation does not allow a detailed outline of animal studies highlighting the link between stress, DAMPs, and the inflammasome in the instigation of neuroinflammation and its behavioral sequel, the induction of the depressive phenotype, it is clear that CNS inflammation is caused by acute or chronic stress in the absence of infection or pathogen exposure (Zhang et al. 2015).

### 2.4.4 Purported Model of Depression

In the light of above considerations, a proposed model of depression is presented as following (Fleshner et al. 2017):

1. Exposure to stressors results in the release of DAMPs within the brain, presumably from damaged or dying neurons.
2. These neuron-derived DAMPs then target their cognate receptors on microglia leading to NLRP3 inflammasome activation and the synthesis and release of inflammatory mediators, including IL-1β.
3. The secreted form of this cytokine may drive the induction of indoleamine 2,3-dioxygenase (IDO).
4. IDO-mediated catabolism of tryptophan feeds into kynurenine pathway, thereby diverting the pool of this essential amino acid from 5HT synthesis to potentially neurotoxic metabolites and reducing the availability of the neurotransmitter.
5. Decreased availability of serotonin provokes a depressive phenotype with attendant psychological, neurovegetative, and somatic symptoms.

As a summarizing note, it must be appreciated that understanding the processes involving sterile inflammation, DAMP/MAMP/PAMP signaling in the periphery and CNS and inflammasome activation are critical for efficacious therapeutics of affective disorders. While notable advances are made in this respect in neurological disorders such as stroke, novel agents have not yet been tested in psychiatric patients. New therapeutic modalities emerging from enhanced knowledge can pave the way for curative treatments for otherwise recalcitrant conditions (Alcocer-Gomez and Cordero 2014). Figure 2.3 gives a schematic representation of this supposed model of depression and depicts the key role of NLRP3 inflammasome and IL-1β in the expression of depressive phenotype (Fig. 2.3).

## 2.5 Treatment of Mood Disorders: The Current Perspective

Mood disorders are lifelong, recurring, and devastating psychiatric conditions that are a leading cause of suffering and have grave personal and societal consequences. Major depressive disorder and bipolar disorder are difficult to manage ailments because of heterogeneity in presentation, neuropsychiatric and physical comorbidities, and refractoriness to currently available psychopharmacological agents (Fountoulakis and Vieta 2008). At different points in the illness, patients

require complex medication regimens to treat the varied manifestations, and compliance is very low due to a whole host of adverse effects caused by the psychotherapeutic agents. In this event, there is an immediate unmet need for more effective and tolerable drugs that are actually curative rather than palliative in nature. With this preamble, in the present section of the manuscript, focus will be directed to promising therapeutic options, and a concise overview will be presented of the recent trends in mood disorder psychopharmacology.

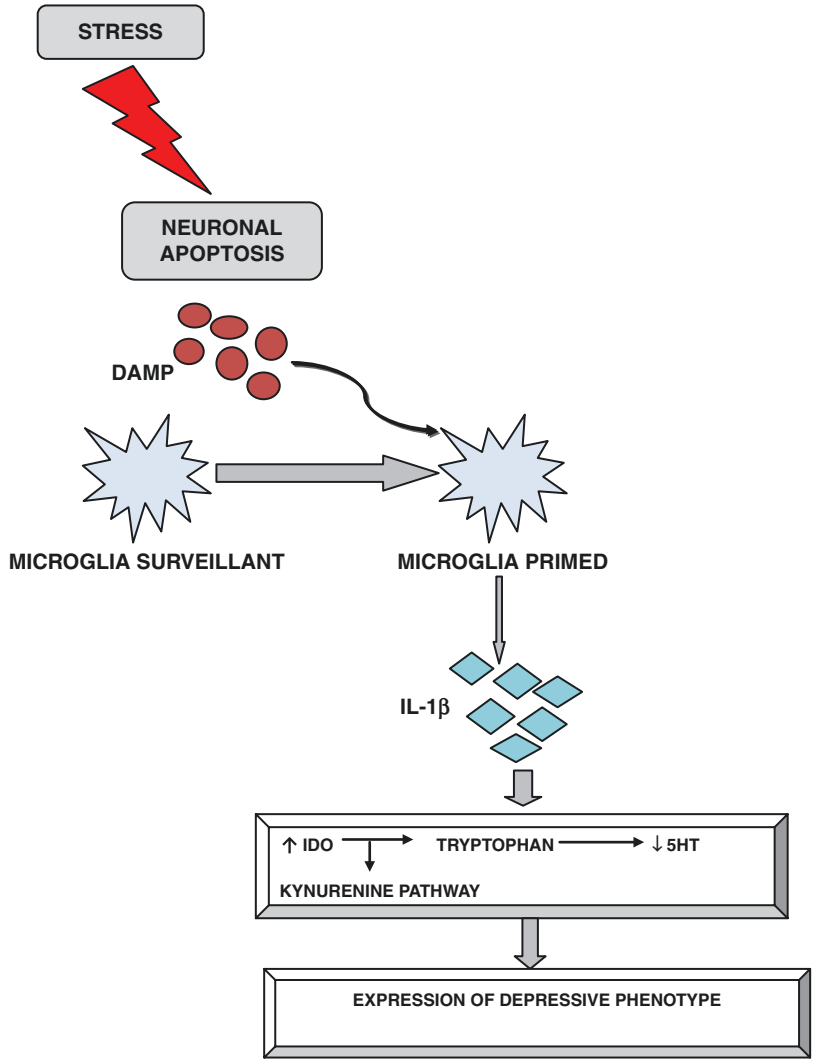


**Fig. 2.3** Stress-induced sterile inflammation and expression of the depressive phenotype. In a supposed model of depression, psychological stressors cause damage to neurons with efflux of a broad range of signals or damage-associated molecular patterns (DAMPs). These bind to pattern recognition receptors like toll-like receptors (TLR 2/4) and purinergic receptors (P2X7R) on microglia and cause the formation of NLRP3 inflammasomes via transcription, translation, and protein synthesis. Primed microglia release mature IL-1β via activated inflammasomes, and further this proinflammatory cytokine induces the enzyme indoleamine 2,3-dioxygenase (IDO). The later catabolizes tryptophan, an essential amino acid required in the synthesis of serotonin. Diversion of tryptophan metabolism toward the kynurenine pathway leads to a deficiency of serotonin, as well as the formation of potentially neurotoxic metabolites like quinolinic acid. As a final step, reduction of this key neurotransmitter at the synapse leads to the provocation of sickness behavior and depressive symptoms

### 2.5.1 The Emerging Role of Atypical Antipsychotics

These medications comprise of second- and third-generation antipsychotics, and although the first prototype, clozapine, was discovered in the 1970s, vast strides have been made, and several new agents have been introduced into clinical practice. Amazingly, there has been a steady increase in their licensed and off-label prescribing in a wide range of neuropsychiatric conditions (Maher and Theodore 2012). Initially indicated for schizophrenia, these medications have become first-line agents for the treatment of manic, mixed, and depressive episodes of BD and more recently have established a niche as an augmentation strategy along with standard antidepressants in MDD. In the present paper atypical antipsychotics will be discussed with reference to the treatment of MDD to highlight their importance in the current psychopharmacological landscape (Pompili et al. 2016).

In spite of the availability of several classes of antidepressants, most MDD patients do not achieve an adequate response or remission with such treatment. This issue is underscored by the STAR*D trial in which a 12-week treatment with SSRI monotherapy (citalopram) only resulted in 30% remission rate in unipolar depression cases (Rush et al. 2009). Further, a large meta-analysis including 182 antidepressant RCTs ($n$ = 36,385) revealed that the response rates were around 54 and 37%, for drug and placebo, respectively (Papakostas and Fava 2009). In this situation, most guidelines recommend augmentation strategies for MDD partial or nonresponders which mainly comprise of atypical antipsychotics, mood stabilizers (lithium and various anticonvulsants), and thyroid hormones (Patkar and Pae 2013). Among these steps, the addition of second- and third-generation antipsychotics to existing antidepressant regimens has received approval by licensing authorities such as the United States Food and Drug Administration (FDA). In this regard, based on evidence from randomized, placebo-controlled trials, the FDA first approved aripiprazole in 2007, followed by quetiapine XR and olanzapine/fluoxetine in 2009 and most recently brexpiprazole in 2015 (Greig 2015).

### 2.5.2 Pharmacodynamic Considerations

In the case of new-generation antipsychotics, the exact mechanism responsible for therapeutic effect in MDD has not been clarified, but based on current understanding of the etiopathogenesis of mood disorders, their pharmacodynamic actions can be as following (Rahola 2012):

1. Modulation of key neurotransmitter receptors and transporters, namely, dopamine, serotonin, and norepinephrine
2. Effects on the circadian machinery and manipulation of the sleep-wake cycle
3. Exploitation of the steroid hormone homeostasis, particularly the hypothalamic-pituitary-adrenal axis involved in the management of stressful stimuli
4. Modification of the immune system with alterations in pro- and anti-inflammatory proteins
5. Balancing out the antioxidant process with net decrease in pro-oxidant radicals
6. Increase in trophic support to the neurons, principally through brain-derived neurotrophic factor

Specifically, the chief pharmacological mechanism of atypical antipsychotics as antidepressant augmentation agents could be explained by their effects on monoamine neurotransmission. Third-generation antipsychotics, namely, aripiprazole, brexpiprazole, and cariprazine, act as partial agonists at D2 and/or D3 receptors and may increase dopamine neurotransmission in the prefrontal cortex. These agents also act as 5-HT1A receptor partial agonists, and this property may further enhance dopamine neurotransmission in the prefrontal cortex through an indirect mechanism (Stahl 2016). The characteristic of 5-HT2A receptor antagonism is shared by all atypical antipsychotics, and this attribute may also mediate their antidepressant boosting effect in MDD nonresponders. Furthermore, the antagonism of

5-HT2C receptors is incriminated in enhanced dopamine and norepinephrine transmission in corticolimbic regions of the brain (Stahl 2014). While both 5-HT6 receptor agonists and antagonists exert antidepressant-like effect in rodent models of depression, this phenomenon is marked when standard antidepressants are augmented with 5-HT6 antagonists (Liu et al. 2015). With respect to 5-HT7 receptors, preclinical models consistently show their relevance in different experimental paradigms such that new-generation antipsychotics exhibiting antagonism at this site may have potential therapeutic role in MDD (Bawa and Scarff 2015). Some atypical antipsychotics have high affinity for $\alpha_2$-adrenergic receptors which enhances the release of norepinephrine from the presynaptic neuron. Unlike any other new-generation antipsychotic, ziprasidone has been reported in vitro to block the synaptic reuptake of monoamines via inhibition of their transporters. Ionotropic and metabotropic glutamate receptors are being increasingly incriminated in the pathophysiology of treatment-resistant depression so that modulation of these sites by newer antipsychotics could lead to normalization of glutamate neurotransmission, decrease in excitotoxicity, and enhanced neuronal viability (Bjorkholm et al. 2015). Table 2.3 gives an overview of atypical antipsychotics in the treatment of MDE in major mood disorders (Table 2.3).

**Table 2.3** Atypical antipsychotics in the treatment of major depressive episodes in MDD and BD

| Medication | FDA indication | Mechanism of action | Dose range (mg/day) | Evidence |
|---|---|---|---|---|
| Aripiprazole | Augmentation to AD | 5-HT1A/2C partial agonism, 5-HT2A/2B antagonism, weak 5-HT7 antagonism, D2/3 partial agonism, enhancement of neuroplasticity | 5–15 | RCT (adjunctive to AD in MDD). Negative RCT in bipolar I depression |
| Brexpiprazole | Augmentation to AD | 5-HT1A and D2 partial agonism, 5-HT2A antagonism | 1–3 | RCT (adjunctive to AD) |
| Quetiapine XR | Augmentation to AD | α-2 Receptor antagonism, norepinephrine transporter inhibition in PFC (metabolite norquetiapine), 5-HT7 antagonism | 50–300 | RCT (monotherapy as well as adjunctive to AD) |
| Olanzapine/ fluoxetine combination | Treatment-resistant depression | 5-HT2A/2C antagonism, 5-HT7 antagonism | 5–20 | Positive RCT in MDD. Positive RCT in bipolar I depression (monotherapy) |
| Cariprazine | None for MDD | D2/3 partial agonism, 5-HT1A partial agonism, 5-HT2A/5-HT7 antagonism | 1.5–3 | Positive RCT in bipolar I depression (monotherapy) |
| Lurasidone | Indicated for bipolar I depression | 5-HT7 antagonism, 5-HT1A partial agonism, weak 5-HT2C antagonism, weak α-2 antagonism | 60–120 | Positive RCT in bipolar I depression (monotherapy) |
| Ziprasidone | None for MDD | 5-HT2A/2C antagonism, 5HT1A agonism, 5-HT, NE, DA transporter inhibition | 40–160 | RCT (adjunctive to AD) |
| Risperidone | None for MDD | 5-HT2A antagonism, α-2 receptor antagonism, 5-HT7 antagonism | 0.5–3 | RCT (adjunctive to AD) |
| Paliperidone | None for MDD | 5-HT2A antagonism, α-2 receptor antagonism, 5-HT7 antagonism | 3 | Anecdotal reports or expert opinion |
| Asenapine | None for MDD | 5-HT2A/2B/2C antagonism, 5-HT6/7 antagonism, 5HT1A partial agonism, α-2 antagonism | 10–20 | Anecdotal reports or expert opinion |
| Iloperidone | None for MDD | 5HT-2A antagonism, 5-HT6/7 antagonism | Not available | Anecdotal reports or expert opinion |

*AD* antidepressants, *BD* bipolar disorder, *DA* dopamine, *NE* norepinephrine, *MDD* major depressive disorder, *PFC* prefrontal cortex, *RCT* randomized controlled trial, *5-HT* serotonin

### 2.5.3 Individual Medications

#### 2.5.3.1 Brexpiprazole

This is a serotonin-dopamine activity modulator and structurally related to aripiprazole. In July 2015 it received FDA approval for schizophrenia and augmentation therapy of MDD. It shows partial agonism at the D2 receptor and possibly functional selectivity at this site. Compared to aripiprazole, brexpiprazole has lower intrinsic activity at the D2R, but exhibits tenfold higher affinity at the 5-HT1A receptor where it acts as a partial agonist. Two recently published phase III trials investigated the potential of brexpiprazole as an augmentation agent in treatment-resistant MDD. The two identically designed studies included subjects who had inadequate response to one to three standard antidepressants for their current depressive episode. All patients entered a prospective 8-week phase of open-label antidepressant therapy, and those who failed to sufficiently respond were randomized to AD + brexpiprazole or AD + placebo and followed in a double-blind fashion for a total of 6 weeks. The primary outcome measure was change in Montgomery-Asberg Depression Rating Scale (MADRS) from baseline to week 6. In the first study, brexpiprazole 3 mg/day was superior to placebo on MADRS total score (−8.29 versus −6.33; $p = 0.0079$), but brexpiprazole 1 mg/day failed to separate from placebo (−7.64 versus −6.33; $p = 0.0737$). In the second study, brexpiprazole 2 mg/day showed superior efficacy over placebo in changes from baseline to week 6 on MADRS total scores (−8.36 versus −5.15; $p = 0.0002$). Further, the active agent was also better than placebo on the Sheehan Disability Scale (−1.35 versus −0.89; $p = 0.0349$). The most common treatment-related adverse events were weight gain (brexpiprazole, 8%; placebo, 3.1%) and akathisia (7.4% versus 1.0%). Taken as a whole, brexpiprazole addition to standard antidepressants was safe and well tolerated in the two phase III RCTs (Thase et al. 2015a, b).

#### 2.5.3.2 Aripiprazole

This third-generation antipsychotic, first introduced in 2002 for schizophrenia, is well studied as an adjunctive therapy in MDD. With regard to controlled studies, three matching RCTs showed that aripiprazole augmentation of traditional antidepressants was statistically superior to placebo in MDD patients who were nonresponders to one to three adequate antidepressant trials. A post hoc analysis of the abovementioned three RCTs divided patients into two categories—in one group were minimal improvers on antidepressant monotherapy after 6–8 weeks of administration and in the second batch were non-improvers as defined by Clinical Global Impression scale (CGI-I). After 6 weeks of adjunctive aripiprazole or placebo, the remission rates were higher for the active drug in both groups (minimal improvers, 38.8% versus 26.6%, $p < 0.05$; non-improvers, 24.0% versus 10.3%, $p < 0.05$). The most common adverse events with add-on aripiprazole were akathisia, restlessness, and insomnia (Casey et al. 2014). Another pooled analysis of the same RCTs stratified patients according to baseline MADRS scores as follows: mild ≤24; moderate 25–30; and severe ≥31. The results showed that aripiprazole produced greater improvement than placebo in the MADRS scores regardless of MDD severity at baseline (Stewart et al. 2014). A third post hoc analysis investigated the efficacy of adjunctive aripiprazole in MDD patients whose symptoms worsened with antidepressant monotherapy. In the prospective, open-label phase, 106 subjects out of 1065 antidepressant monotherapy non-responders actually deteriorated as assessed by MADRS. Those cases, who worsened, showed higher response and remission rates with aripiprazole compared to placebo during the 6-week double-blind part of the studies (36.6% versus 22.5% and 25.4% versus 12.4%, respectively). Similarly, aripiprazole was superior to placebo for the 905 subjects who did not show deterioration on antidepressant monotherapy (Nelson et al. 2014). Lastly, a subgroup post hoc analysis of a more recently conducted RCT

in an Asian population (the ADMIRE study) revealed that the efficacy was consistently greater with aripiprazole than placebo and was not related to any clinical factors such as gender, age, onset of MDD, number of previous episodes, duration of current episode, length of illness, MDD specifiers, and type of SSRI/SNRI used in the prospective phase (Ozaki et al. 2015).

#### 2.5.3.3 Quetiapine

This second-generation antipsychotic has been well studied in MDD, both as monotherapy and adjunctively to first-line antidepressants. In this context the first RCT was published in 2007, in which quetiapine augmentation of SSRI/venlafaxine was compared to placebo in a small group of MDD patients ($N = 58$) with comorbid anxiety (HAM-A $\geq$ 14) and residual depressive symptoms (CGI-S $\geq$ 4). The mean change in HAM-D and HAM-A total scores from baseline to study endpoint (week 8) was significantly greater with quetiapine (average dose 182 mg/day) than placebo: −11.2 versus −5.5, $p = 0.008$, and −12.5 versus −5.9, $p = 0.002$, respectively. The onset of quetiapine efficacy (HAM-D/ HAM-A/CGI-S) was rapid by week 1 and continued through to week 8. Response, defined as ≥50% decrease in baseline HAM-D scores, was numerically but not significantly higher for quetiapine than placebo. Similarly remission rate (HAM-D total scores ≤7) was also higher for the active agent (31% versus 17%), but this difference did not reach statistical significance. Adverse events for quetiapine were in line with its known side effect profile, and sedation and somnolence were most frequently reported. In conclusion, quetiapine was shown to be effective as augmentation of SSRI/venlafaxine therapy in patients with major depression, comorbid anxiety, and residual depressive symptoms, with no unexpected tolerability issues (McIntyre et al. 2007). The efficacy of quetiapine XR augmentation was shown in two similarly designed (150, 300 mg/day and placebo) 6 week RCTs ($N = 936$). In both trials, the primary endpoint was mean changes in MADRS total score from baseline. In these studies quetiapine XR was statistically superior to placebo on the primary efficacy measure, and this change was evident from week 1 (Bauer et al. 2009; El-khalili et al. 2010). In a revealing study, quetiapine was added to the antidepressant regimen of unipolar depressed patients who were treatment refractory and had failed to respond to 3 weeks of lithium augmentation. They were assigned to flexible dose adjunctive quetiapine + CBT or placebo + CBT and followed for 12 weeks. The former group of subjects had statistically significant improvement on the two efficacy measures of HAM-D and MADRS. Although the total number of patients was small ($N = 22$), this pilot study showed that in refractory MDD patients, flexible dose quetiapine (12.5–200 mg/day) was a valid option in conjunction with standard antidepressants and CBT (Chaput et al. 2008). Finally, quetiapine in combination with an SNRI (venlafaxine) was studied under controlled conditions for the treatment of MDD with psychotic features. Subjects ($N = 122$) were randomized to 7 weeks imipramine (plasma levels 200–300 μg/L), venlafaxine (375 mg/day), or venlafaxine + quetiapine (375 + 600 mg/day). Primary outcome was response on HAM-D-17, while secondary outcomes were response on CGI and remission on HAM-D-17. On the primary measure, quetiapine + venlafaxine was superior to venlafaxine monotherapy and equivalent to imipramine, while secondary outcome measures also showed similar results. It was revealed that for the treatment of unipolar psychotic depression, quetiapine in combination with an SNRI was superior to the latter alone, but similar conclusion could not be drawn with regard to the TCA, imipramine (Wijkstra et al. 2010).

Quetiapine XR monotherapy has been studied in several short-term RCTs in MDD, both in fixed or flexible dose designs. In the majority of these trials, the active drug showed superiority over placebo on such validated efficacy measures as the MADRS. The dose of quetiapine XR was up to a maximum of 300 mg/day and trial durations varied from 6 to 8 weeks; the active agent separated from placebo as early as week 1 and

this superiority was maintained until the end of the study period. The most common adverse events associated with quetiapine XR were dry mouth, sedation, and somnolence, EPS were distinctly uncommon, but metabolic changes like increased serum glucose and lipids were more often observed (Brotnick et al. 2011). The following conclusions can be drawn from the extant literature:

1. Quetiapine alone or adjunctively to standard antidepressants has valid efficacy in the treatment of nonpsychotic MDD.
2. In patients suffering from major depressive disorder with psychotic features, quetiapine in conjunction with first line antidepressants is superior to antidepressant monotherapy.
3. Quetiapine augmentation is a convincing option in treatment-resistant depression.
4. It has shown therapeutic worth in both adults as well as the elderly with MDD.
5. It has value in unipolar depressive patients with comorbid conditions such as anxiety and fibromyalgia.
6. It is effective despite such demographic variables as age, gender, and race.
7. The medication has valid efficacy in MDD regardless of such illness factors as severity, duration, and number of depressive episodes.
8. The effective dose in MDD is from 100 to 300 mg/day which is less than the maximum recommended dose of 600 mg/day in schizophrenia.
9. While an approved therapy in MDD, it should be used with the caveat that it has the potential to cause metabolic abnormalities and careful monitoring is warranted in this regard.

#### 2.5.3.4 Olanzapine/Fluoxetine

Treatment-resistant depression can be conceptualized as an illness that has failed to respond to at least two different antidepressant monotherapy trials of adequate duration and dose. An enlightening meta-analysis of RCTs revealed that the antidepressant response rate was 53% compared to 36% for placebo ($p < 0.05$), so that clinicians must employ other strategies to overcome this underperformance (Papakostas and Fava 2009). On such approach is augmentation with atypical antipsychotics, which has become an important second step as emphasized in current guidelines. In this regard, adjunctive olanzapine has been studied in at least four RCTs and specifically olanzapine/fluoxetine combination (OFC) has been compared to both placebo and active comparators. A pooled analysis of these studies showed that OFC had clearly demonstrated significantly greater improvements in MADRS (primary efficacy measure) total score than fluoxetine or olanzapine alone and also resulted in higher remission rates. The short-term efficacy of OFC for treatment-resistant depression was supported by these trials (Trivedi et al. 2009). In a more recently published long-term trial of up to 27 weeks, relapse rates were compared for fluoxetine monotherapy and OFC in stabilized patients on the combination treatment (Brunner et al. 2014). Time to relapse was significantly longer in the OFC group than in the fluoxetine monotherapy group ($p < 0.001$). Additionally, with regard to safety no significant differences emerged between treatment groups in terms of adverse events ($p = 0.621$). However, the rate of patients who experienced clinically significant (>7%) weight gain was greater for OFC than fluoxetine (OFC: 11.8%, fluoxetine: 2.3%; $p < 0.001$). At the endpoint, the mean differences were significant for weight gain (OFC: +1.14 kg, fluoxetine: −2.78 kg; $p < 0.001$). Finally, it must be mentioned that OFC is not only FDA approved in treatment-resistant unipolar depression; it also has this endorsement for major depressive episodes in bipolar I disorder.

**Conclusion**

In this paper an endeavor has been made to outline the most pertinent aspects of major mood disorders. The current nosological classifications do not differentiate between MDD and BD as far as the diagnostic criteria for a major depressive episode are concerned. However, these are discrete disorders with etiopathologic differences and distinct man-

agement protocols, dissimilar illness trajectories, and disparate prognostic implications. It is imperative for the practitioner to be alert for masquerading bipolarity when treating a patient with a major depressive episode and in the absence of validated biomarkers, clinical judgment is essentially empirical. In the management of an MDE, standard antidepressants are the first-line option, but when there are features suggestive of bipolar spectrum disorders, the clinician must use evidence-based strategies to treat mood disturbances which pose therapeutic challenge. In this regard second- and third-generation antipsychotics have emerged as compelling treatment options and have received FDA approval for licensed use in mood disorders. Moreover, there is a growing literature on the utility of newer antipsychotics as add on treatment or monotherapy in refractory MDD and bipolar depression. Since no curative treatments are available for the most prevalent affective disorders, i.e., MDD and BD, physicians must use clinical judgment in managing their patients on a day-to-day basis and employ the biopsychosocial model to achieve the best results.

**Conflict of Interest** I, Dr. Ather Muneer state that I am the sole author of this manuscript. I received no funding for this work and have no conflict of interest to report.

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# Biomarkers of Depression: Potential Diagnostic Tools

3

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## 3.1 Major Depressive Disorder

Major depressive disorder (MDD) is a mental illness that causes a tremendous societal, economic, and emotional burden, results in impairment in social or occupational functioning, and therefore impairs daily living, and it is common, recurrent, and costly due to the frequent disability-adjusted life years (DALYs) and morbidity (Kessler and Bromet 2013). The prevalence of MDD is increasing worldwide, and MDD was pointed to be a primary cause of global disease burden. The MDD prevalence, as an isolated disorder, ranges from 1 to 17% in adults, 3 to 6% in adolescents, and 12 to 38% in elderly (Gururajan et al. 2016; Kessler and Bromet 2013; Rantamaki and Yalcin 2016). However the prevalence of MDD comorbid with somatic diseases such as diabetes, asthma, and arthritis ranges from 9 to 23% (Kupfer et al. 2012). MDD is also frequently associated with neurodegenerative disorders such as Alzheimer's disease, Parkinson's disease, and Huntington's disease (Du and Pang 2015). The presence of MDD increases the risk for dementia, cardiovascular, metabolic, respiratory, and other somatic diseases (Breitenstein et al. 2014; Kessler and Bromet 2013) and is associated with the poor outcome and more severe symptoms (Du and Pang 2015). Therefore, it is important to diagnose MDD early, in the primary care, especially if patients who suffer from other chronic illnesses (Kupfer et al. 2012). The prevalence of MDD is more frequent in women than in men (Kessler and Bromet 2013).

MDD is a disease with high degrees of heterogeneity and has a complicated clinical picture, consisting of symptoms and signs associated with mood, cognition, interest, decision-making, anxiety, anhedonia, volition and motivation, psychomotor changes, energy, appetite, weight, speech, sleep, suicidal behavior, circadian effects, melancholia, depersonalization, and derealization (Kendler 2016). Characteristic symptoms of MDD (according to DSM-V criteria) are the symptoms of depressed mood (sadness, emptiness, or hopelessness) or a loss of interest or pleasure in daily activities that must last for more than 2 weeks, associated with impaired social, occupational, and educational functions. It is associated with specific symptoms, at least five of these nine symptoms, that have to be present nearly every day: depressed mood or irritable mood present most of the day; reduced interest or pleasure in most activities, most of each day; major alterations in weight or in appetite (weight loss or weight gain); altered sleep, insomnia or hypersomnia; alterations in activity, psychomotor agitation or retardation; fatigue or loss of energy; feelings of guilt/worthlessness; problems

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with concentration, reduced ability to think or concentrate, or indecisiveness; and suicidal behavior, recurrent thoughts of death or suicide, recurrent suicidal ideation without a specific plan, or a suicide attempt or a specific plan for committing suicide. The diagnosis of MDD is based on patient interviews that offer insight into the clinical symptoms which are common with other psychiatric disorders and therefore the diagnosis, based on physician-administered or patient self-administered interview, is still subjective since it depends on the individual clinical judgment (Bilello 2016; Young et al. 2016). Additionally, between clinicians with experience in psychiatry, there is a poor inter-rater reliability in diagnosing MDD (Bilello 2016), and because of this inaccuracy, there is an unmet need to develop validated and objective blood-based and cerebrospinal fluid (CSF) biomarkers for MDD (Young et al. 2016).

## 3.2 The Etiology of MDD

The etiology of MDD is complex and still not clearly defined, but it includes alterations in heterogeneous biological mechanisms, vulnerability associated with particular biological background (genetic, epigenetic, neuroendocrine, and neuroimmune), stress exposure, and interaction with other psychosocial and environmental factors (Rantamaki and Yalcin 2016; Schneider and Prvulovic 2013). In MDD, neuronal circuits are affected and neuronal connectivity is altered, leading to the functional neuroanatomy modifications (Rantamaki and Yalcin 2016). The key neurobiological pathways altered in MDD are monoaminergic systems (Di Giovanni et al. 2016), neuroendocrinological systems (hypothalamic-pituitary-adrenal (HPA) axis and thyroid dysfunction), neurotrophins (such as brain-derived neurotrophic factor or BDNF), oxidative stress pathways, and inflammatory processes (Belvederi Murri et al. 2014; Rantamaki and Yalcin 2016). Besides the genetic background that includes risk or protective gene variants, reduced monoaminergic, i.e., serotonergic, dopaminergic, and noradrenergic neurotransmission, decreased concentration of the neurotrophin BDNF, elevated proinflammatory cytokine levels, increased immune response, and a dysregulated activity of the HPA axis, as well as cortical and subcortical functional and structural brain changes in the limbic and prefrontal cortex, are associated with the etiology of MDD (Belvederi Murri et al. 2014; Young et al. 2016).

## 3.3 Biomarkers

The key biological substrates that are altered in MDD (hormones, neurotransmitters, neurotrophins, cytokines, metabolic, genetic, and neuroimaging markers) are also the possible biomarkers, i.e., indicators of health or normal biological processes and disease or pathogenic processes (Young et al. 2016). Due to the MDD heterogeneity, complicated clinical picture and heterogeneous clinical symptoms (anhedonia, depressed mood, loss of interest, pleasure and energy, problems with cognition, weight, appetite and sleeping, fatigue, anxiety, feelings of worthlessness or guilt, psychomotor problems, and suicidality) that frequently overlap with symptoms in other psychiatric disorders, no single biomarker is sensitive and specific for MDD diagnosis. To overcome these problems, it has also been proposed (Bilello 2016) to determine a MDD diagnosis based on the endophenotype/s, defined as reliable and specific measurable characteristics that segregate with illness in the general population, cosegregate in non-affected family members, and are heritable, state independent, and present at a higher rate within affected families than in the general population. Endophenotypes might include biological, behavioral and cognitive characteristic, and they are more restrictively defined than biomarkers (Bilello 2016). Both biomarkers and endophenotypes are crucial diagnostic instruments that might enable personalized medicine, a tailoring therapeutic approach to individual patient (Prendes-Alvarez and Nemeroff 2016). Therefore, a well-defined biomarker set or panel, that would include particular biological markers or a multi-analyte biomarker panel, is proposed for establishing MDD diagnosis

(Leuchter et al. 2014; Young et al. 2016). A panel of selected biomarkers, particular endophenotypes or the research domain criteria (RDoC), all seek to determine more accurate diagnosis of MDD (Young et al. 2016). Biomarkers of MDD diagnosis are based on genetic, epigenetic, molecular, and neuroimaging studies. In addition, intermediate endophenotypes (i.e., "quantifiable physiological traits or processes that are interposed between gene and clinical phenotype") were also suggested for characterization of more homogenous subgroups of patients with MDD, as biomarkers to help in diagnosis or therapeutic response in MDD (Leuchter et al. 2014).

## 3.4 Neurotransmitter Markers

### 3.4.1 Serotonin (5-HT)

Although according to the "serotonergic theory" MDD is in general characterized with reduced serotonergic activity (Gururajan et al. 2016), due to many contradictory results, the exact nature of serotonergic dysfunction in depression still remains uncertain (Andrews et al. 2015). Regarding serotonin (5-HT) levels in various brain regions, postmortem analyses yielded inconclusive data. However, decreased 5-HT concentrations in the brainstem of depressed suicide victims were consistently found (Mann et al. 1989). Lower number of 5-HT uptake sites has been found in samples from postmortem brains (Leake et al. 1991) and platelets (Suranyi-Cadotte et al. 1985) of MDD subjects, but these results were not confirmed (Gross-Isseroff et al. 1989). In the CSF of depressed patients, decreased (Lidberg et al. 2000), increased (Reddy et al. 1992), or unchanged (Roy et al. 1985) levels of 5-hydroxyindolacetic acid (5-HIAA), a metabolite of 5-HT, have been reported. In MDD, lower (Quintana 1992) or similar (Muck-Seler et al. 2002) platelet 5-HT concentrations were detected. Studies investigating 5-HT1A receptor changes in depression have reported opposing findings (Kaufman et al. 2016). Reduced number and mRNA of 5-HT1A receptors have been reported in the hippocampus and prefrontal cortex of depressed patients and animal depression models (Cheetham et al. 1990). However, no changes in 5-HT1A receptor expression associated with depression have been found in dorsal raphe nucleus (Cheetham et al. 1990) or in blood (Fajardo et al. 2003). Higher levels of 5-HT1A and 5-HT2 receptors have been also reported in the brain (Hrdina et al. 1993; Matsubara et al. 1991) and platelets (Zhang et al. 2014) of depressed subjects. Although at the periphery, increases (Tsao et al. 2006), decreases (Lima et al. 2005), and no changes (Belzeaux et al. 2010) in serotonin transporter (5-HTT) mRNA levels have been reported in patients with MDD, recent meta-analysis of in vivo and postmortem findings suggested reduced 5-HTT availability in key regions of the limbic system of patients with MDD (Kambeitz and Howes 2015). Protein and mRNA levels of several enzymes involved in the synthesis of monoamine neurotransmitters, such as tryptophan hydroxylase (TPH) and monoamine oxidase (MAO), were also altered in depression (Bach-Mizrachi et al. 2006; Meyer et al. 2009). In addition, variations in gene coding for 5-HTT, various 5-HT receptors, TPH, MAO, etc., have been investigated as potential candidates for increased risk of depression (Flint and Kendler 2014; Lohoff 2010). Recent epigenetic studies also support the role of serotonergic system in the pathophysiology of depression, demonstrating for instance changes in methylation status of *5-HTT* gene promoter (Menke and Binder 2014).

### 3.4.2 Dopamine

The results obtained in both preclinical and clinical studies indicated the important role of dopaminergic system in the pathophysiology of depression (Dunlop and Nemeroff 2007; Nestler and Carlezon 2006). Using genetically selected Flinders sensitive line (FSL) of rats, as an animal model of depression, Yadid et al. (2000) reported increased dopamine levels in nucleus accumbens, striatum, hippocampus, and hypothalamus, suggesting higher synthesis or lower release of dopamine from these limbic regions. On the other

hand, depletion of dopamine levels in humans has been found in depressed patients (Ruhé et al. 2007). Various symptoms of depression have been associated with decreased levels of dopamine in the frontal cortex (Krishnan and Nestler 2008) and striatum (Nestler and Carlezon 2006) of patients with MDD. Human studies also reported the downregulation of dopamine transporter (DAT), as a result of dopamine declining process. Namely, reduced DAT binding potential in striatum (Meyer et al. 2001) and decreased DAT levels in basal ganglia (Savitz et al. 2009) have been found in subjects diagnosed with MDD. In addition, reduced density of striatal dopaminergic D2 receptors has been suggested to underlie depressive symptoms (Klimke et al. 1999; Meyer et al. 2006). Studies using chronic mild stress in rats, as another animal model of depression, demonstrated a decrease in dopaminergic D2 and D3 receptor number in the nucleus accumbens (Papp et al. 1994). Regarding dopaminergic D4 receptors, the association of some specific gene polymorphisms with depression has been investigated (Frisch et al. 1999; López León et al. 2005). Although some postmortem analyses found increased dopaminergic D4 receptor mRNA expression in the amygdala of depressed patients (Xiang et al. 2008), other studies reported decreased (Rocc et al. 2002) or unchanged blood D4 mRNA levels in subjects with depression (Iacob et al. 2014).

### 3.4.3 Norepinephrine

Although plenty of evidence support the involvement of norepinephrine in depression (Moret and Briley 2011), data from preclinical models of depression are limited. However, in FSL rats, two- to threefold higher levels of norepinephrine were found in the nucleus accumbens, prefrontal cortex, hippocampus, and median raphe nucleus (Yadid et al. 2000; Zangen et al. 1999). On the other hand, a reduction of norepinephrine levels has been observed in depressed patients (Ruhé et al. 2007), and depression was shown to be related to increased urinary norepinephrine excretion (Hughes et al. 2004). Postmortem studies reported lower levels of norepinephrine transporter (NET) and higher levels of α2-adrenoceptors in the locus coeruleus (Klimek et al. 1997; Ordway et al. 2003). Moreover, altered functional status of α2A-adrenoceptors in the frontal cortex was observed (Valdizán et al. 2010), suggesting an association of depressive disorders with increased α2-adrenoceptors sensitivity and responsiveness (Cottingham and Wang 2012).

### 3.4.4 Glutamate

More recent studies suggested that dysfunction of the glutamatergic system may be also implicated in MDD (Hashimoto 2009). Increased activation of glutamatergic neurotransmission and elevated glutamate levels have been observed in depressed patients (Sanacora et al. 2004; Zarate et al. 2003). The involvement of glutamatergic system in depression is also supported by reports of antidepressant effects of glutamate NMDA-receptor antagonists such as ketamine (Dutta et al. 2015). In study using FSL rats as an animal model of depression, it has been suggested that chronic stress is necessary in order to demonstrate altered glutamate-NO signaling (Wegener et al. 2010). Increased glucocorticoid levels, which are released under conditions of chronic stress associated with depression, enhance glutamatergic transmission, expression of NMDA receptors, as well as synthesis and extracellular glutamate levels (Lu et al. 2003). Upregulated glutamate action via NMDA receptors leads to an influx of $Ca^{2+}$ into the neuronal cells, resulting in the brain excitotoxicity (Müller and Schwarz 2007), accumulation of reactive oxygen species (ROS) (Coyle and Puttfarcken 1993), and these processes, together with increased nitric oxide (NO) concentrations, are involved in the pathophysiology of depression (Dhir and Kulkarni 2011; Suzuki et al. 2001). Higher expression of glutamatergic genes *GRIN1*, *GRIN2A-D*, *GRIA2-4*, *GRIK1-2*, *GRM1*, *GRM4*, *GRM5*, and *GRM7* was detected post-mortem in the dorsolateral prefrontal cortex of female patients with MDD (Gray et al. 2015). On the

other hand, in the perirhinal cortex of depressed patients, decreased mRNA expression of *GRIA1*, *GRIA3*, *GRIN1*, *GRIN2A*, *GRIN2B*, and *GRIK1* genes was determined (Beneyto et al. 2007). Lower protein expression of the glutamate receptor subunits NR2A, NR2B, and mGlu2/3 in the prefrontal cortex of depressed patients was found (Feyissa et al. 2009, 2010).

### 3.4.5 γ-Aminobutyric Acid (GABA)

Various studies implicated GABA in the pathophysiology of depression (Krystal et al. 2002; Luscher et al. 2011). Although some authors reported no change (Post et al. 1980; Roy et al. 1991), other reports demonstrated decreased levels of GABA in the CSF of depressed patients (Gold et al. 1980; Kasa et al. 1982). Since downregulation of GABA was also observed in the plasma of subjects with MDD, plasma GABA levels have been proposed as trait biomarker of depression (Petty et al. 1995). However, the findings regarding the expression of glutamic acid decarboxylase (GAD), the enzyme involved in the GABA synthesis, in patients with depression are contradictory (Pehrson and Sanchez 2015).

## 3.5 Neurotrophic Biomarkers

### 3.5.1 Brain-Derived Neurotrophic Factor

Neurotrophins are a family of growth factors that regulate neuronal plasticity and function during development and adulthood. There are four neurotrophin family members, nerve growth factor (NGF), brain-derived neurotrophic factor (BDNF), neurotrophin (NT)-3, and NT-4/5, known to exist in mammals. Neurotrophins are synthesized as precursor proteins (proneurotrophins) which undergo proteolytic cleavage to produce mature proteins (Matsumoto et al. 2008; Mowla et al. 2001; Yang et al. 2009). Mature neurotrophins bind with high affinity to a specific tyrosine kinase receptor (Trk), while both the mature and unprocessed precursor neurotrophins can interact with pan neurotrophin receptor (p75NTR) (Chao 2003).

Previous studies suggest that acute and chronic stress or depression can lead to hippocampal atrophy (Duman 2004) and decreased neurogenesis in the adult brain (Dranovsky and Hen 2006), which could predict person's susceptibility to certain psychiatric disorders. The neurotrophin hypothesis of depression proposes that reduced *BDNF* mRNA expression and decreased BDNF protein levels in different brain areas, including hippocampus, and at the periphery, could play an important role in the pathophysiology of depression (Neto et al. 2011; Zhou et al. 2013). This hypothesis is supported by studies showing an association between antidepressant treatment and increased peripheral BDNF levels in depressed patients (Cattaneo et al. 2010; Halaris et al. 2015; Sagud et al. 2016). Preclinical studies also support the relationship between neurotrophins, especially BDNF, and stress in rodents (Smith et al. 1995; Ueyama et al. 1997).

Postmortem analysis have detected reduced *BDNF* and *TrkB* expression in different brain areas, such as hippocampus, amygdala and prefrontal cortex, of depressed patients and suicide victims (Dwivedi et al. 2003; Guilloux et al. 2012; Karege et al. 2005). Furthermore, treatment of patients with antidepressants increased hippocampal BDNF protein levels (Chen et al. 2001). However, given the limitations of postmortem studies, there has been a growing interest in exploring the peripheral BDNF as a potential biomarker in psychiatry (Fernandes et al. 2009; Frey et al. 2013). Peripheral BDNF could be a useful biomarker since the assessment of BDNF plasma and serum levels is relatively simple and noninvasive and due to a strong evidence suggesting the correlation between peripheral and central BDNF levels (Karege et al. 2002; Klein et al. 2011) indicating that BDNF has the ability to cross the blood-brain barrier (Pan et al. 1998). Studies report decreased BDNF levels in plasma and serum samples from depressed patients (Lee et al. 2007; Yoshida et al. 2012) which can be normalized with antidepressant treatment (Lee and Kim 2008). There are also reports of reduced

*BDNF* mRNA expression in peripheral blood mononuclear cells (Lee and Kim 2010) and decreased platelet BDNF level (Lee and Kim 2009) in depressed patients. These results suggest that there may be a link between changes in peripheral BDNF levels and predisposition for the development of depression in healthy individuals (Lang et al. 2004).

The most studied variation in *BDNF* gene is a single nucleotide polymorphism (SNP) rs6265 (Val66Met), which results in the substitution of the amino acid valine (Val) by methionine (Met) at codon 66. This variation affects the trafficking of *BDNF* mRNA to dendrites and BDNF protein secretion by the regulated secretory pathway (Egan et al. 2003). Subjects that carry the *BDNF* Met66 variant have smaller hippocampal volumes (Hajek et al. 2012) and abnormal hippocampal function (Egan et al. 2003; Hariri et al. 2003), and these findings might suggest a possible pro-depressive role of *BDNF* Met66 allele. Several studies confirmed reduced hippocampal, parahippocampal, and amygdala volumes in patients diagnosed with MDD (Frodl et al. 2007; Montag et al. 2009), but there are studies that have found opposite results (Jessen et al. 2009). It was suggested that *BDNF* Met66 allele could also contribute to suicidal behavior in depressed patients (Sarchiapone et al. 2008) and that *BDNF* Met66 carriers exhibit a higher vulnerability to stress than *BDNF* Val/Val homozygotes (Brown et al. 2014; Hosang et al. 2014).

Recently, several studies have focused on the relationship between epigenetic alterations and vulnerability to MDD. Higher serum levels of the *BDNF*-related microRNA miR-132 were correlated with more severe symptoms in depressed patients (Li et al. 2013). Preclinical studies in rodents found that increased levels of *BDNF*-targeting microRNAs, miR-16 and miR-124, in the rat hippocampus are associated with depressive-like behavior (Bahi et al. 2014; Bai et al. 2012). The upregulation of *BDNF*, by reducing the expression of specific microRNAs, like miR-30a-5p or miR-206, is the potential mode of antidepressant action (Angelucci et al. 2011; Yang et al. 2014). Changes in DNA methylation could also provide helpful diagnostic information. Hypermethylation at CpG sites, located within *BDNF* gene promoter 4, was reported to be associated with suicidal ideation in depressive patients (Kang et al. 2013) and suicide victims (Keller et al. 2010), while DNA methylation profiles of *BDNF* promoter 1 were found to be a valuable peripheral biomarker in the diagnosis of depression (Fuchikami et al. 2011). *BDNF* promoter 4 hypermethylation could also be a potential biomarker for vulnerability to depression after stressful life events such as stroke (Kim et al. 2013). Further studies should try to evaluate individual DNA methylation profiles, before and after development of depression, to confirm the relationship between such epigenetic modifications and a predisposition to develop depression.

### 3.5.2 Other Neurotrophins

There are indications that other neurotrophins, like NGF and NT-3, could also be associated with the pathophysiology of MDD. Several studies demonstrated lower serum BDNF, NGF, and NT-3 concentrations in depressed patients compared to healthy controls (de Azevedo Cardoso et al. 2014; Ogłodek et al. 2016). Furthermore, study by Diniz et al. (2012) suggested reduced circulating glia cell line-derived neurotrophic factor (GDNF) levels in elderly patients with depression, which were associated with the severity of the disease. Future research, which should include larger samples sizes and reduce variance among different biological parameters, are necessary to finally clarify the role of neurotrophins in depression and their potential as biomarkers for the diagnosis of this neurological disorder.

## 3.6 Hypothalamic-Pituitary-Adrenal Axis-Related Markers

Since MDD is a result of the interactions between genes, gender, personality, family history, and environmental factors, including primarily exposure to stress, early adversity or abuse/neglect,

and adverse family relations (Heim and Binder 2012), stress-related biomarkers might be used to determine vulnerability to develop MDD. The major neuroendocrinological system that regulates stress response or perceived threat is the HPA axis. Stress response initiates the HPA axis activation and release of corticotrophin releasing hormone (CRH) from the paraventricular nucleus of the hypothalamus, a neurohormone acting via CRH receptors in the pituitary and other brain regions. CRH stimulates the release of adrenocorticotropic hormone (ACTH) from the pituitary, and ACTH stimulates the secretion of glucocorticoid hormones (cortisol in humans) from the adrenal gland. Cortisol binds primarily to glucocorticoid but also mineralocorticoid receptors in various brain regions. When the coping mechanisms prevail and adaptation is achieved as a response to stress, the HPA axis goes back to its normal state, since this is a steady system controlled by the cortisol which exerts negative feedback via its receptors to achieve homeostasis (Stetler and Miller 2011). Activation of the HPA axis and subsequent release of CRH, ACTH, and cortisol exerts a myriad of effects on behavioral, cognitive, emotional, autonomic, psychological, and immunologic processes.

HPA axis dysregulation is a frequent finding in MDD, and most data and previous meta-analysis agree that hyper-activation of the HPA axis occurs in MDD (Stetler and Miller 2011). These alterations include higher cortisol values in approximately 73% of MDD patients compared to control subjects and higher ACTH levels in 60% of MDD patients compared to controls, while CRH levels were slightly reduced in MDD patients compared to controls. In addition, altered negative feedback loop in MDD, that can be documented with a non-suppression of cortisol to administration of dexamethasone in the dexamethasone suppression test (DST), was reported (Stetler and Miller 2011). Our previous studies found elevated plasma cortisol levels in medication-free patients with MDD compared to healthy control subjects (Muck-Seler et al. 2002; Pivac et al. 1997) and DST non-suppression in MDD patients (Pivac et al. 1997). A more recent meta-analysis (Belvederi Murri et al. 2014), focusing on a late life depression, confirmed these findings. In older subjects, the HPA axis alterations were more pronounced, and older MDD patients had significantly higher cortisol values, especially during evening and night, and showed stronger non-suppression following DST (i.e., had higher cortisol response after DST), suggesting attenuated negative feedback of the HPA axis in late life depression (Belvederi Murri et al. 2014). Several methodological issues might affect findings of the HPA axis function in MDD, which are divergent across studies (see Belvederi Murri et al. 2014; Stetler and Miller 2011). The discrepant results across studies might be due to the sampling of blood vs. saliva; sampling in the different time of the day, due to the circadian rhythm of the HPA axis hormones; measuring of the basal hormone levels vs. levels after a challenge test; depressive subtypes, antidepressant treatment, and remission; age and gender of participants; symptom severity, hospitalization status, physical disease, and cognitive status (Belvederi Murri et al. 2014; Stetler and Miller 2011). Collectively, all these results suggest that HPA hyperactivity might be a disease mechanism in MDD, associated with disturbed immune, metabolic, and neurocognitive functioning, especially in older subjects (Belvederi Murri et al. 2014; Stetler and Miller 2011).

In the prediction of the development of MDD, Gene × Environment (GxE) interactions were detected for the genetic variants of the corticotrophin receptor 1 (CRHR1), hsp90 co-chaperone FKBP5, and the glucocorticoid receptor (Heim and Binder 2012). Both protective and risk haplotype combinations of the *CRHR1* were found to interact with early adverse experience, child abuse, or physical neglect to increase the risk of MDD (Bradley et al. 2008; Grabe et al. 2010; Tyrka et al. 2009). These findings might suggest that early traumatic experience significantly elevates CRHR1 signaling in adulthood, leading to hyperactivity of the HPA axis and vulnerability to develop MDD (Heim and Binder 2012). The FKBP5, a protein, co-chaperone that modulates binding of cortisol to the glucocorticoid receptor, presumably disturbs the negative feedback of the HPA axis, resulting in the hyperactivity of the HPA axis by the effects

achieved via glucocorticoid receptor (Binder 2009). The genetic variants of the *CRHR1*, *FKBP5*, and glucocorticoid receptor all interact with early life stress and negative experiences and increase the risk for depression in adulthood (Binder 2009; Bradley et al. 2008; Heim and Binder 2012; Tyrka et al. 2009; Zimmermann et al. 2009).

## 3.7 Inflammatory Markers

MDD is associated with immune dysregulation and altered production of the proinflammatory cytokines which mediate a typical inflammatory response, such as C-reactive protein (CRP), interleukin (IL)-1β, IL-2, IL-6, interferon (IFN)-γ, tumor necrosis factor (TNF)-α, the soluble IL-6 receptor (IL-6R), and the IL-1 receptor antagonist (Dowlati et al. 2010; Swardfager et al. 2016). These proinflammatory cytokines induce different depressive symptoms (Maes 2008; Raison et al. 2006) since they affect neuroplasticity, neurotransmission, oxidative stress processes, and neuroendocrine functions, all processes that are disturbed in MDD (see Eyre et al. 2016). In a meta-analysis, increased production of particular proinflammatory cytokines, such as TNF-α and IL-6, has been found in MDD, while other cytokines (IL-1β, IL-2, IL-4, IL-8, IL-10, IFN-γ) were not significantly different between patients with MDD and control subjects (Dowlati et al. 2010). In the other meta-analysis, there was a significant positive association of CRP, IL-6, IL-1, and IL-1 receptor antagonist (that binds to IL-1 receptors and prevents the effects of IL-1) with depression in the large groups of patients with MDD and control subjects (Howren et al. 2009). Recently, these data were confirmed in another meta-analysis (Haapakoski et al. 2015), showing elevated levels of IL-6 and CRP levels in patients with MDD compared to controls. In addition, a meta-analysis detected significantly higher levels of the chemokine monocyte chemotactic protein (MCP)-1/CCL2 in patients with MDD compared to control subjects, while chemokine IL-8/CXCL8 did not differ between cases and controls (Eyre et al. 2016). All these findings suggest the link between MDD and activation of the inflammatory response system (Eyre et al. 2016). The relationship between inflammation and MDD is complex and presumably bidirectional, since inflammation affects the HPA axis and induces its activation, with increased release of CRH, ACTH, and cortisol, while MDD is characterized with reduced parasympathetic tone in the autonomic nervous system, associated with elevated inflammatory processes (Howren et al. 2009). This association might also be tri-directional, since various cardiometabolic risk factors such as high body mass index, hypertension, diabetes, obesity, adiposity, smoking, and cardiovascular disease (i.e., atherosclerosis) are associated with chronic systemic inflammation and MDD (Howren et al. 2009; Swardfager et al. 2016).

## 3.8 Electroencephalography Markers

Electroencephalography (EEG) is a routine diagnostic method for neuronal activity measurement and has a great potential as a diagnostic marker of neuropsychiatric disorders. MDD is characterized with different abnormalities in neuroelectrophysiology and cognition (Kandel et al. 2000). These abnormalities are manifested through EEG in changes of band frequencies, different activation of two brain hemispheres (asymmetry) or aberrant cognitive brain behaviors (Deldin and Chiu 2005). EEG captures electric activity directly and in real time, having a temporal resolution in a time scale of milliseconds which makes this technique so valuable. Electrophysiological activity inside the brain is measured by different frequency ranges: delta (<4 Hz), theta (4–8 Hz), alpha (8–13 Hz), beta (14–40 Hz), and gamma (≥40 Hz) (Noachtar et al. 1999).

The most commonly discussed EEG abnormality in MDD is elevated absolute (Jaworska et al. 2012a) or relative (Prichep and John 1992) alpha activity. There are also reports about increased relative and absolute beta activity in depressed male patients compared to male healthy controls (Knott et al. 2001), as well as

increased alpha, beta, and theta power during the resting EEG in patients with early stage of depression (Grin-Yatsenko et al. 2010).

Frontal alpha asymmetry is another trait observed in MDD, first described as hyperactivation (lower alpha) of the right frontal cortex and hypo-activation (higher alpha) of left prefrontal cortex (Schaffer et al. 1983). Some other studies confirmed these results (Chang et al. 2012; Henriques and Davidson 1991), but there are also studies reporting a lack of alpha asymmetry in MDD patients (Carvalho et al. 2011; Gold et al. 2013; Price et al. 2008). In addition, there are reports indicating low heritability (Smit et al. 2007) and moderate stability (Debener et al. 2000) of alpha asymmetry measures. Besides, results can be influenced by anatomical differences between patients (Myslobodsky et al. 1989), or by the technical implementation of measurements (Hagemann et al. 2001), which complicates the use of this trait as a distinguishing marker between MDD and healthy controls.

When MDD patients were compared to healthy controls, a difference in their EEG was found that indicates increased vigilance in MDD, probably due to hyperactivity of the noradrenergic system (Hegerl and Hensch 2014). Namely, in resting state during the period of falling asleep, changes in EEG activity associated with decline of vigilance occur, which is missing in MDD (Hegerl et al. 2012; Olbrich et al. 2012). This is a promising electrophysiological marker which outlies clinical symptoms of MDD.

Other biomarkers linked with clinical symptoms of MDD, such as sleep initiation problems, early awakening, or disrupted sleep, are EEG biomarkers in sleep. Patients with MDD usually experience sleep disturbances manifested through an increased rapid eye movement (REM) density (Goetz et al. 1991), decreased REM sleep latency (Rotenberg et al. 2002), or changes in delta sleep (Lopes et al. 2007). Delta sleep differences are shown to be discriminative between MDD and healthy controls in patients with early stages of MDD, suggesting even that the maturational time course of sleep EEG disturbances may differ between men and women with MDD (Armitage et al. 2001).

Brain connectivity, defined as network of anatomical, functional, and casual interactions between different areas of the brain (Sporns et al. 2004), could be a contributing factor to disorganization syndrome (impaired cognitive association) in different psychiatric disorders including MDD (Leuchter et al. 2012). Well-established measure of functional connectivity is EEG coherence (Fries 2015). Differences were found in EEG coherence between patients with MDD and healthy control subjects (O'Connor et al. 1979), including decrease (Knott et al. 2001; Lee et al. 2011; Sun et al. 2008) or increase, mostly in the alpha band (Fingelkurts et al. 2007; Jeong et al. 2013; Leuchter et al. 2012), of EEG coherence in MDD. Once the reason for these biased findings clarifies, EEG coherence could be a reliable biomarker of MDD.

Both EEG and event-related potentials (ERP) were used in order to discriminate between MDD and healthy controls. Event-related potentials are determined using EEG to measure electrophysiological response to different sensory, cognitive or motor stimulus (Luck 2005). An ERP signal is a result of averaging the various brain responses of similar types, and it consists of positive and negative peaks that occur at the time points of 100 (N100/P100), 200 (N200/P200), and 300 (P300) milliseconds (Boutros et al. 1997). The P300 component of ERP is included in cognitive information processing, such as memory, attention, or executive function (Polich 2004). Some studies reported decreased amplitude of P300 in MDD (Blackwood et al. 1987; Diner et al. 1985), while other study emphasized a significance of comorbidities in P300 determination, since P300 amplitude was decreased in MDD and increased in patients with anxiety when compared to healthy controls, while patients with MDD with comorbid anxiety had the same P300 amplitude as healthy controls (Bruder et al. 2002).

Additionally, it was shown that P300 latency is often prolonged in MDD (Bruder et al. 2009; Vandoolaeghe et al. 1998). Although it was shown that responsiveness to auditory evoked potentials depends on central serotonergic function (Hegerl and Juckel 1993), which is disturbed

in MDD, no differences of auditory evoked potentials were found between MDD patients and healthy controls (Jaworska et al. 2012b; Linka et al. 2007).

## Conclusion

As recently discussed (Maung 2016), MDD is heterogeneous disorder, with high degrees of causal heterogeneity and complexity and with limited understanding of the possible causal processes and causative pathology. Therefore, although there has been a lot of progress, there is a desperate need for development of validated, specific, sensitive meaningful set of biomarkers as potential diagnostic or prognostic tools. Namely, none of the candidate biomarkers satisfy criteria to be used as a diagnostic biomarker for MDD (Schneider and Prvulovic 2013). The utility of one diagnostic test, so-called MDD Score, consisting of nine nongenetic serum biomarkers and an algorithm, was recently reported to be used as a biochemical conformation of the MDD diagnosis (Bilello et al. 2015). Therefore, the focus of the future research should be a development of a well-defined biomarker set or panel or multi-analyte biomarker panel (Bilello 2016) that would include various biological markers associated with particular alterations on the molecular, cellular, and systems levels, and that will combine genetic, molecular, and neuroimaging measures (Kupfer et al. 2012). These biomarkers, with different laboratory tests based on the genomic, transcriptomic, proteomic, epigenetic, and metabolomic approaches, should be used for better understanding of MDD and its subtypes, to help in establishing MDD diagnosis and early detection of the illness and its subtypes (Bilello 2016; Leuchter et al. 2014; Young et al. 2016).

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# Diagnosis of Major Depressive Disorders: Clinical and Biological Perspectives

4

Marc Fakhoury

## 4.1 Introduction

Major depressive disorder (MDD) is one of the leading causes of mental disability worldwide, with an estimated lifetime prevalence of up to 20–30% (Weissman et al. 1996; Kruijshaar et al. 2005). Also referred to as major depression or depression, MDD affects more females than males (Kessler 2003) and constitutes a major burden to the society in terms of ensuing health-care costs (Kessler 2012). A major depressive episode frequently follows a traumatic or stressful life event (Shapero et al. 2014; Negele et al. 2015), and is often exacerbated by the co-occurrence of substance use disorders such as alcohol and illicit drug abuse (Davis et al. 2008). In the clinic, MDD manifests itself by a wide variety of symptoms and signs including depressed mood, loss of interest, changes in weight or appetite, and increased thoughts of suicide (American Psychiatric Association 2013). MDD is also commonly associated with the presence of cardiovascular and metabolic complications (Dunbar et al. 2008; Hare et al. 2014), making it one of the most significant health problems in modern society.

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The advances in genetic, molecular, and neuroimaging studies over the past few years have significantly improved our understanding of the underlying neurobiological mechanisms of MDD (Fakhoury 2015). Findings from these studies indicate that MDD is characterized by morphological and functional changes in cortico-limbic structures (Drevets et al. 2008), as well as altered level of certain neurotransmitters in the brain, including dopamine, serotonin (5-H), norepinephrine, glutamate, and gamma-aminobutyric acid (GABA) (Kendell et al. 2005; Nutt 2008). Mounting evidence also indicates that inflammatory mediators and growth factors contribute to the development of depression, suggesting that they may constitute a reliable set of biomarkers to identify at-risk patients (Lotrich 2012; Felger and Lotrich 2013). In addition, findings from linkage and association studies have led to the identification of numerous genetic variations that may increase vulnerability to MDD (Lohoff 2010; Dunn et al. 2015), thus revealing important insights about disease mechanisms. However, due to the clinical and etiological heterogeneity of MDD, and the complex interaction between genetic and environmental factors, the underlying pathophysiology of depression is far from being fully understood and still needs further investigation.

Given the vast symptomatic heterogeneity among MDD patients, clinicians may sometimes misinterpret some behaviors and physical signs, leading to inappropriate disease classification



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and treatment care. Standardized diagnostic criteria, such as those outlined in the fifth edition of the *Diagnostic and Statistical Manual of Mental Disorders* (DSM-5) and the 10th revision of the *International Classification of Diseases* (ICD-10), may help guide decisions regarding diagnosis and treatment plan by providing a reliable assessment of disease symptoms and severity. The focus of this chapter will be on the DSM-5, the newest available guideline for diagnosis of MDD. Although most of the criteria for MDD are identical between the previous and current edition of the DSM, several changes were made in the DSM-5 so as to improve the quality and reliability of diagnosis. These are discussed in more details in the following sections. This chapter also provides a detailed overview of biological markers that could potentially serve as reliable tools for the diagnosis of MDD and for tailoring therapies that target individual differences in symptoms.

## 4.2 Diagnostic and Classification Criteria of MDD in the DSM-5

### 4.2.1 Criteria for MDD Diagnosis

The use of reliable and valid diagnostic criteria is essential for making effective clinical decisions and implementing appropriate management strategies. Based on evidence from clinical practice and existing epidemiological and neurobiological research, the DSM-5 has developed new diagnostic criteria that provide the standard language by which clinicians and researchers communicate about mental disorders (American Psychiatric Association 2013). This new edition of the DSM, which was published in 2013, marks the first major overhaul of diagnostic criteria and classifications used by clinicians and researchers since the DSM-IV in 1994 (American Psychiatric Association 1994). To meet criteria for MDD in the DSM-5, at least five of the following symptoms must be present nearly every day during the same 2-week period: (1) depressed mood, (2) loss of interest or pleasure, (3) changes in weight or appetite, (4) insomnia or hypersomnia, (5) psychomotor agitation or retardation, (6) fatigue or loss of energy, (7) feeling of worthlessness or guilt, (8) impaired concentration or indecisiveness, and (9) recurrent thoughts of death or suicide (American Psychiatric Association 2013). In addition, at least one of the existing symptoms must be (1) depressed mood or (2) loss of interest or pleasure, and the patient must not have any experience of mania and hypomania during his lifetime (American Psychiatric Association 2013).

### 4.2.2 Subtypes of MDD

One of the most conspicuous changes in the DSM-5 is the dissociation between "bipolar and related disorders" and "depressive disorders", which are now listed as two separate chapters. In the current edition of the DSM, the chapter on bipolar disorder is placed between the chapters on "schizophrenia/psychotic disorders" and "depressive disorders" in support of findings showing that bipolar disorder shares a similar degree of symptomatology and genetic overlap with schizophrenia and depression (Lichtenstein et al. 2009; Mitchell et al. 2011; Ivleva et al. 2012; Cross-Disorder Group of the Psychiatric Genomics Consortium 2013). However, despite shared pathogenic processes, the degree of neurobiological and cognitive impairments varies between bipolar disorder and MDD, suggesting that these disorders should be viewed as two separate continuums, rather than opposite ends of the same dimension (Cuellar et al. 2005; van der Werf-Eldering et al. 2010). In addition, to reflect the heterogeneous nature of depression, the DSM-5 has increased the number of categories in the "depressive disorders" section, with the addition of disruptive mood dysregulation disorder, persistent depressive disorder, and premenstrual dysphoric disorder (American Psychiatric Association 2013). Given the high prevalence rate of these disorders (Tschudin et al. 2010; Byers et al. 2012; Copeland et al. 2013), and their similar and somewhat overlapping symptomatology with depression (Uher et al. 2014), their inclusion in the DSM-5 will consequently increase the rates of comorbidity of MDD and may have major implications for therapeutic decision-making.

### 4.2.3 Inclusion of Hopelessness

Another amendment proposed by the DSM-5 is the inclusion of the word "hopeless" as a subjective descriptor of depressed mood (American Psychiatric Association 2013). A sense of hopelessness reflects a negative attribution about a particular event or even oneself and the belief that nothing could be done to change it. This small, but potentially important change, will broaden the diagnosis of MDD since individuals who report feeling hopeless but not sad would be able to fulfill the mood criterion in the DSM-5. The inclusion of hopelessness as an indicator of a major depressive episode is bolstered by evidence showing that individuals who struggle with feelings of hopelessness are more likely to develop symptoms of clinical depression (Brothers and Andersen 2009), and show increased vulnerability to suicide (Beck et al. 1989, 1990), suicide intent (Wetzel et al. 1980; Jaiswal et al. 2016), and suicide ideation (Britton et al. 2008; McCullumsmith et al. 2014). Hopelessness has also been suggested as a central dimension of depression insofar as clinically depressed patients endorse significantly higher level of hopelessness than patients suffering from a variety of other disorders (Greene et al. 1982). However, notwithstanding the compelling evidence in support of the inclusion of hopelessness in the DSM-5, several investigations see this subjective descriptor as phenomenologically distinct from a depressed mood (Greene 1989; Beck et al. 1993; Joiner et al. 2001). As such, the specificity of hopelessness as an indicator of a major depressive episode in the DSM-5 is likely to broaden the diagnosis of MDD, but it may also decrease its reliability insomuch as hopelessness often occurs independently of depression.

### 4.2.4 Removal of the Bereavement Exclusion

One of the most controversial changes proposed by the DSM-5 is the removal of the bereavement exclusion from the diagnostic criteria of MDD (American Psychiatric Association 2013). In the DSM-IV, individuals who were exhibiting symptoms of MDD were excluded from diagnosis if they were also bereaved within the past 2 months to account for the fact that a state of intense grief following the loss of a loved one is a normal reaction (American Psychiatric Association 1994). However, diagnosis could be done if the bereavement lasted more than 2 months and resulted in severe functional and behavioral impairments reminiscent of grief reactions (American Psychiatric Association 1994). In contrast, the DSM-5 has lifted the bereavement exclusion from the diagnostic criteria, primarily based on evidence suggesting that depression following bereavement is similar in nature and outcome from non-bereavement-related depression (Zisook and Kendler 2007; Zisook et al. 2012). Indeed, the majority of studies seem to concur with the view that bereavement-related depression is common, long lasting, recurrent, and characterized by clinical outcomes reminiscent of MDD, including worthlessness, suicidality, and impairments in psychosocial and psychomotor functioning (Zisook et al. 2007). However, despite mounting evidence pleading in favor of the removal of the bereavement exclusion, this decision provoked a lot of criticism among scientists and clinicians. Critics have mostly argued that the removal of the bereavement exclusion will recognize ordinary grief as a major depressive episode, resulting in inappropriate increases in false-positive diagnosis and in the number of prescribed antidepressants (Pies 2014). As such, the DSM-5 has added a descriptive guideline to call for clinicians to differentiate between symptoms characteristic of normal grief and those that are reminiscent of depressive disorders based on their clinical judgment and experience in pathophysiology (American Psychiatric Association 2013).

### 4.2.5 Dimensional Ratings

As part of the DSM-5 revision, the introduction of dimensional measures has been proposed as a complement to the current categorical approach of diagnosis (American Psychiatric Association 2013). Similar to the DSM-IV, DSM-5 encourages the use of standardized dimensional rating

scales and self-reporting questionnaires as screening tools to assess the severity of symptoms and to provide clinicians with information relevant for psychiatric diagnosis. In the DSM-5, symptoms are classified as mild, moderate, or severe, and a direction for a four-level rating of new specifiers of MDD is included to allow characterization of additional symptoms (Uher et al. 2014). Compared to the classical categorical assessment of psychopathology, whereby diagnosis is based on the presence or absence of symptoms, dimensional systems have the potential to more richly explain heterogeneity in clinical settings (Brown and Barlow 2005), and are more likely to serve as a putative predictor of antidepressant treatment response (Uher et al. 2012). Such a dimensional approach can be applied across several disorders to assess severity and disaggregate the relevant symptoms, which could eventually provide a more in-depth understanding of the pathological profile of patients and offer a reliable guide for clinicians on future therapeutic strategies. However, despite having greater explanatory power, the dimensional analysis of symptoms may offer lower clinical utility since most decisions in clinical practice are purely categorical, involving a yes-or-no character (Uher et al. 2012, 2014). Careful clinical judgment is therefore needed to determine at which stage dimensional measures are best introduced into the categorical diagnostic system and how they could be used to effectively guide the treatment process.

### 4.2.6 Specifiers of MDD

The number of specifiers in the DSM-5 has been increased to reflect the existence of phenomenological variants of MDD and to define a more homogeneous subgrouping of individuals with the disorder (American Psychiatric Association 2013). The expansion of descriptive specifiers for the diagnosis of depressive disorders will help convey information relevant to treatment decision-making and may also have implications for forensic practice in the context of sentencing, civil commitment, and child custody (Parker 2014). As part of a mixed categorical dimensional approach, a list of uncoded specifiers can now be added in the diagnosis of MDD, including "with anxious distress", "with mixed features", "with melancholic features", "with atypical features", "with mood-congruent psychotic features", "with mood-incongruent psychotic features", "with catatonia", with "peripartum onset", and "with seasonal pattern" (American Psychiatric Association 2013). With respect to the DSM-IV, one major change proposed by the DSM-5 is the addition of the "with anxious distress" descriptive specifier, which was added to account for the high prevalence of anxiety symptoms among individuals with depressive disorders (Lamers et al. 2011; Li et al. 2012). This new addition could have a major impact on clinical practice since individuals with anxious depression respond poorly to antidepressants compared to individuals with nonanxious depression and may therefore require additional treatment care (Fava et al. 2008; Wu et al. 2013). Second, the "with mixed features" specifier was introduced in the DSM-5 to replace the DSM-IV entity of a mixed episode of bipolar disorder and to account for specific treatment requirements for depressed individuals with mixed symptoms (Parker 2014). Finally, the "postpartum onset" specifier of the DSM-IV has been expanded to "peripartum onset" in the DSM-5, which may now be applied if the depressive episode takes place during pregnancy or within 4 weeks of child birth (Parker 2014). This change will help improve the detection of depressive symptoms during the perinatal period and will serve as a prevention tool toward postpartum depression, which could lead to multiple negative effects for both mothers and children if left untreated.

## 4.3 Biological Markers in MDD

A biological marker, or biomarker, is an objective measurement of a normal biological process that can be used to predict or indicate the presence of a disease. In MDD, the advantages of having reliable biomarkers are diverse, ranging from the stratification of the disorder according to severity

and symptomatology, the indication of disease prognosis, to the prediction of therapeutic responses (Gururajan et al. 2016). Validated disease-associated biomarkers are also critical elements of the translational process, enabling the direct transition between ethologically valid animal models and human conditions (McGonigle and Ruggeri 2014). Many different biological measures can be used to detect the presence of depression, including neurotransmitters, proteins, metabolites, and brain activity patterns. The following sections present an overview of the biological measures that may potentially serve as biomarkers in MDD, and discuss key challenges in their use and application in psychiatry.

### 4.3.1 Neurotransmitters

#### 4.3.1.1 Serotonin and Dopamine

One of the most established etiological theories of depression is the monoamine hypothesis, which states that the underlying pathophysiological basis of the disorder is due to specific deficits in serotonin (5-HT) and catecholamines in the central nervous system (Delgado 2000; Albert et al. 2012). This long-standing hypothesis forms the cornerstone of current therapeutic approaches of depression, which primarily use drugs for inhibiting the reuptake of neurotransmitters in the brain, like 5-HT and norepinephrine. In support of the monoamine hypothesis of depression, studies have reported decreased peripheral levels of 5-HT (Maurer-Spurej et al. 2007; Paul-Savoie et al. 2011) and its precursor tryptophan (Cowen et al. 1989; Ogawa et al. 2014) in depressed patients. In addition, postmortem analysis of brain tissues revealed decreased expression of $5\text{-HT}_{1A}$ mRNA in the hippocampus and dorsal prefrontal cortex (Lopez-Figueroa et al. 2004), and increased level of $5\text{-HT}_{2A}$ receptors in the prefrontal cortex (Shelton et al. 2009) of MDD patients, thus bolstering the view that the serotonergic system is dysregulated in depression. Other players of the serotonergic system that are incriminated in MDD include the $5\text{-HT}_{1B}$ and $5\text{-HT}_{2A}$ receptors, as well as the 5-HT membrane transporter protein (SERT) (Fakhoury 2016). As for dopamine, the majority of studies thus far have focused on the role of the dopamine D4 receptor in depression. These studies, however, have yielded conflicting results inasmuch as dopamine D4 receptor mRNA expression was found elevated in the amygdala (Xiang et al. 2008), decreased in lymphocytes (Rocc et al. 2002), and unaltered in leukocytes (Iacob et al. 2014) of MDD patients compared to healthy controls.

#### 4.3.1.2 Norepinephrine

In light of early evidence showing that inhibition of norepinephrine reuptake contributes to the therapeutic efficacy of several classes of antidepressants (Burrows et al. 1998), substantial and consistent evidence has associated MDD with alterations in norepinephrine signaling. Frequently reported findings include the presence of increased density of α2-adrenoceptors (a target of norepinephrine) in the frontal cortex (Callado et al. 1998; Garcia-Sevilla et al. 1999; Valdizan et al. 2010) and temporal cortex (De Paermentier et al. 1997) of depressed suicide victims. In addition, increased α2-adrenoceptor sensitivity (Gonzalez-Maeso et al. 2002) and mRNA expression (Escriba et al. 2004) were found in the frontal cortex of suicide victims diagnosed with mood disorders. Subjects with MDD were also shown to exhibit marked decreases in norepinephrine transporter binding in the midcaudal portion of the locus coeruleus (Klimek et al. 1999). However, studies investigating the density of α2-adrenoceptors in platelets of MDD patients reported opposite results, showing either decreases (Maes et al. 1999) or increases (Gurguis et al. 1999) in receptor density. Despite being contradictory, these findings provide strong evidence for the involvement of α2-adrenoceptors in the pathogenesis of depression, and together with evidence from postmortem studies, indicate that alterations in specific aspects of norepinephrine signaling may serve as potential biomarkers in MDD.

#### 4.3.1.3 Glutamate and GABA

Although the majority of studies investigating the neurobiological mechanisms of depression have focused on monoamines such as serotonin,

dopamine, and norepinephrine, evidence also points to a role of glutamate and GABA neurotransmission in depressive behaviors. Recent postmortem analyses reveal robust decreases in the expression of several key glutamate receptor subunits, including the NR2A and NR2B subunits of NMDA receptors, in the perirhinal and prefrontal cortex of MDD patients (Beneyto et al. 2007; Feyissa et al. 2009). Consistently, neuroimaging studies reported downregulation of glutamate in the ventromedial prefrontal cortex of depressed patients (Portella et al. 2011), and reduced levels of metabotropic glutamate receptor 5 (mGluR5) binding in the prefrontal cortex, the cingulate cortex, the insula, the thalamus, and the hippocampus of individuals with MDD (Deschwanden et al. 2011). Likewise, synaptic alterations in GABA neurotransmission have been shown to substantially contribute to MDD's underlying etiology. The general consensus appears to be that GABA concentrations are downregulated in the plasma (Petty and Schlesser 1981; Petty and Sherman 1984; Petty et al. 1992), cerebrospinal fluid (CSF) (Gold et al. 1980; Gerner and Hare 1981; Gerner et al. 1984), and brain regions (Honig et al. 1988; Sanacora et al. 1999) of patients with depression, though some studies reported no differences between depressed and control individuals (Roy et al. 1991; Godlewska et al. 2015). In addition, reduced protein level (Karolewicz et al. 2010) and mRNA expression (Thompson et al. 2009) of glutamic acid decarboxylase (GAD), the GABA synthesizing enzyme, were found in the prefrontal cortex and orbitofrontal cortex of MDD patients, respectively, indicating that the development of depressive behaviors may be due to a widespread reduction in GABA neurotransmission.

### 4.3.2 Neurotrophins and Other Growth Factors

Numerous studies have implicated neurotrophins and other growth factors in the etiology of depression and in the therapeutic effects of antidepressants. Neurotrophins are a family of proteins that belong to the class of growth factors, mediating functions important for the survival, differentiation, and maintenance of nerve cells. Four neurotrophins are expressed in the mammalian brain, including nerve growth factor (NGF), brain-derived neurotrophic factor (BDNF), neurotrophin-3 (NT-3), and neurotrophin-4 (NT-4) (Huang and Reichardt 2001). Although NGF and NT-3 have been implicated in depression (Hock et al. 2000; Chen et al. 2015; Wysokinski 2016), BDNF has been the most extensively studied thus far, with the large majority of findings reporting decreased level of this neurotrophin in the serum (Karege et al. 2005; Aydemir et al. 2006; Bocchio-Chiavetto et al. 2010; Ristevska-Dimitrovska et al. 2013) and plasma (Kim et al. 2007; Lee et al. 2007; Piccinni et al. 2008) of depressed individuals; effect that is normalized by antidepressant treatments (Shimizu et al. 2003; Aydemir et al. 2005; Gonul et al. 2005; Yoshimura et al. 2007; Huang et al. 2008). Notwithstanding the inconsistency reported in the literature (Serra-Millas et al. 2011; Brunoni et al. 2014), the aforementioned studies strongly suggest that peripheral levels of BDNF are good candidate biomarkers for MDD and could be considered as reliable predictors of antidepressant response.

Besides neurotrophins, growth factors such as vascular endothelial growth factor (VEGF) and fibroblast growth factor (FGF) have also been implicated in the etiology of depression. Originally described as an angiogenic mitogen, VEGF has been shown to play a crucial role in the pathophysiology of depression and to act as a mediator of antidepressant actions (Warner-Schmidt and Duman 2007; Clark-Raymond and Halaris 2013). However, studies evaluating the levels of VEGF in depressed patients have reported inconsistent findings, showing either increased (Kahl et al. 2009; Lee and Kim 2012) or no change (Dome et al. 2009; Kotan et al. 2012) in peripheral levels of this growth factor compared to healthy controls. In another set of studies, altered gene expression of several FGF transcripts was found in the dorsolateral prefrontal cortex (Evans et al. 2004), locus coeruleus (Bernard et al. 2011), and hippocampus (Gaughran et al. 2006) of MDD subjects, suggesting that perturba-

tions of FGF regulation may also serve as a valuable biomarker of depression. In addition, elevated level of FGF-2 has been observed in the serum of MDD patients (Kahl et al. 2009), pointing to a role of this growth factor in the pathophysiology of depression. Other growth factors that may serve as biomarkers of MDD and a predictor of antidepressant response include the vascular growth factor (VGF), glial cell line-derived neurotrophic factor (GDNF), insulin-like growth factor-1 (IGF-1), and nerve growth factor (NGF) (Schmidt et al. 2011; Galvez-Contreras et al. 2016). However, given the numerous discrepancies and missing gaps in the literature, further investigations with sound methodology are warranted to evaluate the reliability of these growth factors as biomarkers of MDD.

### 4.3.3 Inflammatory Mediators

Several lines of evidence indicate that inflammatory mediators, including cytokines and immune cells, may have a role in the etiology of MDD. Clinical studies demonstrate that patients with depressive symptoms display increased peripheral (Kahl et al. 2006; Diniz et al. 2010; Dowlati et al. 2010) and cerebrospinal (Levine et al. 1999; Lindqvist et al. 2009) levels of pro-inflammatory cytokines, including tumor necrosis factor-alpha (TNF-α), interleukin-1beta (IL-1β), and IL-6; effect that can be reversed upon treatment with antidepressants (Basterzi et al. 2005; Himmerich et al. 2010; Hannestad et al. 2011). Consistent with the notion that elevated inflammatory response contributes to the etiology of depression, inhibition of pro-inflammatory cytokines using TNF-α antagonists (Krishnan et al. 2007; Raison et al. 2013) or COX-2 selective nonsteroidal anti-inflammatory drugs (Muller et al. 2006; Nery et al. 2008) results in improved symptomatology in patients with depressive symptoms. Alterations in other markers of inflammation and oxidative stress, including C-reactive protein (CRP), superoxide dismutase (SOD), myeloperoxidase (MPO), and inducible nitric oxide synthase (iNOS), are also found in depressed patients (Lopresti et al. 2014; Gururajan et al. 2016) and may potentially be used to aid in the detection and prediction of depressive symptoms.

Glial cell dysregulation, which ultimately leads to increased cytokine production and chronic inflammation, is also believed to constitute a prominent pathological feature of MDD (Rajkowska and Stockmeier 2013; Rial et al. 2015). Postmortem studies have repeatedly reported decreased glial cell density in cortical regions of depressed patients, including the anterior cingulate cortex (Cotter et al. 2001; Gittins and Harrison 2011), the dorsolateral prefrontal cortex (Cotter et al. 2002), the subgenual prefrontal cortex (Ongur et al. 1998), and the orbitofrontal cortex (Rajkowska et al. 1999). Consistent with these findings, patients with depression were also shown to have a lower density of numerous proteins involved in glial cell activation and function within cortical regions, including glial fibrillary acidic protein (GFAP) (Si et al. 2004), excitatory amino acid transporters 1 and 2 (Miguel-Hidalgo et al. 2010), aquaporin-4 (Rajkowska and Stockmeier 2013), and connexin 43 (Miguel-Hidalgo et al. 2014).

Altogether, the aforementioned findings propose that depression is characterized by conspicuous changes in immune and inflammatory markers. Although these changes may show great potential in helping clinicians make appropriate diagnosis and treatment decisions, their use remains limited by the fact that it is still not clear whether the inflammatory response in depressed patients contributes to the etiology of MDD or takes place as a consequence of a depressive state. A better understanding of inflammation and its relationship with the development of depressive behaviors is thus of paramount clinical importance.

### 4.3.4 Endocrine and Metabolic Markers

The hypothalamic–pituitary–adrenal (HPA) axis, a major endocrine system that regulates the physiological response to stress, is believed to play a

pivotal role in the pathophysiology of depression (Varghese and Brown 2001; Du and Pang 2015). Activity of the HPA axis is governed by the production and release of corticotrophin-releasing hormone (CRH) and arginine vasopressin (AVP) from the paraventricular nucleus of the hypothalamus, which in turn activate the secretion of adrenocorticotrophic hormone (ACTH) from the pituitary (Pariante and Lightman 2008). This results in an increased secretion of glucocorticoids (cortisol in humans and corticosterone in rodents) from the adrenal cortex, which then exert a direct feedback inhibition of the HPA axis (Pariante and Lightman 2008). Reported findings from depressed patients concur with the view that MDD is associated with an upregulation of the HPA axis, including elevated levels of cortisol (Vreeburg et al. 2009), CRH (Austin et al. 2003), and AVP (van Londen et al. 1997); effect that is reversed following chronic treatment with antidepressants (Piwowarska et al. 2009, 2012). However, HPA axis activation is not always abnormally increased in individuals with MDD (Watson et al. 2002; Van Den Eede et al. 2006) and appears to be differentially regulated in specific subtypes of depression (Levitan et al. 2002; Lamers et al. 2013). Notwithstanding the inconsistency in the existing literature, monitoring the changes in cortisol and CRF levels, as well as other HPA axis factors, could prove beneficial in characterization distinct subtypes of MDD and assessing treatment response to antidepressants.

Evidence also demonstrates an association between depressive disorders and metabolic syndrome, the latter being defined by a cluster of symptoms that include increased waist circumference, high blood pressure, high glucose level, elevated triglycerides, and low high-density lipoprotein (HDL) cholesterol (Foley et al. 2010; Marazziti et al. 2014). The prevalence of metabolic syndrome among patients with depression is markedly higher compared to that of healthy individuals (Heiskanen et al. 2006; Lasic et al. 2014), suggesting that some individual metabolic syndrome components may be indicative and predictive of depressive symptoms. Indeed, increased waist circumference (Dunbar et al. 2008; Zhao et al. 2011), low HDL cholesterol level (Dunbar et al. 2008; Lehto et al. 2008), and elevated blood pressure (Reiff et al. 2001) show significant and independent associations with depression. Increased waist circumference was also suggested as a very strong predictor of depressive symptoms (Pulkki-Raback et al. 2009), thus urging the need for individuals with abdominal adiposity to consider lifestyle changes, such as adopting a healthy dietary pattern to prevent depression later in life. Consistent with these findings, circulating levels of leptin and ghrelin, which regulate hunger and metabolism, were found to be differentially regulated in individuals with depressive behaviors (Kraus et al. 2001; Gecici et al. 2005; Tuncel et al. 2016) and were shown to play a role in the mechanisms of actions of antidepressants (Schilling et al. 2013; Ozsoy et al. 2014). Thus, altered metabolic function should be routinely assessed in the clinic since it could be used as a viable biomarker for decisions pertaining to clinical diagnosis and treatment care in depressed patients.

### 4.3.5 Neuroimaging-Based Markers

Methods for identifying neuroimaging-based biomarkers over the past few years have shed new light on the underlying mechanisms of MDD. Notably, techniques such as structural magnetic resonance imaging (MRI), diffusion tensor imaging (DTI), functional magnetic resonance imaging (fMRI), and positron emission tomography (PET) have allowed for a better understanding of the relationship between depression and brain structure and function (Dunlop and Mayberg 2014). One of the most frequently reported findings is reduced hippocampal volume in patients with MDD (Cole et al. 2011), which normalizes after remission (Ahdidan et al. 2011) or treatment with antidepressants (Malykhin et al. 2010). Other structural changes, including decreased volumetric asymmetries in the basal ganglia (Shah et al. 2002; Lacerda et al. 2003) and smaller volume of the orbitofrontal cortex (Bremner et al. 2002), cingulate cortex (Caetano et al. 2006), and amygdala (von Gunten et al. 2000; Hastings

et al. 2004), were also reported in individuals with MDD, thus advocating changes in cortico-limbic structures as potential diagnostic biomarkers for depression.

In addition to the reported structural changes observed in depression, MDD patients show marked impairments in resting and task-evoked activation of several brain regions. For instance, task-based fMRI studies in depressed patients reported aberrant activation of numerous structures within the cortico-limbic system, including increased activation of the amygdala (Mingtian et al. 2012; Ruhe et al. 2012), decreased activation of the prefrontal and cingulate cortex (Ruhe et al. 2012), and increased activation of the insula (Surguladze et al. 2010) in response to facial stimuli. Depressed patients also exhibit decreased activation of the right hippocampal and left parahippocampal gyrus during recollection memory trials, implicating abnormalities in memory retrieval processes in MDD (Milne et al. 2012). Similarly, resting-state fMRI studies have revealed the presence of aberrant patterns of effective connectivity among cortical, limbic, and paralimbic structures (Greicius et al. 2007; Hamilton et al. 2011), implicating abnormalities of the default-mode functional connectivity in the etiology of depression. Last but not least are PET measures of neural activity revealing multiple abnormalities in glucose metabolism and/or regional blood flow in cortical-limbic structures (Drevets et al. 1997) and in limbic structures (Neumeister et al. 2006) of individuals with MDD.

Taken together, findings collected over the past few years have consistently shown that MDD is characterized by specific patterns of structural and functional abnormalities in cortico-limbic regions. These abnormalities, if sufficiently important to be detectable by neuroimaging tools, may have the potential to translate into robust clinical biomarkers for the diagnosis of depression. Neuroimaging-based biomarkers could also be reliably used to predict treatment outcome (Drysdale et al. 2017), stratify patients into distinct clinical subgroups (Drysdale et al. 2017), and might even serve to detect predispositions to MDD.

## Conclusion

The diagnostic criteria of MDD have undergone major changes from the DSM-IV to DSM-5. Some of the most significant amendments include the inclusion of hopelessness as a descriptor of depressed mood, the removal of the bereavement exclusion, and the introduction of new dimensional measures and specifiers. Notwithstanding the major revisions made by the DSM-5, the latter has been largely criticized for being based on pragmatic judgments rather than scientific evidence. Among some of the controversial issues surrounding the new set of diagnostic criteria, critics have argued that the introduction of mixed features and the removal of the bereavement exclusion may lead to misdiagnosis of MDD with a resultant increase in the number of prescribed antidepressants (Koukopoulos et al. 2013; Pies 2014). Caution should therefore be taken when making a diagnosis of MDD. Decisions made by clinicians should not only rely on the DSM-5 criteria but also on their prior experience and knowledge of psychopathology.

Over the past few years, tremendous efforts have also been made toward the identification of potential biological markers that could aid in the diagnosis of MDD and serve as predictor of antidepressant response. Some of the frequently reported findings include abnormalities in neurotransmitter systems, such as those for 5-HT, dopamine, norepinephrine, glutamate and GABA, and alterations in the levels of growth factors, such as BDNF, VEGF, and FGF. Evidence also indicates the presence of conspicuous changes in the levels of inflammatory, endocrine, and metabolic markers, and the presence of structural and functional abnormalities in specific cortico-limbic regions of depressed patients. Dysregulations of these biological markers, if sufficiently important, may constitute reliable indicators of depressive behaviors and even serve to predict predispositions to MDD. However, future studies are needed to indicate whether these changes constitute a direct cause of depression or a compensatory mechanism for spe-

cific neurobiological alterations. Correlational studies are also warranted to determine whether the changes in biomarker levels correlate with disease severity. This could have important implications in the clinic regarding both diagnosis and treatment decision.

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# 5 Application of Neuroimaging in the Diagnosis and Treatment of Depression

Ayla Arslan

## 5.1 Introduction

Depression is a brain disease deriving from the complex interplay of genes and environment. According to World Health Organization, it is a common mental disorder affecting more than 300 million people worldwide and major contributor to the overall global burden of disease (WHO, Depression Fact Sheet, 2017).

Despite its devastating impact on quality of life, the neurobiological mechanism of depression is not fully understood. Thus, diagnosis of depression is grounded on clinical guidelines. These guidelines such as *Diagnostic and Statistical Manual of Mental Disorders* (DSM-V) or *International Classification of Diseases* (ICD-10) lack biological validity, despite being clinically reliable.

The classification criteria of the DSM-V or ICD-10 involve clinical signs, symptoms, and course of illness causing patients with different phenotypes to be diagnosed in the same way and to receive same pharmacotherapy. Consequently, two third of the patients, diagnosed with major depressive disorder (MDD), do not respond to initial pharmacotherapy regimen, for example (Krishnan and Nestler 2010). Also, existing treatments are neither optimally effective nor without adverse effects (Goodwin 2008). For instance, side effects of selective serotonin reuptake inhibitors (SSRI), one of the most prescribed antidepressant drug (AD), are prominent (Price et al. 2009). Moreover, patients diagnosed as depressive but unresponsive to AD treatment or more difficult to treat have higher probability of bipolar disorder (BPD) diagnosis (Li et al. 2012). So, problems for the differential diagnosis of depression and other psychiatric conditions exist. Figure 5.1 summarizes the problems associated with clinical classification of depression.

One way to address these problems is the use of biological markers rather than relying on clinical soft signs and symptoms for the classification of depression. This in turn would certainly guide better disease diagnosis. Besides, the discovery of relevant biomarkers would help predict the risk for developing a disorder as well as its course and treatment outcome. Are there such biomarkers?

But, before that, what is a biomarker exactly? According to Webster's New World Medical Dictionary, a biomarker is defined as "a biologic feature that can be used to measure the presence or progress of disease or the effects of treatment". For psychiatric conditions, this sounds very ambitious yet challenging.

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Psychiatrists would like to know if a specific drug is going to treat depression or if a person with depression is in danger of committing suicide. Thus, a biomarker is expected to give the opportunity to evaluate drug response and disease risk based on biological data. Addressing the former, such a biomarker can be named as treatment-selection biomarker (TSB) which is defined as a biological moderator that can be measured before treatment to guide selection of the optimal treatment for patients (McGrath et al. 2013). Also, a biomarker for psychiatric condition is expected to assist better diagnosis, providing opportunity to classify the disease and its subtypes precisely.

This type of biomarker can be named as "diagnostic biomarker". Another group of biomarkers can be used to identify the utility of an ongoing intervention early in the course of illness, thus decreasing the time required to determine treatment outcome. In this chapter, we will examine the potential of neuroimaging derived data as biomarkers to be used in the diagnosis and treatment of depression (Fig. 5.2 shows examples for candidate neuroimaging biomarkers).

## 5.2 Neuroimaging: A Window to the Black Box

Imaging of brain (or neuroimaging) was unthinkable until the late nineteenth century, when the discovery of X-rays has opened a window to this black box. Since then, different types of neuroimaging techniques have been increasingly used for the studies of brain structure and function such as positron emission tomography or magnetic resonance imaging (Box 5.1).

**Box 5.1: What Is Neuroimaging?**

Neuroimaging corresponds to a range of noninvasive methodologies such as magnetic resonance imaging (MRI) or positron emission tomography (PET) to obtain, identify, analyse, and interpret the images of brain structure and functionality.

Positron emission tomography (PET) is a type of neuroimaging, which can be used to identify resting-state metabolic features as well as density

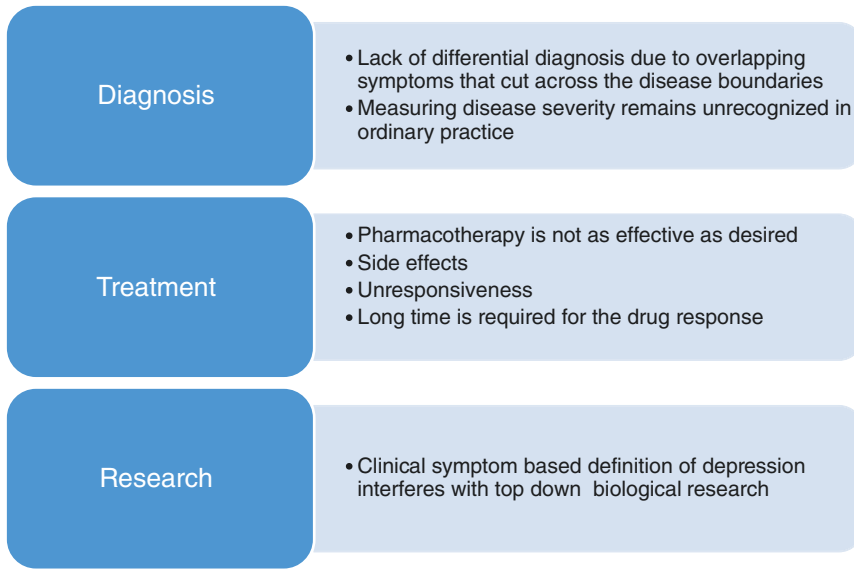


**Fig. 5.1** Current problems associated with classification of depression

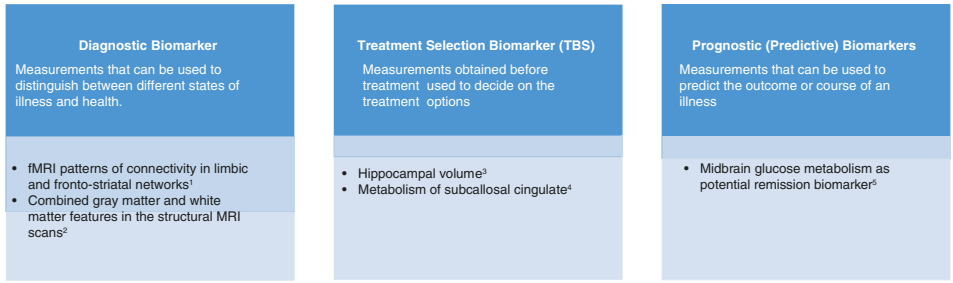


**Fig. 5.2** Types of depression biomarkers discussed in the chapter and examples for candidate neuroimaging biomarkers. *fMRI* functional magnetic resonance imaging, *MRI* magnetic resonance imaging, *DFN* default mode network, *OFC* orbital frontal cortex, *DLPFC* dorsolateral prefrontal cortex, *sgACC* subgenual anterior cingulate cortex, *VMPFC* ventromedial prefrontal cortex. [1]Drysdale et al. (2017), [2]Sankar et al. (2016), [3]Fu et al. (2013), [4]McGrath et al. (2014)

of neurotransmitter receptors and neurotransmitter transporters. Using radioactive tracers and ligands, a PET scan, can show how the brain and its tissues are working. As the late 1970s have witnessed the increase in the development of radioactive tracers for brain, many human studies of PET have been conducted. The first examples of such studies involve the imaging of regional amino-acid metabolism or drug kinetics in brain tumours (Bergstorm et al. 1983; Diksic et al. 1984) or neurotransmitter function (Garnett et al. 1983) followed by many others.

Magnetic resonance imaging (MRI) can be used to determine volume of different brain regions such as hippocampus and amygdala. The MRI measurements, then, can be used to determine individual differences in these structures and their correlation with the biological parameters such as genetic variations and/or disease states. MRI utilizes a strong oscillation of magnetic field to make exogenously added contrast agents (or endogenous atoms such as hydrogen) to emit radio waves. The radio waves are then used to generate two- and three-dimensional images of the brain in vivo.

The diffusion tensor imaging (DTI) was first proposed in the 1990s for use in magnetic resonance imaging (MRI) (Basser et al. 1994a, b). In principle, DTI measures a specific direction of water diffusion by gradients of magnetic field generated by MRI. A repetition of this process in multiple directions is used to derive a 3D diffusion model called the tensor, estimated for the imaging of white matter (WM) pathways (reviewed by O'Donnell and Westin 2011). WM pathways are bundles of axons connecting the brain parts by commissural tracts like the corpus callosum and by association tracts like the arcuate fasciculus. These features can be assessed by several methodologies of DTI: (1) diffusion property of the white matter such as fractional anisotropy (FA) or mean diffusivity (MD), (2) 3D geometrical models of fibre paths derived from tractography, and (3) connectivity matrices of brain connection networks (Arslan 2018). Thus, DTI can identify microstructural WM abnormalities with high resolution enabling the characterization of WM tracts related to critical brain regions implicated in emotion and cognition. Moreover, it can address the genetic effects on the WM structures. The twin or sibling studies of brain asymmetry and development (Jahanshad et al. 2010; Chiang et al. 2011) or studies analysing the individual differences of white matter tracts (Schotten et al. 2011) have shed light on the dissection of these effects on the WM parameters. Conversely, DTI is a valuable tool for the determination of white matter integrity and density as measures of structural connectivity.

Also, by combining DTI with functional magnetic resonance imaging (fMRI), a neuroimaging method that reflects states of brain metabolic activity in the resting state or during a specific neural task as blood oxygenation level-dependent (BOLD) contrast, the model of connectivity (connectome) can be studied (reviewed by

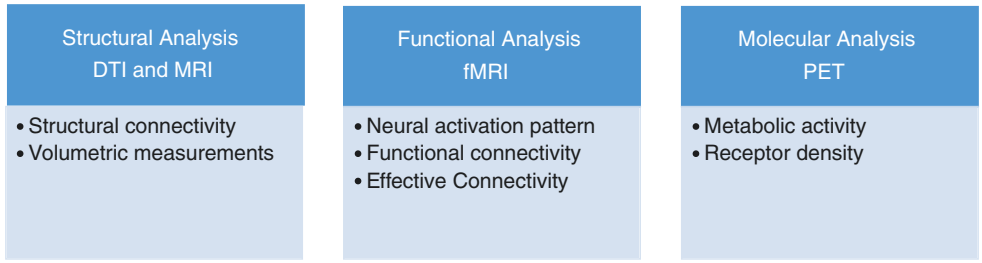


**Fig. 5.3** Summary of neuroimaging methods described in the present study

Glasser and Rilling 2008; Schotten et al. 2011). As ultrahigh magnetic fields increase the BOLD sensitivity (Uğurbil 2012), fMRI studies are increasingly used to measure neural activity in a specific brain region during a cognitive or emotional task. Elaborating on this, functional connectivity analysis is used to examine neural activation patterns in coordinated temporal patterns of activity across multiple regions (functional connectivity MRI [fcMRI]) (Fox and Raichle 2007). Moreover, effective connectivity is an approach of fMRI, which identifies a cause and effect relationship to determine how one part of the brain regulates activity in another during a specific task of emotion or cognition (Arslan 2018).

Because of these increasing capabilities, neuroimaging is widely used to probe neurobiological characteristics in almost every field of neuroscience (Patel et al. 2016) despite controversies (Vul et al. 2009). Since the first functional brain mapping of human subjects in the early 1990s (Belliveau et al. 1991; Ogawa et al. 1992), for example, the number of research articles published in NCBI PubMed relevant to) fMRI hit to 27,995 papers in between January 1, 2016, and January 1, 2017. Why is it so?

The appeal of neuroimaging lies behind the irresistible idea of decoding the activation patterns and algorithms of the brain to sense, perceive, and respond to the world during health and disease. However, the outcomes were below the expectations: At present, utilization of neuroimaging biomarkers for clinical practice is restricted to neurological conditions such as presurgical evaluation of epilepsy, differential diagnosis of coma, and brain-computer interfaces for locked-in patients. For psychiatric conditions including depressive disorders, this is yet to be established for routine clinical applications; however, neuroimaging in collaboration with other fields holds a strong potential for this goal. In fact, there is a tremendous progress in molecular and cellular mechanisms underlying neural function and plasticity, but translation of this knowledge to clinical practice was not very fruitful, either. Thus, it was argued that clinical psychiatry did not benefit from genomic revolution as desired (Arslan 2015).

One way to address this "bottleneck" is to accelerate the screening of reliable biomarkers, which can link neuroscience research with clinical studies. Put it together, a good repertoire of biomarkers is not only needed to address problems of disease classification, personal pharmacotherapy, and preventative medicine but also for better research climate. Thus, neuroimaging studies (Fig. 5.3) are particularly critical in this context as there is a huge potential in line with the advancements in the field. Here we will describe this in terms of PET, MRI, DTI, fMRI, the promises, and the challenges.

## 5.3 The Depressed Brain

Neuroimaging can shed light on how dysfunction in specific brain structures and circuits might underlie depression. Accordingly, many studies attempted to identify molecules, regions and circuits involved in this process. Two circuitries are reported as associated with depression and other mood disorders most consistently: The serotonergic circuitry centred on amygdala and differ-

ent medial prefrontal cortical regions, and the circuitry centred on the ventral striatum and medial prefrontal cortex (Phillips et al. 2015). The former circuitry is involved in the modulation of implicit emotion regulation, and the latter is a dopamine-regulated reward circuit. It is suggested that different dimensions of depression symptoms might be linked to abnormalities in these circuitries thus can serve as biomarkers for treatment selection. For example, abnormalities in the implicit emotion regulation circuitry may cause poor affect and anxiety, while abnormalities in reward circuitry may cause indifference and anhedonia (Pizzagalli 2011; Keedwell et al. 2005).

One of the mediators of implicit emotion regulation is thought to be serotonergic transmission particularly in the amygdala and medial prefrontal cortical regions (Phillips et al. 2015). Addressing this, PET studies reported differences in the levels of serotonin receptors (5-$HT_{1A}$ and 5-$HT_{2A}$) between healthy people and patients with , MDD (Drevets et al. 1999; Meyer et al. 2003); Sargent et al. 2000; Savitz and Drevets 2009; Smith and Jakobsen 2009). Patients of major depressive disorder (MDD), who have high levels of pessimism, show an elevation in 5-$HT_{2A}$ receptor levels (Bhagwagar et al. 2006; Meyer et al. 2003), and patients with major depressive episode show a reduction in 5-$HT_{1A}$ receptors (Drevets et al. 1999; Sargent et al. 2000). Also, 5-HT1A density was determined by using the PET tracer [carbonyl-C-11]-WAY-100635, a selective 5-HT1A antagonist in a study of 50 patients with MDD (34 female, 16 male) and 57 healthy controls (32 female, 25 male). Results show that 5-HT1A density of male subjects diagnosed with MDD was significantly higher across 13 brain regions compared with male controls ($p < 0.0001$), suggesting that 5-HT1A density could be a biomarker for depression in males (Kaufman et al. 2015).

In particular, several studies analysed the metabolic features of MDD by PET. Given that glucose is the major substrate for brain metabolism, studies of glucose metabolism using 2(18F)-fluoro-2-deoxy-D-glucose (FDG) by PET (FDG PET) have been conducted. For example, a meta-analysis (Su et al. 2014) confirmed the association of several brain regions with MDD including bilateral insula, left lentiform nucleus putamen, and extranuclear, right caudate, and cingulate gyri, which show a significant decreased metabolism in patients with MDD, whereas right thalamus pulvinar and declive of posterior lobe and left culmen of vermis in anterior lobe have significantly higher metabolic activity in MDD patients (Su et al. 2014).

One of the first systematic, well-controlled studies to identify the first potential biomarker that distinguishes between treatment responses was published not so long ago (McGrath et al. 2013). The group first measured glucose metabolism of the brains of 82 treatment-resistant depressed patients using PET scans. Then, they randomly assigned the patients to two different treatment groups. While one group received the SSRI escitalopram for 12 weeks, the other group received 16 sessions of cognitive behavioural therapy (CBT) over the same period. Results show that the rate of glucose metabolism in the right anterior insula—which is related to depression-relevant behaviours such as emotional self-awareness and decision-making—predicted the treatment response. The patients who have higher rate of insula glucose metabolism than the average metabolism rate for the whole brain responded to pharmacotherapy, whereas those who did not respond showed a below-average insula metabolism rate. Moreover, MDD patients who fail to achieve remission as a result of CBT or escitalopram, either alone or in combination, showed a distinct brain metabolic pattern compared to patients who achieve remission (McGrath et al. 2014): Metabolism of subcallosal cingulate—the portion of the cingulum that lies ventral to the corpus callosum including Brodmann area 25 and parts of 24 and 32—was significantly higher in non-remitters. Besides, increased activity of superior temporal sulcus—the sulcus inferior to the lateral fissure and separating the superior temporal gyrus from the middle temporal gyrus in the temporal lobe—was also associated with no responsiveness to two treatments. In a follow-up study, metabolism of the right part of the anterior insula, the cortical region folded in the depth of the lateral sulcus, has been

tested as treatment predictor for psychotherapy in 30 escitalopram-treated non-remitters who took combination treatment. Results show that patients whose added treatment matched the anterior insula metabolism-indicated treatment remitted more often than anterior insula metabolism-mismatched patients (Dunlop et al. 2015). Other clinically relative studies compare two pharmacotherapy options. For example, some studies reported the predictors between two classes of antidepressant response, but the results, to date, have been difficult to interpret and apply clinically (Little et al. 2005; Wagner et al. 2010; Frodl et al. 2011). Nevertheless, a study of meta-analysis (Fu et al. 2013) focusing on functional and structural neuroimaging studies of pharmacological and psychological therapies confirmed several brain regions within a fronto-striatal-limbic network which can predict treatment outcome.

## 5.4 The Structural Degenerate

Regarding depression perhaps one basic question is to ask if there is any structural difference between a healthy brain and a depressed brain. If so, can it be measured precisely by structural MRI?

As reviewed by Kempton et al. (2011), accumulating studies of structural MRI show that MDD is linked to larger lateral ventricle, larger cerebrospinal fluid volume, and smaller volumes of the basal ganglia, thalamus, hippocampus, frontal lobe, orbitofrontal cortex, and gyrus rectus.

Neuroimaging studies of these structures report associations between structural variants to treatment response. Among these, it was proposed that the ACC and hippocampus may provide an estimate of response to treatment (Vakili et al. 2000). Many other studies suggest that hippocampus may be used to predict treatment outcome (Frodl et al. 2008; MacQueen et al. 2008; Lorenzetti et al. 2009; Fu et al. 2013). Especially, individuals during depressive episodes are associated with smaller volume of hippocampus compared to individuals during remission. This is well supported by meta-analysis approach showing that depressed patients had significantly decreased left and right hippocampal volumes compared with controls (Campbell and MacQueen 2004). Particularly, according to a meta-analysis, structural MRI studies show that there is an association between larger hippocampal and cingulate volume with remission response to AD treatment (Chi et al. 2015). Volumes of the left middle frontal and the right angular gyri have been reported as reliable predictors for no remitters to AD treatment (Korgaonkar et al. 2014).

Also, some findings of structural measurements may lead to differential diagnostics. For example, when compared with patients of bipolar disorder, patients of MDD are differentiated by larger corpus callosum and smaller hippocampus and basal ganglia. On the other hand, there is also an overlap between the brains of MDD and BD patients: larger lateral ventricle and subcortical grey matter when compared with healthy controls.

One of the subjects of structural neuroimaging, the cortical thickness, is of great interest in both normal development and psychiatric disorders (Fischl and Dale 2000) and may offer some other opportunities for neuroimaging of depression.

## 5.5 Measuring Neural Activity

Measurement of neural activity in distinct brain regions may be considered as another neuroimaging methodology useful to predict treatment response. Indeed, such measurements as done by functional MRI indicate an important role for the amygdala for this purpose (Phillips et al. 2015). For example, one study reported that greater pretreatment amygdala activity predicted better outcome for cognitive behavioural therapy (CBT) (Siegle et al. 2006), while the opposite was found for the outcome of ketamine treatment (Salvadore et al. 2009).

Other brain regions such as the prefrontal cortex (PFC) or ACC have also been studied. For example, a lower pretreatment activity in the ventrolateral prefrontal cortex during an emotional task was associated with better response to either fluoxetine or venlafaxine in depressed subjects (Light et al. 2011). A lower baseline activity in the dorsal anterior cingulate cortex was associated with an improved clinical outcome with an

8-week treatment with fluoxetine was reported by one study (Walsh et al. 2007).

Indeed, accumulating evidence strongly suggests the activity of ACC as a predictor of a clinical response to antidepressant medication or other treatments (Ebert et al. 1991; Wu et al. 1999; Mayberg 1997) For example, a meta-analysis suggest that ACC activity has also been positively related to a variety of treatment responses, including antidepressant pharmacotherapy and experimental treatment strategies, such as sleep deprivation suggesting that ACC response can be used as a general predictor across different treatment types (Pizzagalli 2011).

Another meta-analysis focusing on fMRI and PET studies reports that increased ACC activity extending into the orbitofrontal cortex and decreased baseline activation of right striatum and anterior insula in acutely depressed patients can predict clinical response to AD or CBT (Fu et al. 2013).

Some other studies focus on the classification of depression by functional neuroimaging. One fMRI study (Fu et al. 2008) addressed the pattern of brain activity during the neural processing of sad facial expressions, which correctly classified up to 84% of patients ($p < 0.0001$). Moreover, this classification of patients' clinical response at baseline, prior to the initiation of treatment, appears to be predictive for treatment response (Fu et al. 2008).

One recent paper (Drysdale et al. 2017) has flustered this year, bringing us inspiring news that depression can be subdivided in to biological types, i.e. "biotypes" (Williams 2017). fMRI scans of more than 1100 patients with clinical depression and healthy individuals revealed that patients with depression can be divided into four subtypes based on distinct patterns of connectivity in limbic and fronto-striatal networks and different clinical symptoms (Drysdale et al. 2017). For instance, a finding for the reduction in the frontoamygdala connectivity, a network involved in the regulation of fear and reappraisal of negative emotional stimuli, led to the differentiation depression subtypes which was most severe in types 1 and 4. These subtypes are associated with symptoms of increased anxiety. Reduced connectivity in anterior cingulate and orbitofrontal areas, were most severe in types 1 and 2, which were characterized by increased fatigue. These areas are involved in motivation and incentive-salience evaluation. On the other hand, connectivity involved in reward processing, adaptive motor control, and action initiation, i.e. thalamic and fronto-striatal pathways, was especially prominent in type 3 and type 4, related to increased anhedonia and psychomotor retardation. These four subtypes of depression were also associated with differences in treatment outcome.

Conversely these data suggest that measures of activity in the ACC, medial prefrontal cortex, and amygdala may suggest guidance for treatment selection between CBT and pharmacotherapy as well as between different options of pharmacotherapy. Moreover patterns of connectivity in limbic and fronto-striatal networks may be used to classify depression subtypes. However more studies are required.

## 5.6 The Connectivity Problem

Studies focusing of structural connectivity show that patients with MDD is consistently associated with a decreased fractional anisotropy in the white matter fascicles connecting the prefrontal cortex within cortical (frontal, temporal, and occipital lobes) and subcortical areas (amygdala and hippocampus) (Liao et al. 2013). Moreover, one study reports that lower frontal fractional anisotropy is associated with sertraline response in late-life depression, for example (Taylor et al. 2008). Are these features specific to MDD or common in other depression subtypes or other psychiatric conditions? This is crucial to identify the prognostic and diagnostic potential of DTI measurements. The current evidences require further investigation of this matter as the number of studies and sample sizes are very small. For example, the study of Liao et al. (2013) included 11 studies with a total sample size of 231 patients with MDD and 261 comparison participants. Thus, more studies with standardized patient groups with increased sample sizes are required.

On the other hand, studies of structural and functional analysis of MDD are increasing (Qin et al. 2014; Korgaonkar et al. 2014; Lai and Wu

2014; Song et al. 2014; Colle et al. 2016; Choi et al. 2016; Won et al. 2016; Grieve et al. 2016; Myung et al. 2016; Tatham et al. 2017; Tymofiyeva et al. 2017; Petrovska et al. 2017; Repple et al. 2017; Takeuchi et al. 2017; Chen et al. 2017; Connolly et al. 2017). Especially, studies of combined analysis of WM connectivity, antidepressant response, and/or genetic variation are taking attention as candidates of biomarkers for MDD. One study, suggests FA measures of the stria terminalis and cingulate portion of the cingulate bundle (CgC) as prognostic biomarker to identify nonremission to drug therapy (Grieve et al. 2016). Greater specificity for escitalopram and sertraline response has been found in the identification nonremitting MDD patients, which may help managing the drug therapy of depression. Also, resting-state functional connectivity of the amygdala has been linked to longitudinal changes in depression severity in adolescent depression (Connolly et al. 2017).

Another study reported an association between polymorphisms in the genes encoding for 5-HTTLPR and BDNF and uncinate fasciculus connectivity and antidepressant treatment response in MDD (Tatham et al. 2017). Other diffusion MRI studies showed a positive relationship between the fractional anisotropy of the cingulum bundle and remission. White matter signal hyperintensities were also found as predictive for remission rates (Chi et al. 2015).

Many other studies reported potential neuroimaging biomarker that could identify the outcomes of remission and treatment failure to AD treatment or CBT. For instance, an fMRI study published recently reports the resting-state functional connectivity analysis to determine any potential biomarker as predictor for outcomes of remission and treatment failure to CBT and AD treatment (Dunlop et al. 2017). Results show that the resting-state functional connectivity of the left anterior ventrolateral prefrontal cortex/insula, the dorsal midbrain, and the left ventromedial prefrontal cortex with the subcallosal cingulate cortex is differentially associated with outcomes of CBT and AD treatment. Thus, resting-state activity in these areas in the future may serve as a criterion for the type of first-line treatment that will most likely lead to remission.

## 5.7 Clinical Trials

The proposition of depression models especially by PET scans (Mayberg 1997, 2009) was one of the important contributions to our understanding of depression as these depression network models can be used to optimize the antidepressant effect of treatment to more precisely target networks relevant in depression, for example. Addressing these several clinical trials is already on the way.

As neuroimaging studies converge on foundations of neural connections between the cingulate, internal capsule, and other regions of the brain associated with MDD (Dyster et al. 2016), surgical approaches such as deep brain stimulation (DBS) or cingulotomy (Banks et al. 2015) get facilitation for planning and refining or predicting outcomes in psychiatric neurosurgery. For instance, a clinical trial (NCT003670032) is designed to assess the feasibility of stimulation of the subgenual cingulate white matter (Cg25WM) using implantable deep brain stimulation (DBS) for the treatment-refractory major depression.

Other targets for DBS under investigation for clinical potential are trial for lateral to the ventral tegmental area in the midbrain (NCT01095263). An ongoing clinical trial (NCT019847101) involves the patients of treatment-resistance depression, which will be implanted by the "brain radio" system in the subcallosal cingulate cortex to stimulate that area with electricity, to reset the regulation of the network. This effect, as supported by previous experimentation, is expected to result in a significant antidepressant response. The study is also aiming to record patients over 3 years, while they receive electric stimulation. The recordings will be correlated with the primary clinical response which altogether helps understand neurobiology of depression and the antidepressant response.

**Conclusion**

A scan of a depressed brain often shows a pattern of increased neural activity in amygdala, a brain region involved in fear and emotional response and decreased neural activity in the regions of prefrontal cortex which is involved

in executive control. Accumulation of such neuroimaging findings leads to the proposition of molecular, structural, and functional brain states, which may be used for diagnosis or prediction of treatment outcome (Crane et al. 2017). Among these, limbic-cortical circuitries have been identified as the key brain network that may guide treatment of depression. Thus, in this chapter, studies addressing these links have been presented such as hippocampal and cingulate volume as the predictor of AD response (Chi et al. 2015), activity of amygdala as a predictor of CBT response (Siegle et al. 2006), and activity of ACC as a predictor of a clinical response to antidepressant medication or other treatments (Wu et al. 1999; Mayberg 1997; Pizzagalli 2011). Several clinical trials, targeting these and other associated regions were described (see also Sect. 5.7). In addition, whole brain neuroimaging measures and pattern classification methods were underlined as they may aid diagnosis and prognosis. Especially limbic and fronto-striatal network-based classification (Drysdale et al. 2017) seems promising (see also Sect. 5.5).

On the other hand, neuroimaging and its utility for clinics and especially for depression are still a relatively new field with its own intrinsic problems such as reproducibility, inconsistency, and validity. For example, neuroimaging studies especially functional neuroimaging with "puzzlingly high correlations" or "entirely spurious correlations" were highly criticized (Vul et al. 2009; Bennett et al. 2009). Sirotin and Das (2009) claimed that "Anticipatory haemodynamic signals in sensory cortex not predicted by local neuronal activity" suggesting that the BOLD signals of functional MRI (fMRI) can arise without any measurable neuronal activity, despite objections (Handwerker and Bandettini 2011; Kleinschmidt and Müller 2010).

Thus, more analysis with well-coordinated standardized, better planned neuroimaging studies with increased sample size and accurate analytics is required. Yet, the field is developing rapidly (Dubin et al. 2017). For example, initiatives like Research Domain Criteria (RDoC), classification framework for research on mental disorders (Insel et al. 2010), will increasingly contribute standardization of neuroimaging studies. Other initiatives such as the Consortium for Reliability and Reproducibility (CoRR), aiming to establish test-retest reliability as a minimum standard, will trigger development of new methodologies for functional connectomics (Zuo et al. 2014).

In parallel, there is growing evidence that opportunities of better data quality of neuroimaging are increasing. For example, one study (Glasser et al. 2016) by using the information derived from structural and functional MRI data mapped the 180 areas per brain hemisphere—more than twice the number previously known. This in turn suggests a better analysis of individual variations in brain cortical architecture, functionality, connectivity, and topography for better understanding of neurobiology, personalized and predictive treatment, and prevention of mental disorders (Trivedi et al. 2016). Moreover, another study reported the use of a radioligand of synaptic vesicle glycoprotein for (PET) to quantify synaptic density in living human brains (Finnema et al. 2016). This brings the possibility to perform an in vivo synaptic quantification which could aid the diagnosis of disease associated with synaptogenesis and synapse loss.

In summary, the continuous progress described so far, together with well-coordinated standardized, better planned neuroimaging studies, will help produce better consistent data which will contribute our, so far limited, knowledge of depression leading to the identification of biomarkers for personalized, prognostic, predictive, and preventative medicine.

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# 6 Pathophysiological Voice Analysis for Diagnosis and Monitoring of Depression

Shinichi Tokuno

## 6.1 Introduction

The diagnosis of depression is ordinarily conducted by a psychiatrist using an interview. However, when screening an extremely large population for stress or depression, it is impossible for a psychiatrist or clinical psychologist to conduct an interview with each and every subject. Therefore, the method commonly applied in such cases involves screening using a self-assessment questionnaire, which leads to an interview with a psychiatrist or a clinical psychologist. A self-assessment questionnaire, however, is based on a subjective self-assessment by the subject, and, as such, it has a tendency for significant bias. Therefore, what is expected is screening based on objective indicators by biomarkers. In recent years, extensive studies have been conducted on biomarkers relating to stress and depression; nevertheless, none of them have reached the practical level, yet tests conducted on blood and saliva generally tend to offer more reliable information on the subject; however, these tests are invasive and involve cost consideration issues, as special equipment and reagents are required to perform such measurements. Physiological methods are less invasive but are problematic because the information can vary owing to a variety of factors. Recently, voice screenings for stress and depression have been reported. Methods involving the screening of voices offer advantages, such as the lack of a requirement for special equipment, low running cost, as well as the possibility for remote procedures. This paper discusses the potential for screening voices to monitor stress and depression.

### 6.1.1 Depression and Voice

The occurrence of atypical characteristics in the quality of the voices of depression patients has been observed clinically for a considerable amount of time (Newman and Mather 1938; Cobb et al. 1943; Moses 1954). Much effort has been devoted to subjectively categorizing such characteristics (Darby 1981; Darby et al. 1984). On the other hand, attempts have also been made to objectively evaluate the voice of depression patients. Hargreaves and his associates attempted to perform a spectral analysis of the voices of depression patients (Hargreaves et al. 1965). Weintraub discovered that depression patients tend to speak slowly (Weintraub and Aronson 1967), while Szabadi and colleagues proposed that this slow speech was affected by the pause time (Szabadi et al. 1976). Almost concurrently, most of studies were attempted based on the fundamental frequency of voice (F0), and many findings were based on comparisons of average

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values of the F0 (Newman and Mather 1938; Tolkmitt et al. 1982); however, Darby and Hollien compared the variance of F0 instead (Darby and Hollien 1977). More detailed F0 analyses started in the second half of the 1980s (Nilsonne et al. 1988; Scherer 1987). Nilsonne and her associates provided a detailed introduction to a method that uses a computer program to analyze F0. Scherer conducted an analysis of the voice of depression patients using a voice characteristic referred to as "jitter" which is frequency fluctuation and "shimmer" which is amplitude fluctuation and discovered that the jitter was higher in the voice of depression patients. Another report indicated that a voice characteristic referred to as the harmonic-to-noise ratio (HNR), used to evaluate hoarseness of voice, was greater in individuals with depression (Low et al. 2011). Analyses have been conducted on the formant frequency, defined by the resonance formed when the vibration of the vocal cord passes through the vocal tract (Flint et al. 1993; Cummins et al. 2011). The shimmer, jitter, and HNR are feature quantities considered fundamental to sound analysis, and various studies are currently being conducted using software capable of analyzing several thousand feature quantities (Eyben et al. 2010). An attempt has also been made to identify ailments based on machine learning and deep learning by using large numbers of feature quantities (Maxhuni et al. 2016).

### 6.1.2 Emotion and Voice

Efforts to estimate and scale the emotions of people based on their voice began approximately in the 1990s, when the evaluation of depression based on voices became popular (Cahn 1990; Murray and Arnott 1995). Evaluations of emotions were conducted primarily using formant analysis (Cahn 1990; Murray and Arnott 1995; Burkhardt and Sendlmeier 2000). This may be because research on speech and languages became popular and software development advanced. The analysis of the formant region is strongly affected by the vocal tract and indicates voluntary emotional changes. Capturing more primitive involuntary components (rapid emotion) is difficult for all types of emotions. For that reason, prosodic rules are often employed in addition to formant analysis in recent years. In the same era, Mitsuyoshi developed a technology for identifying emotions by using only F0 analysis, which is a prosodic feature value.

The expression of emotion is inhibited by depression. The manifestation of depression, sorrow, or loss of joy daily for 2 weeks is considered as the standard for diagnosis for depression, according to the *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, Text Revision* (DSM-IV-TR). We therefore considered that deriving an objective index for depression must be possible by capturing emotional changes (Mitsuyoshi 2015).

## 6.2 Voice Emotion Recognition

### 6.2.1 Sensibility Technology

Our system is based on the emotion recognition technology (sensibility technology, ST; AGI Inc., Tokyo, Japan) developed by Mitsuyoshi and his associates (Mitsuyoshi 2002), who focused on F0 changes during conversation and selected the F0 variation parameters in a voice labeled for emotions. They then extended that to many F0 variation parameters, which were labeled for emotions. The labeling of emotions in voices consisted of the four emotions of joy, sorrow, anger, and calmness, as well as a fifth aspect, excitement. The labeling of a voice for F0 was conducted using voice in which judgment of emotion and excitement by speaker, listener, and third party matches. ST determines in real time what percentage of each emotion and excitement parameter is contained in the voice by the parameter of F0-labeled emotion (Mitsuyoshi et al. 2006, 2007).

According to fMRI studies, emotions determined with ST have been reported to almost coincide with emotional activities of the brain. In this research, conversations conducted with test subjects during fMRI measurements confirmed that the activities of the amygdaloid corpus of the right hemisphere, the bottom of the forehead (in the vicinity of BA12), and the prefrontal cortex,

which are emotional region of the brain, coincided (Mitsuyoshi et al. 2011).

In Japan, ST is no longer limited to the entertainment domain, portable games, and smartphone applications but is also being utilized in industries such as call centers. Currently, implementation development on automobiles and robots is progressing.

### 6.2.2 Emotional Changes Due to Stress

We conducted a verification test to determine whether emotional changes due to stress can be captured using ST (Tokuno et al. 2011). The voices of nine individuals who were dispatched overseas with disaster duties were acquired. Those who worked in a stress-full environment for a long time showed a tendency that joy decreased and sorrow increased as compared with those who worked in a similar environment for a short time (Fig. 6.1). However, significant individual differences were observed in emotional changes due to stress, and it was concluded that a detection of depression solely based on a comparison of emotions is difficult. On the other hand, a discovery that confirmed the correlation between emotions derived by ST and GHQ-30 scores was made by another study (Nakamura et al. 2015). This research indicated that there was correlation between the emotional index of anger and the GHQ-30 scores, as well as between the index of excitement and suicidal ideation and depression, which scored at the lower scales of the GHQ-30. An investigation of the correlation between the amount of change of voice emotional indicators and GHQ score on two different time examinations indicated a correlation of the amount of change in the emotional index with that in the GHQ-30 scores, while the amount of change in the emotional index of joy exhibited correlation with that in "general disorder trends," "physical conditions," and "social activity disorders," which score at the lower scales of the GHQ-30. Based on these findings, mental health state screening through voice emotion recognition was considered possible.

## 6.3 From Emotional Recognition to Pathologic Analysis

### 6.3.1 Development of Psycho-Analyzer

A program (psycho-analyzer; AGI Inc.) that provides a prototype for determining the extent of stress based on the stress indices (joy, sorrow, anger, calmness, and excitement) derived by ST was prepared (the relevant paper is currently being drafted). The research defined an algorithm for quantifying the intensity of the emotional state recognized by ST based on the characteristics of mood disorders which is defined by the DSM-IV-TR. In other words, the emotional characteristics of the voice, which were derived by voice emotion analysis, were calculated as vocal affect displays (VADs). Based on the emotional indices derived by ST, the low VAD (VAD-L), which indicates negative emotional states, and the high VAD (VAD-H), which indicates positive emotional states, were calculated. These were then used to derive the scale of the VAD ratio (VAD-R). First, the algorithm for calculating VAD-L focuses on the excite parameter of ST and classified roughly according to the value of excite. Next, VAD-L was determined with the focus on anger and joy. The algorithm for calculating VAD-H was classified roughly according to the value of excite similarly; then, VAD-L was determined with the focus on sorrow and calmness. The VAD-R value was defined as the ratio of VAD-L to VAD-L. The application of this method to the nine individuals described earlier obtained a result that indicated that the individuals who remained in the disaster area for longer periods of time had greater VAD-L and VAD-R and lower VAD-H in comparison to those who remained in the area for shorter periods of time.

### 6.3.2 Overcoming Reporting Bias

We conducted an evaluation of individuals on a greater scale than this prototype (psycho-analyzer) (Tokuno et al. 2014). Psychological tests consisting of self-assessment questionnaires

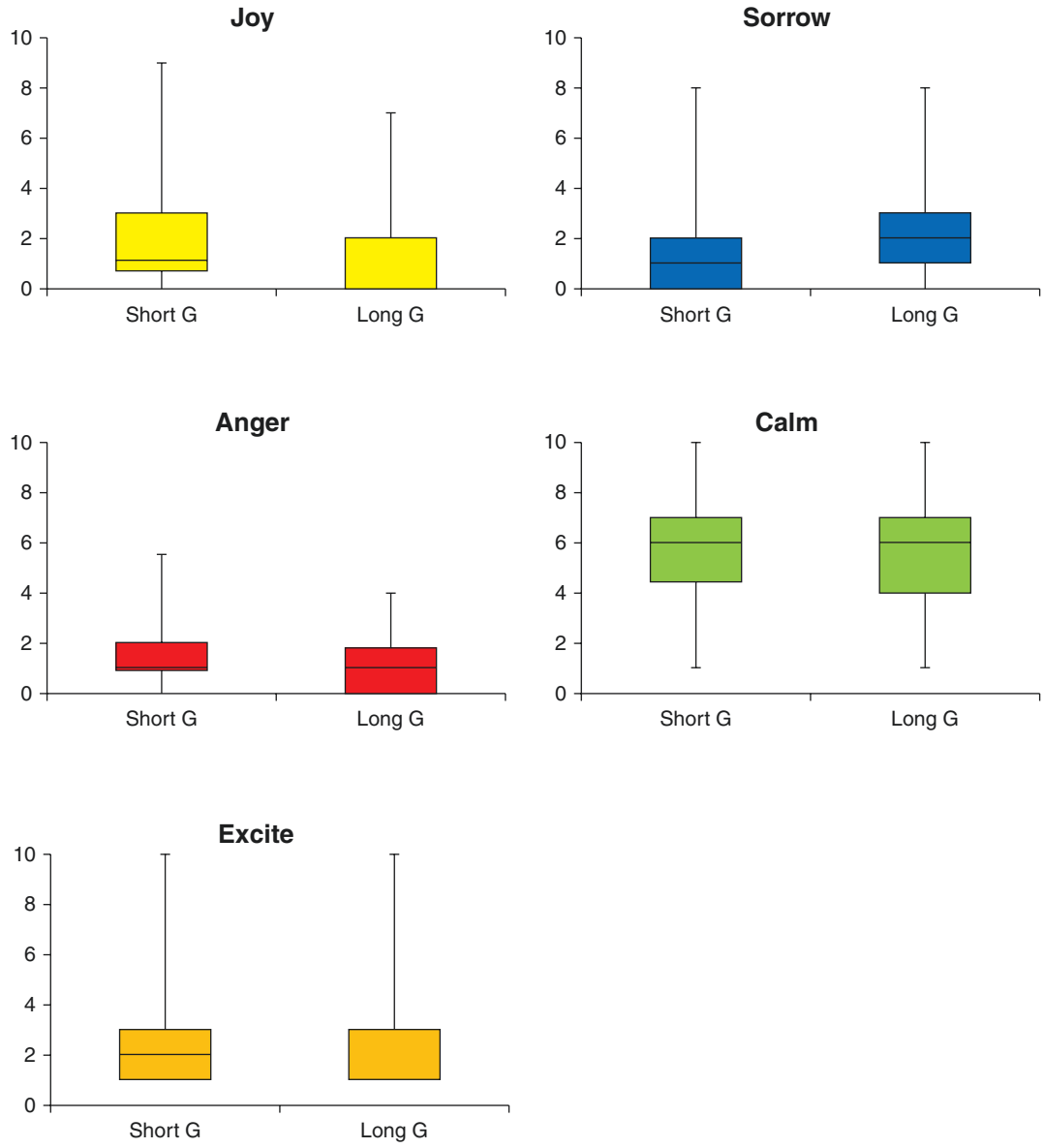


**Fig. 6.1** Emotional change due to stress. Those who worked in a stress-full environment for a long time showed a tendency that joy decreased and sorrow increased as compared with those who worked in a similar environment for a short period (Tokuno et al. 2011)

(GHQ-30 (Goldberg and Blackwell 1970); K10 (Kessler et al. 2002); IES-R (Weiss 2004); CES-D (Radloff 1977); eC-SSRS (Mundt et al. 2010, 2013)) and voice stress evaluations were conducted on 444 employees of the Japan Self-Defense Forces (JSDF) who were assigned ordinary routine duties and 1004 employees of JSDF dispatched on emergency duties following the Great East Japan Earthquake. Two hundred and twenty-five individuals who were determined to be abnormal in even one of the five psychological tests and consented to an interview were categorized by a single specialist (a specialist that is unique to JSDF, equivalent to a clinical psychologist) into two groups: one in need intervention (medical treatment or counseling required)

and one under observation. The voice-based stress evaluation was then compared with the results of the interviews. The emotional analysis revealed that all emotions of joy, anger, and sorrow were observed to have declined in the members of the group needing intervention. Furthermore, a comparison with the findings from the GHQ-30, which demonstrated the highest sensitivity among all self-assessment questionnaires, indicated approximately the same level of sensitivity in determining the level of depression, whereas in terms of specificity, the results did not compare with those of the GHQ-30 (Table 6.1). The voice-based evaluation assessed that two participants were highly stressed, although they exhibited no problems according to the GHQ-30; however, during the interview, they were immediately diagnosed with serious conditions that required urgent medical treatment. In other words, the voice-based evaluation allowed the prevention of the reporting bias that occurs with self-assessment questionnaires (Fig. 6.2). The reporting bias is a conscious or subconscious undervaluation or overvaluation by the test subjects. Its detection rate has been reported to be lower within organizations with established hierarchy, such as fire departments, police departments, or military organizations (Hoge et al. 2004; Perrin et al. 2007; McLay et al. 2008). Resistance, prejudice, and discrimination against mental health issues or insecurity about repercussions in their professional careers can be reasons that cause such undervaluation in self-assessment screening (Hoge et al. 2004). Our study suggested that by combining self-written questionnaires and evaluations by voice, it would be possible to pick up patients who could not be screened with self-contained questionnaire alone due to reporting bias.

**Table 6.1** The comparison between voice analysis and self-assessment questionnaires

| Voice analysis | | Need intervention + | Need intervention − | | |
|---|---|---|---|---|---|
| VAD-L | 50=< | 26 | 162 | 188 | Sensitivity, 0.897; Specificity, 0.173; Positive predictive value, 0.138; Negative predictive value, 0.919 |
| | 50> | 3 | 34 | 37 | |
| | | 29 | 196 | | |

| Self-assessment questionnaires | | Need intervention + | Need intervention − | | |
|---|---|---|---|---|---|
| GHQ-30 | 7=< | 27 | 123 | 150 | Sensitivity, 0.931; Specificity, 0.372; Positive predictive value, 0.180; Negative predictive value, 0.973 |
| | 7> | 2 | 73 | 75 | |
| | | 29 | 196 | | |

## 6.4 Monitoring System

### 6.4.1 Development of MIMOSYS

The voice-based stress evaluation with the psycho-analyzer obtained favorable sensitivity but was not satisfactory with regard to specificity. It also involved other issues, such as deference in the results between males and females. To overcome such issues, we developed a new program and an application for smartphones to facilitate the use of the program. This application is called MIMOSYS (Mind Monitoring System; PST Inc.) (Tokuno 2015a, b; Omiya 2016; Omiya et al. 2016).

Excitement, anger, and joy were used to calculate VAD-L, with the psycho-analyzer. However, MIMOSYS first calculates an index referred to as "vivacity" for joy, which tends to be greater for females, and sorrow, which tends to be greater for males, while the index referred to as "relaxation" was similarly calculated for calmness and excitement. This was followed by the calculation of the index "vitality," which represents the state of the mind based on vivacity and relaxation (Shinohara et al. 2015; Mitsuyoshi 2016) (Fig. 6.3). By conducting such dual-level calculations, we successfully eliminated the difference between males and females (Fig. 6.4). The vitality index is an index characterizing a positive emotional state, and, as such, it decreases owing

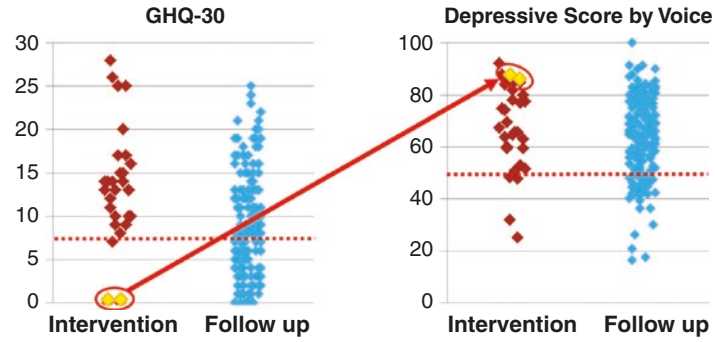


**Fig. 6.2** Emotional change due to stress. Self-assessment psychological tests and stress assessments by voice were conducted on 444 SDF personnel who are in constant operation and 1004 SDF personnel dispatched during the Great East Japan Earthquake. Among them, for 225 people who approved clinical psychologists' interview, we compared the result of GHQ-30 with the voice stress evaluation. Two were judged to be normal in GHQ-30 and high stress was judged in voice. They were judged to be a serious case requiring medical treatment immediately at the interview. We thought that the reporting bias could be overcome by voice evaluation (Tokuno et al. 2014: Revised from presentation slide)

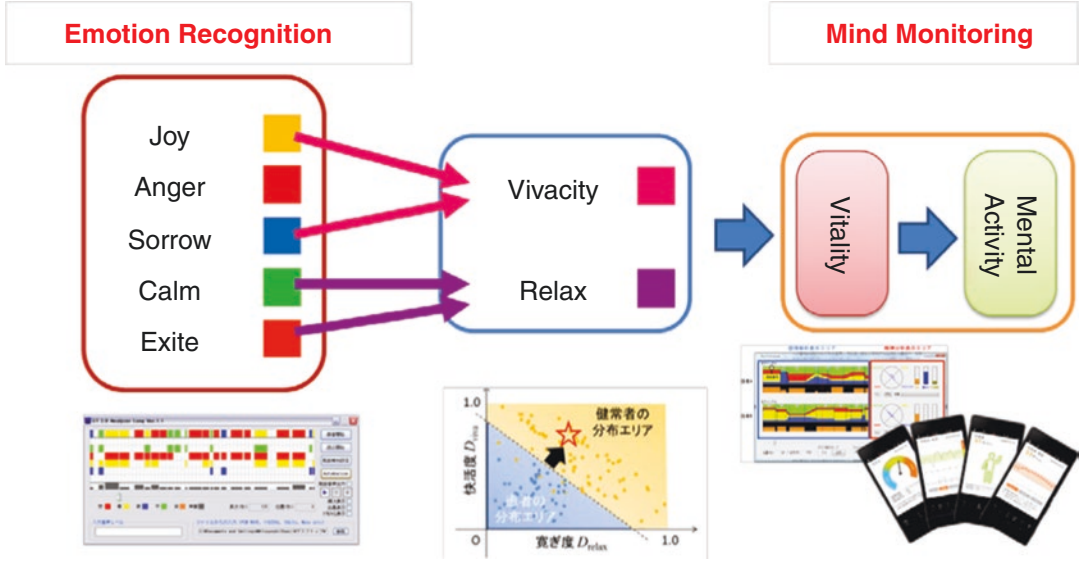


**Fig. 6.3** Vitality and mental activity in MIMOSYS. In MIMSYS (Mind Monitoring System), in order to eliminate gender differences, we first calculated vivacity index from joy that tends to be higher in women and sorrow that tends to be higher in men and similarly calculated indices of relaxation from calm and excite. Then, from the values of vivacity and relaxation, we calculated the index called vitality as an indicator of the condition of the mind. Furthermore, we devised an index called mental activity, which is an index that adds the moving average of vitality and the variation of that period (Mitsuyoshi 2016: Presentation slide)

to stress reactions or a depressed state. Based on previous data (Tokuno 2016), the sensitivity of the vitality index was confirmed to be similar to that of VAD-L. However, no difference was observed in terms of specificity from that of VAD-L. Therefore, the difference between the vitality distributions of depression patients and healthy individuals was investigated. In this pilot study, when multiple measurements of an individual subject were obtained, it became evident that the vitality index of depression patients had lower values, whereas that of healthy individuals

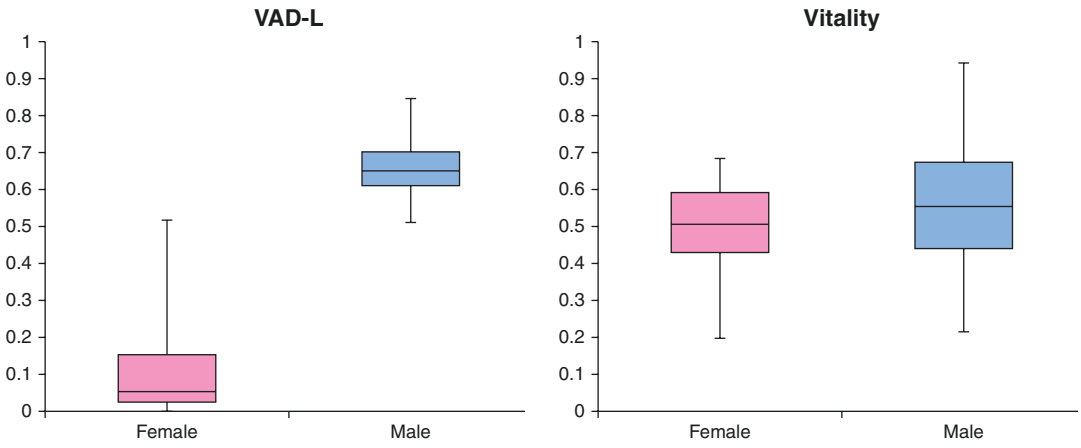


**Fig. 6.4** Gender difference in VAD-L and vitality. We compare VAD-L and vitality with 38 male and female each. Vitality succeeded in excluding gender differences by calculating in two steps

was distributed over a wide range, with occasionally very high and very low values. We proposed an index referred to as "mental activity," which considers the average change of vitality and its variation within a given period; we consider this distribution difference to correspond to the difference between depression patients and healthy individuals. A period of 2 weeks was adopted as the average period of transition, as indicated by the DSM-IV-TR. The mental activity index indicates the trend of vitality and its implementation allows the distinction between healthy individuals and depression patients with sufficient sensitivity and based on specificity (Tokuno 2016). Vitality may be considered as an instantaneous index on the time when the voice is recorded, while mental activity can be considered a medium- to long-range index. Using these indices together can describe the current mental state of an individual.

Subsequently, we produced a smartphone application to make this technology available for general use by a wide range of people. Methods for capturing voice using a smartphone include the automatic recording of voices from a conversation conducted during an ordinary telephone call, as well as the recording of voices by manually starting an application. In manual recordings, methods for recording freely spoken speech and the subject reading a prescribed text are also available. Although freely spoken speech tends to manifest emotions more readily, there are often occasions where the speaker becomes hesitant, not knowing what to talk about. We adopted the automatic recording system for voice conversations from telephone calls, which can be used without the user becoming conscious of the process. This decision was made because we believe that a system that does not require any special operation on the part of the user would be more likely used for longer periods of time. Actually, it has been confirmed that the automatic recording of conversations facilitates the acquisition of data over a longer period more than the manual recording of prescribed text (Hagiwara et al. 2016a, b). The application MIMOSYS starts automatically when a telephone is used to make or receive a call and records only the voice of the user. Voice analysis is performed after the call has been terminated and the results are displayed to the user. Once the analysis has been completed, the voice recording is deleted automatically. Previous results can also be viewed by operating the application. To easily illustrate the levels of vitality and mental activity, the vitality index is displayed on a meter, while mental activity is shown in a symbolic image with five stages (Fig. 6.5). The vitality and the mental activity levels are only displayed for each measurement, but it is also possible to present the chronological changes of both indices in a graph. A review on the graph is expected to help provide insight


**Fig. 6.5** Screen display of MIMOSYS. For ease of image, vitality is displayed with a meter, and mental activity is displayed in a symbolic five-level image

regarding changes and trends to illustrate the behavioral transformations of the user (Tokuno 2015a, b; Omiya 2016; Omiya et al. 2016).

### 6.4.2 Medical Verification of MIMOSYS

We released the application to the general public to verify the effectiveness of MIMOSYS. The number of downloads reached 3400 in a year and half since the release, and approximately 1000 users are currently using the application. Since the use of the application began, a self-assessment questionnaire (Beck Depression Inventory, BDI) evaluation has been conducted every 3 months (Beck 1961; Beck et al. 1961). Various results were obtained from the analysis of 1 year after starting the research. For instance, vitality and mental activity were both lower in females than in males; in other words, a higher depression tendency was confirmed for females than for males (Fig. 6.6). The same trend was indicated by the concurrent BDI, and this result is believed to be accurate considering that there are more female than with male depression patients in Japan. It also became evident that vitality and mental activity were influenced by age, income, and even the extent of obesity (Tokuno 2016). The Kumamoto Earthquake occurred during the course of this research, and a small number of studies were conducted before and after the earthquake. A comparison of such results for the seismic epicenter and the surrounding areas indicated different changes. Although no significant changes were confirmed before and after the earthquake in other areas, regions that sustained damages from the Great East Japan Earthquake 5 years ago were confirmed to have experienced changes that differed from those observed in any other areas. Since no other investigations have been conducted, this is purely a speculation; however, these changes may portray psychological changes, such as PTSD (Tokuno et al. 2016) (Fig. 6.7).

We compared speech evaluation with blood biomarkers in another study. We have reported that during military training conducted in an extremely stressful environment, there is a decline in the brain-derived neurotrophic factor (BDNF) and the vascular endothelial growth factor in the blood (Suzuki et al. 2014). Subsequently, an investigation conducted in approximately the same environment confirmed that the vitality scores obtained from the BDNF and MIMOSYS and the GHQ-30 changed with the same trends (Tokuno 2016).

An industrial hygiene survey derived a weak correlation based on a voice-based evaluation of

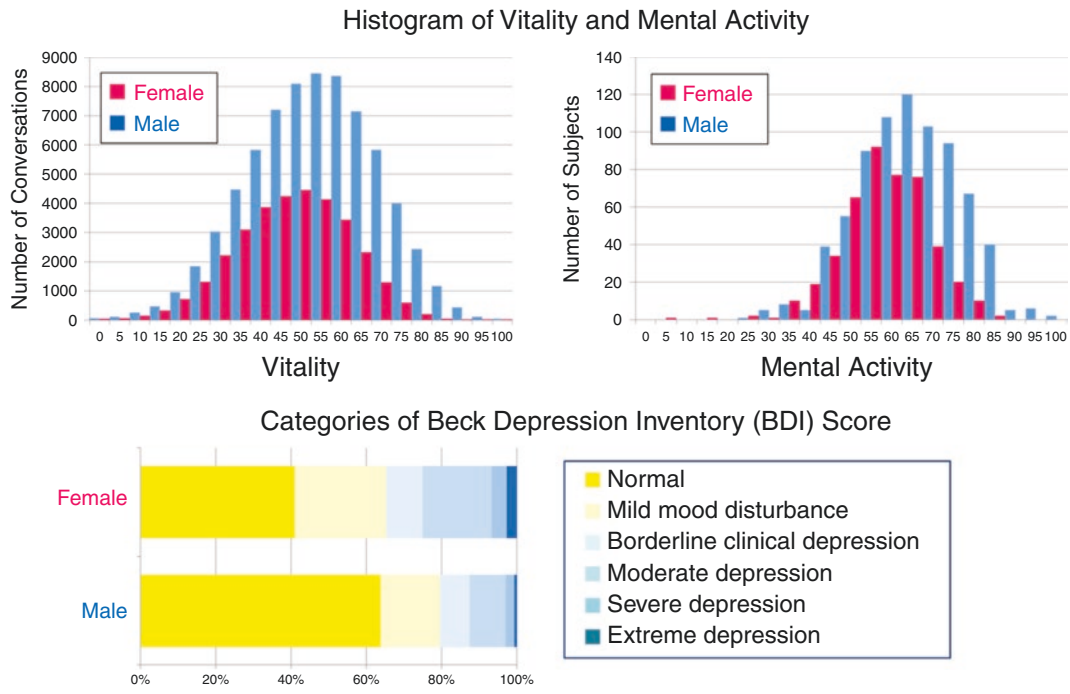


**Fig. 6.6** Comparison between female and male in MIMOSYS analysis. Female are lower than male in both vitality and mental activity. In other words, female tend to be more depressed. The same trend is also shown in BDI which was done at the same time (Tokuno 2016: presentation poster)

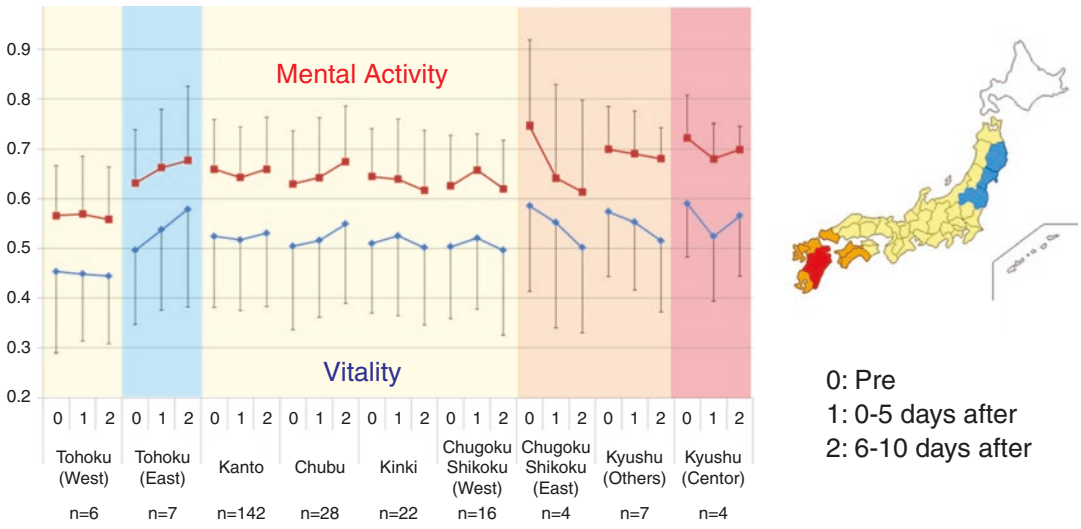


**Fig. 6.7** Psychological impact of Kumamoto Earthquake. There is a big earthquake in Kumamoto, the west part of Japan, thus we investigate the effect of the disaster on the mind of residence. In the comparison of before and after earthquake, different reaction depending on the region has been observed. The largest swing areas which close to the epicenter, initially, the mind health score is inclined to depressive tendency strongly, then it tends to be somewhat recovery was seen. In a little remote area from the epicenter, it was mutated to gradually depressive tendency after the earthquake. In areas affected by the disaster in the Great East Japan Earthquake 5 years ago, tendency to gradually become high was observed after the earthquake. It might be affected by flashback of post-traumatic stress disorder (PTSD). In other areas, there was no particularly significant change (Tokuno 2016: presentation poster)

the BDI score when comparisons were made at ordinary businesses using utmost care to ensure that no reporting bias was involved (Hagiwara et al. 2016a, b). In some reported cases, the results of continuous monitoring with MIMOSYS led to referrals of patients to industrial physicians (Miyazaki 2016). Continuous monitoring using MIMOSYS can detect depression states that are caused by stress originating from changes in the environment associated with work, and it has been confirmed that this can be effective in implementing countermeasures against early resignations from work (the relevant paper is currently being prepared).

This system is also useful for determining the effectiveness of medical interventions, and we have reported that it can also be used to determine the efficiency of a stress resilience program (Shinohara et al. 2015; Miyazaki 2016). We implemented the stress resilience program developed by the JSDF for 100 volunteers from the JSDF and measured its effect. The program consisted of a course of 15-min sessions 5 days every week for a total of 50 days. After participation in the course, a decline in the GHQ-30 was observed in personnel that participated in 13 or more sessions (Tokuno et al. 2013). Additionally, an improvement in vitality was observed in personnel who participated in 13 or more sessions (Shinohara et al. 2015) (Fig. 6.8). A variety of data is currently being collected to ensure that depression screenings become more reliable and to verify the possibility of judgment of treatment effect by depression.

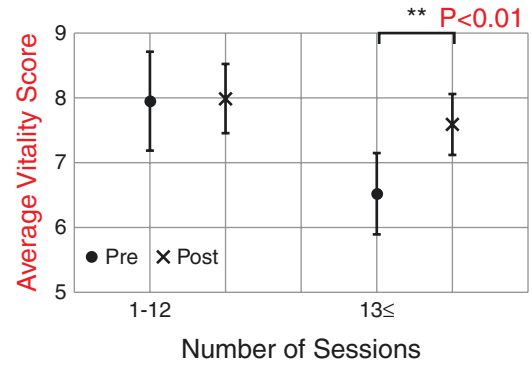


**Fig. 6.8** Determining the effect of stress resilience program by voice. We invited 100 SDF personnel to participate in the stress resilience program developed by the Japan Self-Defense Force and measured its effect. The course is 15 min per week, 5 days a week, 50 days in total. Members who participated in this course more than 13 times showed improvement in vitality before and after the course in members who participated 13 times or more

### 6.4.3 Engineering Verification of MIMOSYS

Various engineering verification studies have also been conducted to expand the range of applications of MIMOSYS. For example, voice is coded for transmissions over telephone lines. The coding includes irreversible processes focusing on the reproduction of voices that are easier to comprehend, which incorporates the aural characteristics of people. The analysis results of a variety of codings were compared to investigate the impact of coding. These confirmed a sufficient correlation between the analysis results before and after the coding and verified that the impact of coding is not very strong (the relevant paper is currently being drafted). This suggests that analysis can be performed on either the initiator or the receiver of a telephone call. In other words, in cases where medical treatments are provided remotely and interviews are conducted via telephone lines, the voice of the patient can be analyzed by the provider of the medical treatment. This means that the same level of service can be provided even to patients that do not own a smartphone.

## 6.5 Remaining Challenges

### 6.5.1 Verification on Nonlanguage Dependence

Our technology utilizes F0 and, as such, it is theoretically independent of language. Since almost all existing studies were conducted in Japan, no evidence of language independence exists. We therefore recruited research collaborators overseas to

start joint studies for verification using multiple languages. Thus far, the verification has begun for a limited number of languages, and we plan to increase the number of partners for joint studies in the future.

### 6.5.2 Differentiation of Depression

MIMOSYS is a technology based on emotion recognition and detects the suppression of emotional manifestations due to depression. It was therefore not possible to differentiate healthy individuals that were feeling unhealthy from those that were in a state of depression or suffering from depression based on vitality. For this reason, an index referred to as "mind activity" was conceived by considering the continued disappearance of joy and persistence of sorrow over longer periods. However, this method has difficulty in distinguishing a variety of mood disorders. In other words, while MIMOSYS is useful for observing the progress of rough screening or already diagnosed depression, including the effectiveness of treatments, it is however not possible to use mind activity to differentiate between major unipolar depression and bipolar depression. Naturally, it would be possible to diagnose a patient with bipolar disorder by follow-up observation. However, it would be more desirable to differentiate such disorders, for which treatments differ, as soon as possible.

During the development of MIMOSYS, we have been conducting research intended to discover feature quantities that are peculiar in certain disorders directly from voices and without relying on emotions. We are approaching a breakthrough in discovering candidates for such characteristics (Shinohara et al. 2016) and plan to report on the findings in the near future.

### 6.5.3 Differentiation from Other Ailments

Besides the differentiation between major depression and bipolar depression, there are a large number of ailments that must be excluded for the purpose of diagnosing depression. Parkinson's disease and dementia are such examples. These ailments have overlapping symptoms in their early stages and differentiation can be delayed in some occasions. Additionally, MIMOSYS is affected by ailments that modify voice quality. This means that the analysis results are influenced by changes in voice quality that can occur owing to ailments that cause vocal disorders in the otolaryngological region or paralysis due to brain infarction, as well as recurrent nerve paralysis. Furthermore, people tend to manifest less emotion as they lose resilience when an ailment is contracted, even if the ailment is different from psychological diseases. A large number of ailments can coexist with depression, and it is difficult to determine if the decline in vitality or mental activity that is related to such ailments is due to the associated depression or the deterioration of the underlying ailment. Furthermore, voice features that are characteristic to each ailment must be identified without relying on emotions to resolve such issues. We are continuing our search for characteristics of voices that are peculiar for such ailments and feel that we have had some solid results for a number of ailments. However, further research must be conducted to obtain satisfactory results.

**Conclusion**

We introduced voice screening and monitoring technologies used at our laboratory for stress, depression states, and depression.

Based on the existing findings of our research, in February 2017, a business in the area of industrial hygiene launched a service using our system. Similar activities are expanding throughout the world and services are expected to be implemented in a variety of forms.

Although a large number of issues still remain, we hope that research in this field will continue to progress in the future.

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# Part II

# Clinical Manifestations of Depression

# 7 Anhedonia as a Crucial Factor of Depression: Assessment, Neurobiological Underpinnings and Treatment

Troy K. Chow, Sidney Kennedy, and Sakina J. Rizvi

## 7.1 Introduction

Major depressive disorder (MDD) currently remains one of the leading causes of global disability and has significant personal, societal and economic burden (Lam et al. 2016; World Health Organization 2017). MDD can be defined by a myriad of symptoms; however, at least one of two core symptoms must be present. The first of these core symptoms, "a low mood or a feeling of sadness" is a defining symptom of MDD for many. The second of these symptoms is the presence of anhedonia, historically characterized as a "loss of pleasure". More recently, anhedonia has received increased recognition due its potential contribution to the prediction of MDD diagnosis, treatment response and remission (McMakin et al. 2012; Rawal et al. 2013; Uher et al. 2012).

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This chapter will provide an update on the current literature of anhedonia in the context of MDD. Specifically, this chapter will highlight the neurobiology, measurement and treatment of this core symptom of MDD.

Traditionally, conceptualizations of anhedonia have focused on the consummatory aspect of pleasure; however, this simplified definition leads to difficulties in the precise measurement and study of anhedonia (Rizvi et al. 2016). Increasing neuroscientific evidence suggests anhedonia is a more multi-faceted construct that involves interest, anticipation, motivation, effort, expectation and consummatory pleasure (Rizvi et al. 2016; Treadway and Zald 2011). In line with this, there has been an emphasis towards refining the construct of anhedonia and to integrate the underlying neurocircuitry involved in the processing of rewarding stimuli. Ultimately, any deficit in the neural processing of reward could lead to the clinical symptom of anhedonia.

## 7.2 Reward Processing Models

Reward processing models describe the facets of reward-seeking behaviour and their interactions. One conceptualization of reward processing is the Positive Valence System (PVS) from the Research Domain Criteria (RDoC), a National Institute of Mental Health framework for biomarker research in mental disorders (Insel et al. 2010). The goal of RDoC is to utilize a dimen-



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sional approach across "units of analysis" (genes, brain circuits, self-reports) to evaluate causes of mental illness rather than a single predictor in isolation (Hess et al. 2016; Vengeliene et al. 2017). The PVS is not a model of reward processing, per se, but a suggested starting point for the constructs pertinent to a reward processing model which include the ability to make a reward-stimulus association, motivation, effort, expectation and consummatory pleasure. A model based on Kring and Barch (2014) has been put forth to depict the associations among these constructs (Fig. 7.1) (Rizvi et al. 2016). It is important to note that, while reward processing is depicted as a linear process, the facets may act in parallel or vary according to the situation.

Based on the Fig. 7.1 model, the reward process is described as initially building a stimulus-reward association, which then leads to interest/desire, anticipation, motivation, effort, hedonic response and feedback integration. After a reward-stimulus association has been established, an interest in the rewarding stimulus can then develop. Importantly, interest in reward is important to be able to anticipate it or to develop a "wanting" for a reward (Rizvi et al. 2016). The brain also needs to calculate the energy required to obtain the reward. Motivation describes the initial energy expenditure to obtain a reward, and effort describes the sustained energy expenditure. In other words, motivation is required to start the process of reward obtainment, and effort is required to continue this process.

Outcome following reward can be negative, positive (pleasurable) or neutral. Consummatory pleasure describes the pleasure experienced by an individual as they directly interact with a stimulus. Based on the outcomes from previous stimulus-reward associations, individuals develop expectations of reward. These expectations may relate to whether a reward will be present, the likelihood of attainment and magnitude of experienced pleasure or the effort required to obtain it. Reward expectations may influence other facets of reward such as the level of anticipation experienced or motivation to attain a reward (Rizvi et al. 2016). In particular, expectation can also affect the original stimulus-reward association through feedback integration, which is the ability to utilize new information to update existing knowledge of a potential reward. This reward learning ability is crucial to maintain accurate expectations and associations of the stimuli for future encounters. For example, there

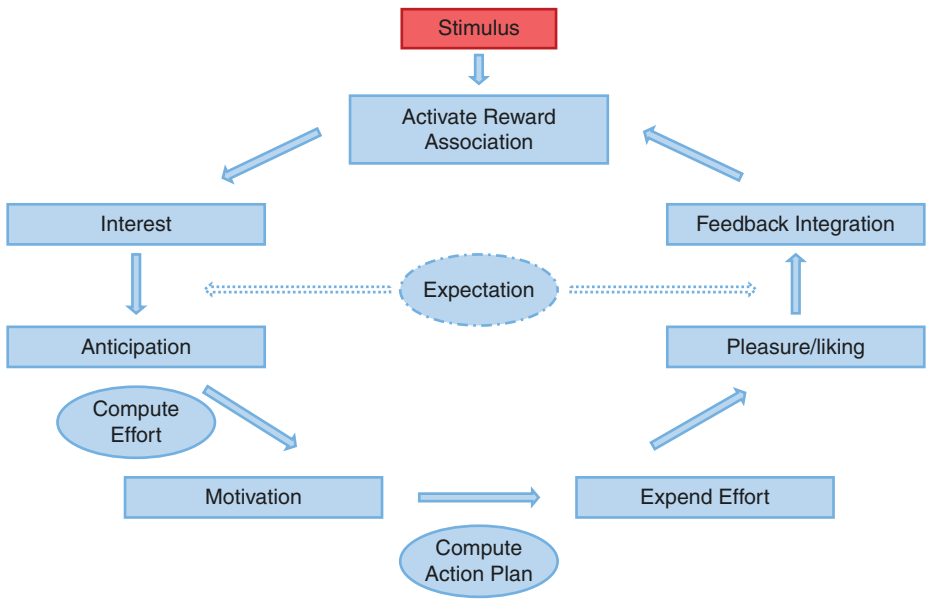


**Fig. 7.1** Model of reward processing (Modified from Kring and Barch 2014)

may be only certain contexts where a stimulus is rewarding or a stimulus may no longer be rewarding at all. In addition, the value one places on a stimulus can vary considerably by several factors including the time to attainment and the magnitude of the reward. MDD patients demonstrate deficits across these facets (reviewed in Rizvi et al. 2016; Treadway and Zald 2011; Tremblay et al. 2005), although the specific factors and conditions that contribute to these deficits need further exploration. Understanding the neurobiology associated with the reward facets can help to elucidate this knowledge gap.

## 7.3 The Neurobiology of Anhedonia

Understanding the underlying neurobiological underpinnings of MDD is essential to identifying subtypes, biomarkers and targeted treatments. Deficits in reward processing have been found to correlate with the clinical symptom of anhedonia (reviewed in Rizvi et al. 2016) and the above described reward facets may have shared and distinct neurobiological mechanisms. In support of this idea, Whitton et al. (2015) reported that separate neurobiological pathways may partially govern the activity of each reward facet. These pathways are superimposed over brain regions that are primarily in the frontal lobe, although other regions are also important.

The nucleus accumbens has long been acknowledged as the "pleasure centre" of the brain and has historically been tied to anhedonia (Wong et al. 1991). However, we now have a deeper understanding of the role of other brain regions in reward processing, which include the prefrontal cortex (orbitofrontal cortex, ventromedial prefrontal cortex, anterior cingulate cortex), amygdala, dorsal and ventral striatum and the insula (reviewed in Der-Avakian and Markou 2012; Treadway 2015). The prefrontal cortex, in particular, is involved in higher cognitive processing of reward, including reward valuation, decision making, context integration and cost-benefit analysis (Elliott et al. 2000; Grabenhorst and Rolls 2011). The orbitofrontal cortex, dorsolateral prefrontal cortex and ventromedial prefrontal cortex are particularly involved in these processes (reviewed in Treadway 2015). In addition, evidence suggests that once a stimulus has been identified as pleasurable, the anterior cingulate cortex (ACC) is a region involved in cost-benefit analysis and effort-related functions required to obtain reward (Salamone et al. 2009; Treadway and Zald 2011; Der-Avakian and Markou 2012). Using this information, the ventromedial PFC (vmPFC) may be responsible for executing the decision to carry out the reward-directed behaviour (Grabenhorst and Rolls 2011). Furthermore, the vmPFC, ACC, orbitofrontal cortex and striatum may also be involved in reward processing by monitoring the rewarding properties of a stimulus (Elliott et al. 2000; Seo and Lee 2007).

Neurotransmitter imbalances in reward processing have historically focused on the role of dopamine, due to its high level of expression in the nucleus accumbens (Salamone et al. 2003). The ventral tegmental area (VTA) is a group of dopaminergic neurons which supplies dopamine to other areas in the mesocorticolimbic pathway including the nucleus accumbens and ventral striatum. Reduced dopamine activity can result in impaired reward function (Malhi and Berk 2007; Salamone et al. 2003). Exposure to pleasant stimuli increases dopamine activity in the ventral striatum; however, this dopamine activity may be reduced in MDD patients (Dunlop and Nemeroff 2007). Interestingly, this reduced dopamine activity in the ventral striatum is correlated with anhedonia severity, but not necessarily depressive symptom severity (Treadway 2015). Furthermore, anhedonia was found to correlate with reduced ventral striatal grey matter, which highlights its role in reward function (Sternat and Katzman 2016). However, preclinical findings have helped to elucidate the role of dopamine as being more linked to anticipation and motivation rather than consummatory pleasure (Salamone et al. 2003; Schultz 1998). For example, animals with reduced levels of dopamine may still experience pleasure, but prefer low cost-low reward options rather than high cost-high rewards. Treadway (2015) also reported that dopamine activity in the insula and ventral striatum had

different effects on effort-based decision making. Increased dopamine activity in the ventral striatum was correlated with increased effort in a dose-dependent manner; however, the opposite trend was observed in the insula.

While substantial evidence has supported dopamine's role in anticipation, expectation, motivation and effort of reward processing, the role of other neurotransmitter systems is less clear. However, recent studies indicate that dopamine does not act in isolation and that serotonin, gamma-aminobutyric acid (GABA), glutamate and opioids may play an important role in reward (McCabe et al. 2010; Wassum et al. 2009; Wong et al. 1991). Reduced serotonin activity has been implicated in the preference for immediate smaller reward than delayed greater reward in MDD. Some studies have suggested this may be due to increased impulsivity and desire for short-term gratification (Der-Avakian and Markou 2012).

GABA is one of the most abundant neurotransmitters in the brain and has a variety of functions. In the context of reward, GABA has demonstrated modulation of dopamine activity and indirect effects on serotonin and noradrenergic activity (Wong et al. 1991). Importantly, some neuroimaging studies have identified lowered GABA concentrations in the anterior ACC and occipital cortex of depressed patients (Gabbay et al. 2012; Kugaya et al. 2003; Sanacora et al. 1999). Interestingly, when depressed patients were grouped according to the presence of anhedonia, only those with anhedonia had reduced GABA levels (Gabbay et al. 2012).

Opioids have primarily been studied in the context of pain, although there has been an increased interest in opioid receptors in MDD. The μ-opioid receptors found in the ventral tegmental area are implicated in the disinhibition of dopamine in the nucleus accumbens (Johnson and North 1992). Further, μ-opioid receptors in the amygdala may mediate the evaluation of a stimulus' incentive properties (Wassum et al. 2009). MDD patients with reduced opioid activity were prone to lower social motivation after rejection and lower pleasure during positive interactions (Hsu et al. 2015). This motivation was positively correlated with opioid release in the nucleus accumbens in healthy controls. Taken together, these findings suggest that opioids may mediate motivation and pleasure responses; however, further studies are needed to confirm its role in reward processing.

While anhedonia is a core symptom of MDD, it is important to recognize that it also plays a significant role in schizophrenia and bipolar disorder (Zhang et al. 2016). Several studies have attempted to elucidate the underlying neurobiology of anhedonia in each of these patient groups (Sharma et al. 2017; Whitton et al. 2015; Zhang et al. 2016). However, a transdiagnostic neurobiological profile of anhedonia has yet to be completely elucidated. In order to identify a common functional connectivity pattern associated with anhedonia across disorders, Sharma et al. (2017) assessed a sample of MDD, schizophrenia and bipolar disorder patients. The authors performed a whole-brain resting state analysis and examined its relationship with the reward responsivity measure on the behavioural activation scale (BAS). Reduced reward responsivity was associated with a specific pattern of dysconnectivity surrounding the nucleus accumbens, which was common to MDD, schizophrenia and bipolar disorder, and characterized by hypoconnectivity with the default mode network (DMN). The DMN is primarily active during internally directed forms of cognition, including memory, prospection and facets of reward processing (Sharma et al. 2017). Some studies have noted that increased connectivity in the DMN was related to anhedonia (Hamilton et al. 2011). The specific regions in the DMN with diminished connections to the nucleus accumbens included the anterior and dorsal prefrontal cortex and the posterior cingulate cortex, which are heavily involved in reward processing (Sharma et al. 2017). Therefore, it is reasonable to expect deficits in reward processing and anhedonia when hypoconnectivity between the DMN and nucleus accumbens is present.

In contrast to the hypoconnectivity with the DMN, the nucleus accumbens was found to demonstrate hyperconnectivity with the cingulo-opercular network, in particular with the insular cortex (Sharma et al. 2017). While the role of the insula in reward is unclear, some evidence has

suggested that it is involved with the effort to acquire rewards (Prevost et al. 2010; Treadway 2015). Interestingly, imaging studies have suggested that decreased insula activation, as a result of decreased dopamine release, may be associated with the selection of high effort reward options (Prevost et al. 2010; Treadway 2015). In summary, several key brain regions and connections have been identified in reward processing, particularly within the prefrontal cortex. It is possible that a neural dysfunction in any aspect of reward processing could lead to the clinical symptom of anhedonia.

## 7.4 Assessment of Anhedonia

Currently, measurement of anhedonia in clinical populations is primarily through self-report scales and behavioural tasks. While both tools allow for the assessment of anhedonia, each provides a unique but equally important perspective on this core symptom. In line with this, Treadway and Zald (2011) strongly assert that both measures should be used in tandem to obtain a more complete understanding of anhedonia. In this section, current scales and behavioural tasks will be described, along with their benefits and limitations.

### 7.4.1 Self-Report Scales

MDD patients often display reduced interest in rewarding stimuli (Uher et al. 2008, 2012); therefore, self-report scales are particularly useful since they are able to directly assess anhedonic symptoms (Kringelbach et al. 2012; Rizvi et al. 2016). The measurement of the explicit components of anhedonia is particularly important due to the subjective nature of reward behaviour. Furthermore, specific activities that are perceived as rewarding and the motivation to obtain rewards vary between each patient. Therefore, self-report scales should ideally be generalizable across cultures and individuals. For the purposes of this chapter, current self-report scales of anhedonia will be grouped into "first-generation" and "second-generation" questionnaires to distinguish older versus more contemporary scales that have been developed in the last decade (Rizvi et al. 2016).

#### 7.4.1.1 First-Generation Scales

The first-generation scales mostly measure consummatory pleasure, but some include motivational and effort components. The Snaith-Hamilton Pleasure Scale (SHAPS) is a 14-item scale designed to assess hedonic capacity and is the current gold standard of anhedonia measurement in MDD research (Snaith et al. 1995). The SHAPS presents participants with several examples of pleasurable situations that span the domains of hobbies, social life, sensory experiences and food/drink. The participants are instructed to select the degree to which they would enjoy situations over the past few days. As a measure of state anhedonia, the SHAPS has demonstrated its ability to detect acute changes in anhedonia, including treatment-related improvements. The scale has demonstrated good divergent and convergent validity in MDD populations. Furthermore, it has been shown to positively correlate with closely related measures such as quality of life and function. However, the SHAPS is a measure of consummatory pleasure and does not probe the other facets of reward processing life effort. In addition, while the items are generalizable across samples ("I would enjoy my favourite meal"), they may not be specific enough to elicit a strong hedonic reaction, thereby limiting the scale's sensitivity. While the SHAPS continues to demonstrate its strength in the assessment of consummatory pleasure, its use in tandem with other measures of anhedonia should be considered.

A similar measure of anhedonia is the Fawcett-Clark Pleasure Capacity Scale (FCPCS), which includes 36 items (Fawcett et al. 1983). Like the SHAPS, the FCPCS solely assesses consummatory pleasure on a scale between extreme displeasure to extreme pleasure. The FCPCS assesses pleasure across several domains including social activities, sensory experiences and the sense of mastery of difficult tasks. Like the SHAPS, the FCPCS has demonstrated good convergent and

divergent reliability and as a measure of state anhedonia is capable of measuring acute changes in anhedonia due to treatment (Clark et al. 1984; Leventhal et al. 2006). However, the FCPCS suffers from a lack of generalizability due to several items possessing high cultural bias. Despite this, the FCPCS has been validated in MDD populations, and the items possess high internal consistency reliability (Leventhal et al. 2006).

Finally, the last two scales, the Revised Chapman Physical Anhedonia Scale (CPAS) and the Chapman Social Anhedonia Scale (CSAS), are designed to measure various facets of reward including motivation, effort and consummatory pleasure in the context of physical anhedonia and social anhedonia, respectively (Chapman et al. 1976). Several criticisms of the CPAS and CSAS as measures of anhedonia in MDD have arisen due to its design. Both scales were developed for use in schizophrenia and thus have several items that are not applicable to MDD populations. Further, some items are not related to anhedonia, such as "I have often felt uncomfortable when my friends touch me". With the large number of items for each scale, 61 on the CPAS and 40 on the CSAS, there is limited use in clinical settings. Furthermore, the construct and discriminant validity of the scales have been questioned, and some have asserted that the items are outdated (Leventhal et al. 2006). Both scales use a binary true or false answer format which hinders a more sensitive assessment of anhedonia. In contrast to the SHAPS and FCPCS, the CPAS and CSAS are measures of trait anhedonia as opposed to state anhedonia. Despite this, both measures can detect changes in anhedonia (Leventhal et al. 2006).

#### 7.4.1.2 Second-Generation Scales

With the increased focus on expanding the construct of anhedonia beyond consummatory pleasure, there has been recent development of anhedonia scales to reflect these changes and to address the limitations of the "first-generation" scales. These new scales are designed to measure various facets of reward function in order to capture a more complete understanding of anhedonia (reviewed in Rizvi et al. 2016).

The Temporal Experience of Pleasure Scale (TEPS) was developed by Gard et al. (2006). Importantly, the TEPS was developed with two subscales that measure anticipatory and consummatory pleasure separately. In particular, the anticipatory items encompass reward responsiveness and imagery, while the consummatory items focus on appreciation of positive stimuli. The items are measured on a 6-point Likert scale which range from "very false for me" to "very true for me". Selected items focus on physical anhedonia as the authors believed it would provide results that are more homogeneous and interpretable. Despite attempts at designing the TEPS to be more generalizable, some items are not applicable to all populations, such as "the sound of crackling wood in the fireplace is very relaxing". While the convergent and discriminatory validity have demonstrated that the subscales are distinct, the anticipatory subscale had low internal consistency reliability. Furthermore, the TEPS has only been validated in bipolar, schizophrenia and opioid-dependent groups with limited studies in MDD populations (Gard et al. 2007; Garfield et al. 2016; Tso et al. 2014). Taken together, the TEPS may require additional validation studies to confirm the reliability of its psychometric properties and its use in MDD.

The Anticipatory and Consummatory Interpersonal Pleasure Scale (ACIPS) is a 17-item scale designed to measure social anhedonia in schizophrenia and address the limitations of the CSAS (Gooding and Pflum 2014). The ACIPS uses a 6-point Likert scale as opposed to a binary outcome. The ACIPS also includes subscales for the anticipatory and consummatory facets of reward; however, factor analysis did not reveal distinct subscales. Nevertheless, when both the CSAS and ACIPS were assessed against the TEPS, the ACIPS demonstrated better correlation with the TEPS subscales than the CSAS. Finally, despite being developed as a substitute to the CSAS in schizophrenia, the ACIPS has not been validated in this population. On a similar note, the ACIPS has not been validated in MDD. Further validation studies are required to assess its utility in several psychiatric populations and to deter-

mine whether their measures of anticipation and consummatory pleasure are distinct constructs.

Lastly, the Dimensional Anhedonia Rating Scale (DARS) is the most recently developed scale by Rizvi et al. (2015). The DARS consists of 17-items on a 5-point Likert scale and was designed to specifically assess anhedonia in MDD patients. In order to increase the generalizability of the scale, participants are asked to fill in personal activities or experiences they perceive as enjoyable across the domains of hobbies, social activities, food/drink and sensory experiences. With the highly subjective nature of rewarding experiences, this feature may allow for a more sensitive measurement of anhedonia. While increasing generalizability, the DARS is designed to maintain specificity by having a specific set of items for each domain assessed. Within each of these domains, items to probe interest, motivation, effort and consummatory pleasure are measured based on how the respondent feels "now". This measurement of state anhedonia has the benefit of increased sensitivity during assessment of treatment response. In contrast to the other "second-generation measures", the reliability and validity of the DARS has been tested in a MDD population and demonstrated good convergent validity with the SHAPS. The DARS may also be useful in predicting subtypes as results from the validation study demonstrated its ability to predict treatment-resistant status over the SHAPS in MDD patients. While promising, further research into the use of the DARS is required to assess its test-retest viability and its use in the study of the neurobiology of anhedonia.

### 7.4.2 Behavioural Tasks

Self-report scales provide direct insight into experiences of anhedonia and have demonstrated important utility in clinical settings; however, they possess several limitations. While many consider rewarding experiences and its associated pleasures, motivations, interests and anticipation, an entirely conscious experience, this may not be the case. Several lines of evidence suggest that these experiences, while often conscious, may include an unconscious component. Kringelbach et al. (2012) asserts that at times, we may be poor at identifying our current emotional states. Further, he suggests that this may lead to an unawareness of what motivates us, why we take interest or what brings us pleasure. Several studies have suggested that reward learning often occurs implicitly. A study by Pessiglione et al. (2008) utilized a behavioural task which presented healthy participants with two cues, one associated with a monetary reward and another associated with a "punishment". As the task progressed, participants were more prone to selecting the cues associated with a reward without their awareness, supporting the occurrence of implicit reward processing. Where self-reports can provide great explicit information, behavioural tasks can tap into both the conscious and unconscious and as such are valuable objective measures in the study of anhedonia.

#### 7.4.2.1 Reward Association

The ability to develop an association between a stimulus and reward is primarily assessed using reward response bias tasks, which are based on signal detection theory (Henriques and Davidson 2000; Pizzagalli et al. 2005). Specifically, these tasks measure the level of "response bias", which is the tendency to select the stimuli associated with greater rewards. In general, these tasks involve the presentation of two or more different stimuli with specific reward contingencies, which can vary. Stimuli can range and include verbal or non-verbal cues. One stimulus may be neutral or associated with a punishment, or all stimuli can be associated with reward but vary in terms of frequency and/or magnitude. Oftentimes, the participants are not informed of the specific reward contingencies. These tasks assess the ability of individuals to discriminate between stimuli according to their rewarding properties. During behavioural tasks that assess stimulus-reward association, healthy individuals display a bias towards rewarding stimuli (Pechtel et al. 2013).

However, several studies have noted that this bias is reduced in depressed individuals, which suggests an impaired ability to form this association (Henriques and Davidson 2000; Pechtel et al. 2013; Pizzagalli et al. 2008).

#### 7.4.2.2 Reward Valuation

Several factors may influence the value of a reward, such as the size and time required to obtain it (Green et al. 1997). Delay discounting tasks manipulate these variables to assess how they affect the value one places on a reward (Kirby et al. 1999). Delay discounting describes the situation where the value of a reward drops as the time to obtain the reward increases (Green et al. 1997). Most delay discounting tasks have been developed with monetary rewards which may vary in size or may be fixed (Kirby et al. 1999; Pulcu et al. 2014; Richards et al. 1999). The more immediate reward is always associated with a smaller size. MDD patients often display greater discounting effects than healthy controls and value immediate rewards more highly despite being offered a larger, albeit relatively delayed reward, suggesting differences in reward valuation (Dombrovski et al. 2012; Pulcu et al. 2014).

#### 7.4.2.3 Anticipation

Several reward tasks designed to probe the other facets of reward are often modified in order to measure anticipation (Knutson et al. 2008; reviewed in Rizvi et al. 2016). These tasks are commonly used in a neuroimaging environment. Changes in brain activity prior to the participant obtaining the reward are used as measures of anticipation (Knutson et al. 2008; Kumar et al. 2014). The monetary incentive delay task was designed to distinguish anticipatory and consummatory facets of reward processing (Knutson et al. 2008). This task is composed of three trial types, a reward trial, punishment trial and no-incentive trial. Each trial is composed of an incentive cue, target stimulus and then a feedback. The goal is to press the correct button associated with the trial type once the target stimulus has been presented to increase win money or to avoid losing money.

#### 7.4.2.4 Expectation

Prediction error tasks assess brain activity associated with changes in dopaminergic activity in the ventral striatum in response to outcomes that are different than expected (Schultz 1998; reviewed in Rizvi et al. 2016; Schultz 2013). Outcomes that are better than predicted are associated with an increased burst of dopamine. In contrast, there is a decrease in dopamine signaling when the outcome is worse than predicted. No changes in activity occur when the result is accurately predicted. Many variations of the task have been created, but they all involve having participants learn a certain reward contingency, which changes and results in a greater or lesser reward than expected (Forbes et al. 2009; Kumar et al. 2008; reviewed in Rizvi et al. 2016). Cohen et al. (2009) developed a prediction error task which was composed of two phases: a learning phase and a choosing phase. In the learning phase, one of two stimuli is presented at one time to allow the participants to learn their reward contingencies. The "safe" stimulus is rewarded 100% of the time, whereas the "risky" stimulus has a chance of loss or gain. Once completed, the participants begin the choosing phase where they are presented with both stimuli and are asked to select one. MDD patients demonstrate reduced prediction error signal compared to healthy controls. There is also some evidence to suggest that MDD and schizophrenia patients have dysfunction in shared as well as disparate brain regions during prediction error tasks.

#### 7.4.2.5 Motivation

Motivation can be assessed using a cued-reinforcement reaction time task which assesses reaction time speed (Chase et al. 2010; Cools et al. 2005; reviewed in Rizvi et al. 2016). Cools et al. (2005) developed this task in order to assess the impact of reduced serotonin levels on motivation. During the task, three circles are presented, with one arranged in a different orientation. The goal is to select the "out-of-place" circle as fast as possible, with faster responses rewarding more points. Prior to each trial, a coloured rectangle will be presented which will signify the probability of receiving a reward. MDD participants tend

to be less affected by motivational cues, thus will respond with lower reaction times than healthy controls (Treadway 2015).

#### 7.4.2.6 Effort

Effort to obtain a reward is necessary for reward decision making via a cost-benefit analysis. Consequently, Treadway et al. (2012) developed the effort-expenditure for rewards task to determine the effect of probability and reward size on effort-based decision making. This task is composed of two trial types, "easy" and "hard". Prior to the start of the trial, the probability of receiving the reward upon successful completion and size of the reward is listed for each trial type. The goal of each trial is to press a button several times to fill a metre in a certain period. The time limit, finger selection and number of button presses required depend on the trial type. Prior to each trial, participants are to select either the low reward and low-cost "easy" trial or the high/low reward and high-cost "hard" trial. This was done in a limited amount of time to ensure that selection was based on effort calculations. As noted in several studies, MDD patients expend less effort to obtain rewards (Prevost et al. 2010; Salamone et al. 2003; Treadway et al. 2009). Treadway et al. (2012) also reported that anhedonia severity was negatively correlated with willingness to expend effort, especially when there was a low probability of a reward.

#### 7.4.2.7 Feedback Integration

Several probabilistic reversal learning tasks have been developed to assess the effect feedback has on reward learning (Hasler et al. 2009; Murphy et al. 2003; Taylor Tavares et al. 2008). These tasks always include the presentation of two stimuli simultaneously, both with an equal probability of being associated with a reward. The first stimulus a participant selects will subsequently be associated with a high probability of reward in future trials. Participants are told to select the stimulus most associated with reward despite any potential reward losses that may arise. However, participants are also told that the rules may reverse with the other stimulus being more rewarded and to then select this one. Learning may occur through positive feedback or negative feedback. For example, participants may obtain more correct answers by focusing on positive feedback or by avoiding negative feedback. MDD patients are more hypersensitive to negative feedback and will often switch their selection to the incorrect stimulus too soon (Thomson 2015). In line with this, Murphy et al. (2003) demonstrated that MDD patients are more likely to view a potentially rewarding stimulus as non-rewarding shortly after any negative association of the stimulus' rewarding properties is received.

In summary, behavioural tasks can evaluate various aspects of reward processing including response bias and learning. Importantly, most tasks use monetary reward, instead of primary rewards (e.g. food, social reward). Levels of monetary reward may also be too small to elicit a strong reward response. Future research should evaluate different types of reward in the above described paradigms.

## 7.5 Treatment of Anhedonia

Currently, there are many treatment options available for MDD; however, the prevalence of treatment-resistant depression remains significantly high (Kennedy et al. 2016; Lam et al. 2016). The inadequacy of current treatment options are highlighted in the Sequenced Treatment Alternatives to Relieve Depression (STAR*D) study (Warden et al. 2007). In this study of over 3000 patients, participants initially received a first-line antidepressant. If the patient failed to achieve remission, they received an additional antidepressant. By the fourth treatment step, 30% of patients failed to achieve remission (Warden et al. 2007). Currently, the serotonin and norepinephrine systems remain the primary target of first-line antidepressants (Kennedy et al. 2016). Most of these first-line treatments are selective serotonin reuptake inhibitors (SSRIs) and serotonin and norepinephrine reuptake inhibitors (SNRIs). Since dopamine and other neurotransmitters play a significant role in the reward system (McCabe et al. 2010; Wassum

et al. 2009; Wong et al. 1991; reviewed in Rizvi et al. 2016), this has important implications in MDD treatment since conventional antidepressants do not significantly target these systems. There has been substantial evidence linking anhedonia to poor treatment outcomes, including treatment resistance (Malhi and Berk 2007; Malhi et al. 2005; Rizvi et al. 2014a, b; Souery et al. 1999). This suggests that targeting the dopamine or other systems involved in anhedonia may benefit MDD treatment. Despite being a core symptom, there are not a significant amount of studies conducted on the effects of antidepressants on anhedonia.

While SSRIs have demonstrated effectiveness in the treatment of MDD, they have been reported to induce emotional blunting effects (McCabe et al. 2009). Healthy controls treated with citalopram had lowered emotional responses to aversive and rewarding stimuli which indicate that SSRIs can impact emotional range (McCabe et al. 2009). Interestingly, when participants were treated with the noradrenergic antidepressant reboxetine, they demonstrated greater response to rewarding stimuli and decreased response to aversive stimuli (McCabe et al. 2010). Norepinephrine is associated with increased attention and is synthesized from dopamine (McCabe et al. 2010). Further, preclinical studies in mice have demonstrated that SNRIs may be effective in minimizing the emotional blunting effects of serotonin while retaining its antidepressant activity (Dekeyne et al. 2002). While promising, further studies are required to confirm whether SNRIs are more favourable than SSRIs in the treatment of anhedonia.

Agomelatine, a melatonergic antidepressant, has demonstrated efficacy in depression (Kennedy and Rizvi 2010). In addition to action on the melatonin system, agomelatine disinhibits the release of norepinephrine and dopamine by acting as a $5\text{-HT}_{2c}$ receptor antagonist. Demyttenaere et al. (2013) demonstrated that agomelatine treatment had a greater reduction in Hamilton depression rating scores relative to SSRIs. Gargoloff et al. (2016) took this further and assessed the effectiveness of agomelatine as a treatment of anhedonia. In this 8-week trial, 143 patients were given agomelatine, and anhedonia was assessed using the SHAPS. Gargoloff and colleagues reported a significant decrease in anhedonia as early as 1 week of treatment. Interestingly, patients who were also on concomitant treatments demonstrated a delayed improvement in anhedonia. The authors suggested that the increase in serotonin levels by SSRIs may dampen the activity of norepinephrine and dopamine, reducing their ability to improve anhedonia. Finally, the authors also performed a separate analysis which compared changes in anhedonia between patients experiencing their first episode to those who are experiencing recurrent episodes. Both groups demonstrated similar reductions in anhedonia.

In response to the high failure rate of first-line antidepressant monotherapy, there has been an increase use of adjunctive pharmacotherapy to target specific neurotransmitter systems, which include stimulants (e.g. methylphenidate, dextroamphetamine) (Kennedy et al. 2016). Rizvi et al. (2014a) conducted a secondary analysis of osmotic-release oral system methylphenidate (OROS-MPH) to determine whether early symptomatic improvements in apathy/anhedonia predicted increased likelihood of treatment response compared to placebo. Using the Apathy Evaluation Scale (AES), the authors determined that early improvements in apathy predicted increased likelihood of treatment response only in the active drug group and not the placebo group. These results support the notion that a personalized treatment approach may be beneficial to alleviate specific symptoms experienced by a patient, including anhedonia.

Deep brain stimulation (DBS) is a neurosurgical procedure that has recently been adapted for use in MDD treatment and was originally used for the treatment of pain and movement disorders (Kennedy and Giacobbe 2007). Certain brain areas associated with reward have been selected as potential targets of DBS treatment in MDD. Currently, DBS use is experimental and only conducted in severely treatment-resistant patients as it is highly invasive. In 2005, Mayberg and colleagues were the first to study the use of DBS in the subcallosal cingulate gyrus (SCG), a

region of the anterior cingulate cortex (ACC) which is responsible for emotion regulation. The SCG is directly connected to the ventral striatum, nucleus accumbens, rostral portions of the prefrontal cortex and the central nuclei of the amygdala, which are areas implicated in reward processing. Dopamine receptors are also expressed in these areas, which suggest that DBS may impact dopamine activity and subsequently anhedonia. Preliminary data suggest that DBS to the SCG and nucleus accumbens has a preferential effect on mood and anhedonia symptoms (Lipsman et al. 2014; Schlaephfer et al. 2008).

### Conclusion

This chapter highlighted key updates in anhedonia research and how modern definitions affected the trajectory of this research. Past constructs of anhedonia were broad and focused primarily on consummatory pleasure, which limited our understanding of the underlying neurobiology and potential development of treatment strategies. Reward processing includes interest, anticipation, motivation, effort and pleasure; a deficit in any of these facets may result in the clinical symptom of anhedonia. Behavioural tasks in tandem with neuroimaging have identified that slightly distinct pathways govern the activity of each reward facet, which underscores that anhedonia is a multi-faceted construct. This has also been reflected in the development of contemporary self-report questionnaires. There are various treatments that target anhedonia symptoms due to their effect on the dopaminergic and noradrenergic systems; however, further research is needed to elucidate the effects of conventional antidepressants on anhedonia. As our understanding of anhedonia progresses, reward processing models may be refined and allow for more personalized treatment strategies.

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# Sleep and Sleep Disorders in Depression

8

Seung-Gul Kang, Heon-Jeong Lee, Leen Kim, and John Weyl Winkelman

## 8.1 Introduction

Depressive disorders are prevalent psychiatric illnesses, and major depressive disorder (MDD) has a lifetime prevalence of 10–15% worldwide (Ferrari et al. 2013). Depression is a serious illness, which produces psychological distress, impairs quality of life, decreases productivity, worsens other medical conditions, and can result in suicide (Gelenberg 2010).

Sleep-wake disturbances such as insomnia and hypersomnia frequently develop during the course of depression. Such disturbances not only are symptoms but also are important diagnostic criteria for depression. In addition, sleep-wake symptoms are associated with the biological mechanism of depression and might be a biological marker for the onset, treatment response, and relapse of depression. The typical sleep structure changes that accompany depression are increased rapid eye movement (REM) density and decreased delta sleep ratio (Wichniak et al. 2013).

Primary sleep disorders such as obstructive sleep apnea (OSA) and restless legs syndrome (RLS) are also common in depression. There are several possibilities for such comorbidities: (1) depression comorbid with a primary sleep disorder; (2) depression-like symptoms caused by a primary sleep disorder; and (3) sleep-wake disturbances, similar to those in a primary sleep disorder, that occur as side effects of medication including antidepressants. Therefore, the differential diagnosis and management of these conditions should be carried out carefully. This article will also discuss the clinical treatment options available for sleep-wake disturbances that are comorbid with depression.

## 8.2 Sleep Changes in Depression

### 8.2.1 Sleep-Wake Symptoms, Polysomnography (PSG), and Sleep Electroencephalography (EEG) Findings in Depression

Sleep-wake disturbances are consistent symptoms associated with MDD; sleep disturbances are reported by 60–90% of MDD patients (Abad and Guilleminault 2005). Two-thirds of depressed patients suffer from insomnia, including initial insomnia, sleep maintenance difficulty, and

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terminal insomnia, while approximately 15% complain of hypersomnia. The relationship between sleep disturbances and depressive symptoms is bidirectional since depressive episodes can precede poor sleep and vice versa.

Depressed patients complain of shallow sleep, and they show changes in their sleep structure. The most common findings in the polysomnographs of patients with depression are the following: (1) prolongation of sleep latency, early morning awakening, reduced total sleep time, and disruption of sleep maintenance, which includes increased waking after sleep onset and decreased sleep efficiency; (2) REM sleep disturbances, which present as shortened REM sleep latency, increased REM density (frequency of rapid eye movements), and an increased proportion of REM sleep; (3) slow-wave sleep (SWS) disturbances, which manifest as decreased non-REM stage 3 (N3) and delta activity (especially in the first 100 min of sleep) (Palagini et al. 2013; Steiger and Kimura 2010; Wichniak et al. 2000).

### 8.2.2 Biological Mechanisms of Sleep Disturbances in Depression

Several hypotheses have been proposed regarding the sleep disturbances and the changes in REM sleep that often accompany depression. One hypothesis is derived from neurotransmitters such as acetylcholine and glutamate having been reported to be involved in this mechanism. Cholinergic (REM-on) dominance over monoaminergic (REM-off) activity is one of the putative core mechanisms for the disinhibition of REM sleep in depression (Jouvet 1972; McCarley 1982) since cholinergic-adrenergic balance is thought to play a crucial role in the etiology of depression and mania (Janowsky et al. 1972). This theory is further supported by a report that the suppression of REM sleep is related to the improvement of depression during antidepressant treatments that enhance monoaminergic neurotransmission (Vogel et al. 1990). Glutamate is also known to be linked to depression and REM/NREM sleep regulation. Glutamate interacts with cholinergic neurons and increases the activity of the reticular system, which is related to the onset of REM sleep (Peterson and Benca 2008). Glutamate neurotransmission is also involved in the thalamocortical generation of sleep EEG oscillations during NREM sleep (Pace-Schott and Hobson 2002; Peterson and Benca 2008).

Dysregulation of the hypothalamic-pituitary-adrenocortical (HPA) system has also been noted as a cause of depression and its sleep disturbances. Abnormally increased activity of the HPA system has been suggested as one of the core mechanisms in the pathogenesis of depression (Holsboer 2000). In depression, there are changes in corticotropin (adrenocorticotropic hormone—ACTH) activity, cortisol secretion, and corticotropin-releasing hormone, and thus corticosteroid receptor signaling is altered accordingly. This overactivity of the HPA axis may in turn cause sleep EEG changes and increased arousal, poor sleep, and promotion of REM sleep (Vgontzas and Chrousos 2002).

The sleep disturbances in depression such as decreased SWS are also attributed to impairment of the homeostatic process S (Borbely 1987). The illness-related neurobiological changes and decreased daytime activity due to depression may lower the level of process S (Borbely 1987).

Some studies have proposed roles for genetic polymorphisms and specific brain regions in depression and insomnia. *CLOCK* genes, the monoamine oxidase A gene, and the serotonin transporter gene have been suggested to influence sleep patterns and to be related to the etiology of MDD and the treatment response to light therapy and antidepressants (Benedetti et al. 2003; Bunney and Potkin 2008; Hu et al. 2007; Serretti et al. 2005). The lateral habenula, which is located adjacent to the medial dorsal thalamus, is also considered to be involved in the regulation of mood and sleep. Stimulation of the lateral habenula inhibits the activity of serotonergic and dopaminergic neurons of the brainstem, and hyperactivity of the lateral habenula may cause the decreased motor activity and REM sleep changes that are characteristic of MDD (Aizawa et al. 2013).

## 8.3 What Does Sleep Disturbance Mean in Depression?

### 8.3.1 Effect of Insomnia and Sleep Disturbances on the Treatment Course of Depression

Sleep disturbances and insomnia are commonly encountered during the course of depression. Conversely, however, sleep disturbances can affect the symptoms and course of depression. MDD develops three times more often in insomniacs than in individuals with healthy sleep patterns (Johnson et al. 2006). In addition, depressive patients with sleep disturbances show more suicidality, severe depressive symptoms, and refractoriness to treatment for depression (Peterson and Benca 2008). From a therapeutic standpoint, sleep deprivation is considered one of the most rapid therapies for depressive patients, although the treatment effect is temporary (Wichniak et al. 2013). Moreover, suppression of REM sleep is considered to be related to the improvement of depression during antidepressant treatment (Vogel et al. 1990). Synchronization of the circadian rhythm in depression has also been reported as a necessary prerequisite for better recovery from depression (Hajak and Landgrebe 2010).

### 8.3.2 Sleep as a Biomarker for Depression

Sleep disturbances and related PSG findings have been recognized as biomarkers for depression. A meta-analysis reported that patients with insomnia without depression have twice as high a risk of developing incident depression as individuals without sleep problems (Baglioni et al. 2011). In an earlier study, subjects at high risk of depression (i.e., healthy first-degree relatives of patients with mood disorders) showed an abnormally increased REM density and decreased SWS amount (Lauer et al. 1995). In addition to this, changes in sleep parameters have been considered trait markers rather than state markers for depression (Steiger and Kimura 2010), given that REM sleep measures were found not to change between depressive episodes and remission periods (Wichniak et al. 2013). Studies have also reported that the sensitivity of REM density as an indicator for monoaminergic/cholinergic dysfunction could be improved by using cholinergic REM sleep induction tests. Depressive patients and subjects at high risk of mood disorders showed REM sleep changes after receiving cholinergic agents such as RS 86 or arecoline (Gillin et al. 1991; Riemann and Berger 1992). Interestingly, it is common clinical knowledge that sleep disturbances differ among depression subtypes. As indicated in the diagnostic criteria for depression, seasonal affective disorder and atypical depression are characterized by hypersomnia, while melancholic depression is characterized by terminal insomnia (American Psychiatric Association 2000; Murphy and Peterson 2015). Therefore, the characteristics of sleep disturbances might be helpful in subtyping depression.

### 8.3.3 Sleep as a Biomarker for Treatment Response and the Relapse of Depression

Sleep disturbances and PSG findings could be biomarkers not only for depression onset but also for treatment response and relapse. Persistent insomnia is a strong predictor of future relapse, even without current mood symptoms (Benca and Peterson 2008). Residual hypersomnia is also known to be associated with an increased risk of relapse of depression (Kaplan and Harvey 2009). Abnormal PSG measures have been regarded as a biomarker, which suggests the advantage of a biological treatment over a psychological approach, since 3/4 of nonresponders to psychotherapy went into remission after subsequent pharmacotherapy (Thase et al. 1997).

Since a change in REM density is the most replicated finding, this could be a valuable biomarker for treatment outcome or recurrence (Wichniak et al. 2013). High REM density after 1 week of paroxetine treatment has been related

to non-response after 6 weeks (Murck et al. 2003). In addition, increased REM density and decreased total sleep time at 2–4 weeks of abstinence from alcohol predicted relapse during the first 3 months in depressed alcoholic patients (Clark et al. 1998). One study suggested that REM activity and density in participants with depression are correlated with remission and recovery and that quantitative measurement of rapid eye movements provides a better correlate of treatment response than do quantitative sleep EEG measures (Buysse et al. 2001).

Slow-wave activity (SWA) in the delta frequency band of an EEG during sleep has also been reported to be related to treatment response. An increase in SWA has been reported to be correlated with treatment response to clomipramine (Kupfer et al. 1989). A low delta ratio and less delta EEG activity at baseline and remission have also been found to be related to depression recurrence after the discontinuation of antidepressants (Buysse et al. 1997; Kupfer et al. 1990). Spectral analysis has shown that the delta sleep ratio based on quantitative EEG is a stronger predictor of the recurrence of depressive episodes than is REM latency (Kupfer et al. 1990).

## 8.4 Comorbid Primary Sleep Disorders Other than Insomnia

In depression, primary sleep disorders other than insomnia are also common. In some cases, the primary sleep disorder may cause depression or has depression-like symptoms. Therefore, in the case of atypical depression, more attention should be paid to differential diagnosis.

Depression is common in patients with OSA. In one study, the odds ratio of MDD in patients with OSA was 2.4 in male subjects and 5.2 in female subjects (Wheaton et al. 2012). OSA can induce depression-like symptoms such as fatigue, hypersomnolence, difficulty concentrating, and lack of energy (Schroder and O'Hara 2005). The converse is also true, in that OSA occurs frequently in depression (Reynolds et al. 1985), which may due to weight gain caused by decreased activity, to irregular activity patterns, and to the effect of medication such as antidepressants. In this case, the refractoriness of depression to treatment becomes worse (Schroder and O'Hara 2005). Some also hold the idea that OSA and MDD share a common etiology. An imaging study has shown that the hypoxemia from OSA has an impact on mood symptoms (Kamba et al. 1997), and the reverse mechanism is that reduced serotonin levels in depression lead to loss of muscle tone of the upper airway dilator muscles and could contribute to the development of OSA (Lipford et al. 2016).

RLS is also a common neurological disease and a distressing sleep disorder. Its core symptoms are restlessness in the legs and an urge to move the legs. According to published studies, 26% of patients with unipolar depression show RLS symptoms, and the odds ratio of RLS symptoms was found to be 1.64 in adults with depression (Foley et al. 2004; Picchietti and Winkelman 2005). The comorbidity of RLS with depression could be attributed to dopamine hypofunction. Decreased dopamine function is one of the most frequently proposed etiologies of RLS and could also induce depression (Picchietti and Winkelman 2005). On the other hand, antidepressants could underlie the increased prevalence of RLS and periodic limb movements during sleep (PLMS) in depressed patients (Picchietti and Winkelman 2005).

REM sleep behavior disorder (RBD) is commonly caused by antidepressants during the course of pharmacotherapy of depression, especially in older people. Probable RBD is significantly associated with depression, and the odds ratio of depression in RBD was found to be 2.99 (Mahlknecht et al. 2015). Participants who take antidepressants have also been found to have greater EMG activity in the submentalis muscle during REM than do controls, and dream enactment symptoms have been found to develop in up to 6% of subjects taking antidepressants (Ju et al. 2011; Teman et al. 2009; Winkelman and James 2004).

Hypersomnia and hypersomnolence sometimes appear in depression. In some cases, these symptoms are more prominent than depressive symptoms, so it is necessary to differentiate this condition from sleep-wake disorders such as

narcolepsy. Depression may be accompanied by narcolepsy. The cause of narcolepsy with cataplexy is known to be hypocretin deficiency, and hypocretin projections may be involved in mood regulation, given that the hypocretin neural circuit projects broadly to the locus ceruleus, raphe nucleus, and limbic area (Dauvilliers et al. 2013). According to an epidemiological study, 19.2% of narcoleptic patients have MDD, while 6.4% of the general population have MDD (Ohayon 2013).

## 8.5 Treatment of Sleep Disturbances in Depression

### 8.5.1 Pharmacotherapy

Antidepressants have diverse effects on sleep and sleep structure. In fact, in depression, the structure and other parameters of sleep usually change more by antidepressants than do subjective sleep-wake symptoms (Wichniak et al. 2013). Antidepressant use acutely and strongly suppresses REM sleep. In particular, antidepressants that block serotonin reuptake have a strong effect on REM sleep (Wilson and Argyropoulos 2005). However, antidepressants can have a variety of effects on sleep depending on the type. Tricyclic antidepressants (TCAs, e.g., amitriptyline and doxepin), noradrenergic and specific serotonergic antidepressants (NaSSAs, e.g., mirtazapine), and serotonin receptor 5-$HT_2$ antagonists and reuptake inhibitors (SARIs, e.g., trazodone) are sedative antidepressants, and they induce sleep through antagonistic action on the serotonergic 5-$HT_{2A}$ and histamine $H_1$ receptors (Wichniak et al. 2013). On the other hand, antidepressants that increase noradrenergic and dopaminergic neurotransmission are classified as activating antidepressants. Serotonin and norepinephrine reuptake inhibitors (SNRIs, e.g., venlafaxine and duloxetine) and norepinephrine and dopamine reuptake inhibitors (NDRIs, e.g., bupropion) are representative activating antidepressants. Selective serotonin reuptake inhibitors (SSRIs, e.g., fluoxetine) can also induce sleep disruption through the activation of serotonin 5-$HT_2$ receptors (Wichniak et al. 2012). Agomelatine is an agonist of the melatonin $MT_1$ and $MT_2$ receptors and has antagonistic action on the serotonin 5-$HT_{2C}$ receptor. Agomelatine is also known to improve sleep measurements such as sleep efficiency and SWS and not to change the latency or duration of REM sleep (Quera-Salva et al. 2010).

In chronic use of antidepressants, the aforementioned acute effect on sleep and sleep structure is alleviated, and beneficial effects on sleep such as increased sleep continuity and amount of SWS can occur as the depressive symptoms are relieved and daytime activity is increased (Wilson and Argyropoulos 2005). In addition, even non-sedating antidepressants might play a role in improving subjective sleep symptoms by relieving tension, anxiety, worry, and cognitive distortion about sleep, which are common in patients with chronic insomnia (Nowell et al. 1999). However, studies have shown that during maintenance therapy with activating antidepressants, 30–40% of patients may continue to experience insomnia (Iovieno et al. 2011). In this case, monotherapy with sedative antidepressants (e.g., trazodone and mirtazapine) or combination therapy with low-dose sedative antidepressants and SSRIs might be useful (Jindal et al. 2003; Jindal and Thase 2004; Wichniak et al. 2012). However, little controlled evidence supports the long-term usage of sedative antidepressants (e.g., mirtazapine, trimipramine, and amitriptyline) for insomnia symptoms (Kurian et al. 2009), and side effects such as excessive sedation and weight gain should be considered. Antidepressants also exert various potentially harmful effects on sleep by inducing (or aggravating) RLS symptoms, PLMS, weight gain and related sleep apnea risk, and RBD symptoms.

Although combination pharmacotherapy using hypnotics such as zolpidem, zaleplon, eszopiclone, or benzodiazepines with antidepressants may improve the patient's sleep, daytime functioning, and quality of life (Franzen and Buysse 2008), clinicians should carefully consider the risks of dependence and tolerance to hypnotics (Murphy and Peterson 2015). In addition, benzodiazepines are shown to attenuate slow-wave activity and to enhance sleep spindles

(Achermann and Borbely 1987), and non-benzodiazepine hypnotics such as zolpidem and zopiclone show similar unfavorable effects on sleep EEG, though the clinical implications of these findings are unclear (Landolt et al. 2000).

Patients with depression who are suffering from serious hypersomnia or hypersomnolence could be candidates for the use of modafinil or psychostimulants if the symptoms persist after treatment of any primary sleep disorders such as OSA (Peterson and Benca 2008).

### 8.5.2 Cognitive Behavioral Therapy for Insomnia (CBT-I)

CBT-I is the treatment of choice for chronic insomnia, and it is also effective for the treatment of insomnia comorbid with depression (Espie 1999). In one study, when CBT-I was combined with escitalopram, greater remission from both insomnia and depressive symptoms was achieved than with escitalopram alone (Manber et al. 2008). According to another study, patients who were treated with brief behavioral therapy for insomnia in addition to antidepressant therapy showed greater improvements in sleep quality and depression, and they showed greater remission of depression after 8 weeks than did a treatment group receiving only antidepressants (Watanabe et al. 2011). Moreover, several studies have shown that CBT-I is efficacious in insomnia patients with depression, as well as in those without depression (Edinger et al. 2009; Hamoen et al. 2014).

Sleep restriction therapy and stimulus control therapy are two core behavioral treatment components of CBT-I. Sleep restriction, which is a typical treatment component of CBT-I, consists of curtailing the amount of time in bed to the total subjective sleep time of insomnia patients. Stimulus control techniques, which constitute another important treatment component, are intended to reduce the conditioned arousal or performance anxiety related to sleep at night. To reassociate the bed with sleep, patients should go to bed only when sleepy and get out of bed when unable to sleep (Bootzin et al. 2010). Other CBT-I elements include distraction techniques, cognitive restructuring, and paradoxical intention. Cognitive restructuring addresses the patient's negative and dysfunctional beliefs about sleep. Paradoxical intention consists of reducing worry about negative effects due to poor sleep by staying awake intentionally at night (Perlis et al. 2010). There are several different relaxation therapies, including progressive muscle relaxation therapy and diaphragmatic breathing (Perlis et al. 2010).

Some patients with depression fail to adhere to CBT-I because of motivational deficits, avoidance, and automatic negative thoughts. In addition, insomnia patients with depression have worse sleep hygiene, more mental arousal at bedtime, and more dysfunctional beliefs about sleep than do insomnia patients without depression (Carney et al. 2007). Therefore, it is recommended that CBT-I therapy also include the elements of CBT for depression in the depressive population (Haynes 2015). Cognitive behavioral social rhythm therapy (CBSRT), which was designed to improve mood and sleep by stabilizing social rhythms and changing dysfunctional bed associations, might be useful for insomnia patients with depression or post-traumatic stress disorder (Haynes 2015; Haynes et al. 2016).

### 8.5.3 Sleep Deprivation and Light Therapy

Sleep deprivation is the fastest-acting treatment for depression and has comparable short-term efficacy to antidepressants. According to a meta-analysis, total sleep deprivation led to a transient improvement in mood in 50–60% of depressive patients (Wu and Bunney 1990). Partial sleep deprivation also produced mild to moderate improvements in depression scores (Benedetti and Colombo 2011) that persisted longer than those from total sleep deprivation, although the therapeutic effect was rather weak (Giedke and Schwarzler 2002). Regardless, the effect of sleep deprivation is not sustained, and the effect is lost after recovery sleep. Although the clinical efficacy has not yet been established, the effects of

combination therapy consisting of light therapy in the morning and sleep deprivation might be stronger and longer lasting (Murphy and Peterson 2015). This combination therapy may have a similar effect to sleep time restriction, especially for depressive patients with insomnia who spend a long time in bed owing to decreased motivation and energy.

### Conclusion

Sleep-wake disturbances not only are prevalent symptoms of depression but also are a biological marker for depression. Primary sleep disorders such as OSA, RLS, and RBD are also prevalent in depression. During depression, the sleep structure frequently changes because of the depression itself and the medications that are prescribed for depression. Antidepressants can have a variety of effects on sleep depending on their mechanism and characteristics. To treat insomnia associated with depression, antidepressants, hypnotics, and CBT-I can be used effectively. For depressed patients with persistent insomnia, monotherapy with sedative antidepressants (e.g., trazodone or mirtazapine) or combination therapy with low-dose sedative antidepressants and SSRIs might be useful. CBT-I, which is the treatment of choice for chronic insomnia, is also effective for the treatment of insomnia comorbid with depression.

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# Chronobiology and Treatment in Depression

9

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## 9.1 Introduction

Major depressive disorder (MDD) affects more than 5% of the general population with a lifetime prevalence about 14% (Waraich et al. 2004). This is such a leading public health problem that MDD is ranked as the second worldwide cause of disability, associating decreased quality of life and an increased mortality (Ferrari et al. 2013; Whiteford et al. 2013). "Traditional" treatments for MDD are antidepressant drugs and psychotherapies. Unfortunately, remission rates are low despite good adherence of patients and the wide range of existing antidepressant drugs. For instance, the large STAR-D study observed that only one out of three patients respond to the first-line antidepressant treatment, and, after four lines of treatments, only 67% of all patients manage to present with remission (Rush et al. 2006). In this context, new treatment options are necessary and highly expected.

Treatments acting on sleep and circadian rhythms are promising antidepressant treatments. Indeed, such treatments may relieve numerous sleep homeostasis abnormalities and circadian rhythm disruptions that are observed from the molecular to the behavioral level in MDD (McClung 2011, 2013). Some of the characteristic symptoms reported in MDD are delayed sleep onset, non-restful sleep, early-morning wakening, daytime fatigue, and blunting or reversal of the normal morning peaks in subjective energy, mood, and alertness (Hickie and Rogers 2011). These symptoms may persist during remitted phases and are associated with depressive recurrences but also a poor global functioning, a

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decrease quality of life, and an increased risk of metabolic syndrome (Sylvia et al. 2012; Kaplan et al. 2011; Jackson et al. 2003). Thus chronotherapies that aimed to (re)synchronize and stabilize biological rhythms (including sleep/wake patterns), such as bright light therapy, melatonin and its agonists, sleep deprivation, and social rhythm therapies, may be useful treatments in MDD (Germain and Kupfer 2008).

## 9.2 Bright Light Therapy

### 9.2.1 Why Use Bright Light Therapy in MDD?

First, we should remind that bright light therapy (BLT), also named phototherapy, is the first-line treatment for MDD with seasonal patterns. Its efficacy is well demonstrated and equivalent to typical antidepressants like selective serotonin reuptake inhibitors (SSRIs) (Nussbaumer et al. 2015). BLT is thus the cornerstone treatment of seasonal affective disorders (SAD). Interestingly, it has been recently demonstrated that BLT may also be useful in nonseasonal MDD. Indeed, BLT appeared efficacious and well tolerated in the treatment of adults with nonseasonal MDD, of moderate to severe intensity, with an effect size equal or superior to SSRIs (Golden et al. 2005; Lam et al. 2016).

First evidence of BLT efficacy comes from a case series recently published in 1984 by Rosenthal and colleagues (Rosenthal et al. 1984). Artificial bright light appeared more effective than dim light but also showed the effects of lengthening the photoperiod (defined as the length of light period during a night/day cycle) and suppressing the melatonin secretion (i.e., the sleep hormone that may have a depressive role) (Rosenthal et al. 1984). The antidepressant effect of BLT may come from its action on serotoninergic and catecholaminergic systems but also via an action on circadian rhythms by advancing the phase when using BLT in the morning (Lam et al. 1996; Neumeister et al. 1998; Lewy et al. 1987). These actions lead to a resynchronization of circadian rhythms and restore monoaminergic dysfunctions (Lewy et al. 2006). Indeed, it has been observed that morning exposures with BLT (inducing phase advance of circadian rhythms) is more efficient in reducing depressive symptoms than evening BLT (inducing phase delay) (Sack et al. 1990). Moreover, this action on circadian rhythms of phase advance may not be the sole explanation of its antidepressant efficacy, as phase advance has not consistently been correlated with therapeutic response (Lewy et al. 2006; Skene and Arendt 2006; Burgess et al. 2004). BLT seems to also directly act on monoaminergic transmissions. Indeed, it has been demonstrated that a quick serotonin and catecholamine depletion may reverse antidepressant effects of BLT in SAD (Neumeister et al. 1998). So BLT seems to have both an indirect action on MDD symptoms by a resynchronization of circadian rhythms and a direct action on monoaminergic dysfunctions.

A recent meta-analysis of randomized controlled trials (RCTs) confirmed that BLT is effective in treating seasonal MDD with a comparable effect size to antidepressant pharmacotherapies (8 studies, effect size = 0.84, 95% confidence interval = 0.60–1.08) (Golden et al. 2005) but also in treating in nonseasonal MDD (3 studies, effect size = 0.53, 95% CI = 0.18–0.89). Moreover, dawn simulation appears also effective in seasonal MDD (5 studies, effect size = 0.73, 95% CI = 0.37–1.08) (Golden et al. 2005). Nevertheless, this meta-analysis does not inform about the unipolar or bipolar profile of patients included. However, some specificities linked to bipolar disorders (BD), such as the manic switch, warrant evidence-based therapeutic guidelines and so deserve more studies in BD (Geoffroy et al. 2015b). Finally, in MDD, the combination of BLT and SSRIs may be superior to both monotherapies (Lam et al. 2016), and BLT antidepressant effects appeared sooner in seasonal (1–2 weeks) than in nonseasonal (4 weeks) MDD (Lam et al. 2016).

### 9.2.2 How to Treat with Bright Light Therapy?

The BLT use a device that produces a fluorescent light between 2000 and 10,000 lux and must have an ultraviolet filter to protect retina (Sohn and

Lam 2004). There are several kinds of BLT devices available, and a particular attention is needed to the quality of the device (international medical norms like 93/42/CEE). Standard BLT and dawn simulation devices have well demonstrated their efficacy (Golden et al. 2005). The light intensity to use for antidepressant effects depend on the length exposition. A similar effect is recognized for the following expositions: 2 h at 2000 lux, 1 h at 5000 lux, and 30 min at 10,000 lux (Tam et al. 1995). For a maximal exposition at 10,000 lux for 30 min, the BLT device should be placed at 30 cm from the subject and at eye level (Terman and Terman 2005). The goal is for retina photoreceptors to benefit from a direct exposition to BLT.

When using BLT? It is well demonstrated that a morning exposure is the most effective in MDD (Sohn and Lam 2004). Indeed, the antidepressant effect of BLT is demonstrated to be potentiated by early-morning administration in circadian time, optimally about 8.5 h after melatonin onset or 2.5 h after the sleep midpoint (Terman et al. 2001). For instance, a BLT exposition 7.5–9.5 h after melatonin onset allows to double the antidepressant response in comparison to an exposition 9.5–11 h after this melatonin onset (remission rates of 80% and 40% respectively) (Terman et al. 2001). Also, these scientific data may be difficult to translate in clinical practice with such precision. Nevertheless, the Composite Scale of Morningness (CSM) (Greenwood 1994; Caci et al. 2000) or the questionnaire of Horne and Ostberg (1976)), for instance, may be used in clinical practice to adapt the schedule of exposition to BLT. Indeed, it has been observed that the total score from these scales is correlated to the nocturnal melatonin secretion (Terman and Terman 2005). In routine, it is possible to propose the use of BLT directly when the subject wakes up at fixed time. Lastly, in patients with BD, it should be safer to avoid too early expositions to diminish the risk of manic switch (Geoffroy et al. 2015b; Sit et al. 2007). For at-risk subjects, a midday exposition (noon) should be the start of the BLT, and then exposures may be advanced in the situation of antidepressant inefficacy (Terman and Terman 2005).

How often and how long? The therapeutic response to BLT is generally quick (1–2 weeks), especially in seasonal MDD. BLT should be daily used and the treatment should include a minimum of 4-day exposure to at least 3000 lux in 1 h (or 1500 lux in 2 h) (Golden et al. 2005). It should be noted that a relapse can occur quickly upon discontinuation of BLT, and it is therefore advisable in these cases to continue BLT exposition until the period of natural remission in the situation of seasonal MDD. A strategy for introducing preventive BLT is also indicated for the following year during the at-risk period.

What are the side effects of BLT? Possible side effects of light therapy include headache, eye fatigue, nausea, and restlessness (Levitt et al. 1993; Labbate et al. 1994; Terman and Terman 1999). Furthermore, there does not seem to be any retinal toxicity associated with luminotherapy (Gallin et al. 1995). It is also well established, as previously mentioned, that BLT, like pharmacological antidepressants, can induce manic switch in patients with BD or at risk to BD (Kantor et al. 1991; Chan et al. 1994). The most important strategy in BD is thus to use BLT only with a mood stabilizer at therapeutic dosage, as for all antidepressants, especially in patients with BD I subtype (Sohn and Lam 2004; Golden et al. 2005). Regarding the type mood stabilizers, there are no solid data, but lithium seems to have a particular efficacy in reducing seasonal depressive symptoms (Sakamoto et al. 1995; Faedda et al. 1993). Another therapeutic adaptation in BD may be to shift the schedule of exposure to light therapy, for example, at midday, in case of tachypsychia, logorrhea, increased energy and activities, irritability, or aggressiveness (Sit et al. 2007; Leibenluft et al. 1995). Finally, BLT may precipitate or aggravate suicidal thoughts sporadically (Praschak-Rieder et al. 1997) but appears to have a protective antisuicidal effect in the majority of patients (Lam et al. 2000) both in unipolar (Sahlem et al. 2014) and bipolar patients (Benedetti et al. 2014).

Table 9.1 summarizes some of these guidelines for using BLT in seasonal or nonseasonal MDD.

**Table 9.1** Utilization of bright light therapy (BLT) in seasonal or nonseasonal depression

| | Bright light therapy in seasonal or nonseasonal depression |
|---|---|
| Therapeutic light flux | 2000–10,000 lux |
| Light devices | Bright light or dawn simulators |
| Time/lux | 30 min—10,000 lux<br>or<br>2 h—2000 lux<br>or<br>1 h—5000 lux<br>*If bipolar disorder: increase gradually starting with 15 min* |
| Position | Lamp at eye level<br>Distance of about 30 cm<br>Direct exposure |
| Frequency | Daily<br>7 days a week |
| Time of the day | Morning (when get up)<br>Fixed hours<br>If bipolar disorder: begin at midday, with progressively advanced schedule if ineffectiveness (Avoid schedules too early to prevent the manic switch) |
| Time to response | From 1 to 2 weeks |
| Treatment duration | Until reduction of depressive symptoms or until the period of natural remission if relapse at the stop (if seasonal depression) |
| Prevention | BLT a few weeks before the usual seasonal depressive relapse |
| Preventing manic switch | If bipolar disorder: BLT only with a mood stabilizer |
| Monitoring side effects | Headache, eyestrain, nausea, agitation, and manic switch |

## 9.3 Melatonin

### 9.3.1 Melatonin Physiology and Effects

Melatonin is considered as the "sleep hormone" because it promotes sleep (as it lowers central temperature and alertness) and is secreted at night by the pineal gland, following circadian rhythms, in response to day/night cycles (Claustrat et al. 2005; Claustrat 2009). In addition, melatonin, even at the small physiological dose, may lead to phase advance or delay (e.g., advance or delay of sleep/wake cycles) depending on when it is administered in relation to its response curve—i.e., before or after the central temperature dip (Lewy et al. 2006). Melatonin, or its agonists, binds to its specific melatonergic receptors (MT1 and MT2). Melatonin acts, at the molecular level, by stabilizing the circadian rhythms of the neurotransmitter systems involved in the pathophysiology of depression and sleep/wake cycles (Anderson et al. 2016). Serotonergic, dopaminergic, and noradrenergic neurotransmitters regulate mood and follow circadian rhythms in their secretion, catabolism, and expression of their receptors (Milhiet et al. 2014). The synthesis of melatonin in the pineal gland derives also directly from the catabolism of serotonin (Takahashi et al. 2008). This synthesis of melatonin from serotonin is regulated and synchronized by suprachiasmatic nuclei (SCN), which are the central "pacemaker" of circadian rhythms (Takahashi et al. 2008). It has also been observed that serotonin metabolites, such as tryptophan or 5-hydroxyindoleacetic acid (5-HIAA), exhibit circadian fluctuations in their concentration (Kennedy et al. 2002). Indeed, tryptophan shows an increase in overnight rates and a decrease at midday (Kennedy et al. 2002). It has also been demonstrated that therapeutic doses (well above physiological doses) of melatonin result in the inhibition of serotonin reuptake in platelets (Valevski et al. 1995). In addition, dopamine has a major role in circadian rhythms, especially in the retina as a chemical messenger of adaptations

to light (Witkovsky 2004). During this process, the amacrine cells of the retina release dopamine which activates in return the dopaminergic receptors located throughout the retina (Witkovsky 2004). The noradrenergic neurotransmission is also involved in these processes. Indeed, the maximum concentrations of melatonin and its enzyme arylalkylamine *N*-acetyltransferase (AANAT) are related to changes in the beta-adrenergic receptor activity of the pineal gland (Yocca et al. 1983), where the noradrenaline appears necessary to synthesize the melatonin secreted by the pineal gland (Simonneaux and Ribelayga 2003).

In conclusion, melatonin levels and its circadian secretion, through serotonergic, dopaminergic, and noradrenergic systems, are directly involved in the regulation of mood via the retino-hypothalamic-pineal tract.

### 9.3.2 Why Melatonin May Be Useful in Depression?

Interestingly, the exogenous melatonin has shown efficacy in (1) treating chronic insomnia with modest efficacy (Buscemi et al. 2005; Ferracioli-Oda et al. 2013); (2) treating phase delay syndrome, where it is part of the therapeutic recommendations (van Geijlswijk et al. 2010); and (3) improving sleep quality on a set of objective parameters such as sleep latency and total sleep time (Ferracioli-Oda et al. 2013). Melatonin also showed an interest in psychiatry as an adjunctive treatment for children with autism spectrum disorders to improve sleep and behavioral disturbances (Rossignol and Frye 2011; Doyen et al. 2011; Cortesi et al. 2010). Finally, melatonin appears useful in remitted BD (euthymic) to prevent mood relapse when a complaint of insomnia, poor quality of sleep, or phase delay syndrome is associated (Geoffroy et al. 2015a).

But is melatonin effective as an antidepressant? The scientific data are less robust here, at least in monotherapy use on mood symptoms. Nevertheless, melatonin has shown antidepressant properties in animals (Rogers et al. 2003), as well as a decrease in chronic stress-related side effects (Kopp et al. 1999). This contrasts with data in humans which tends rather to show that melatonin in monotherapy does not appear to be sufficiently effective in MDD (Carman et al. 1976), even if this is associated with improved sleep and stabilization of sleep/wake rhythms (Dalton et al. 2000). However, melatonin monotherapy demonstrated efficacy in the treatment of MDD when a phase delay syndrome is associated (Rahman et al. 2010). In addition, the use of melatonin as an adjunctive treatment to traditional antidepressant strategies appears to potentiate the effect of these antidepressants effectively (Wirz-Justice 2009). Same observations are made for melatonin agonists, which improve sleep quality, are effective treatment of insomnia and phase delay syndrome (Lemoine et al. 2007; Roth et al. 2006; Rajaratnam et al. 2009; Reynolds et al. 2005). In the bipolar MDD, melatonin and its agonists also appear to be useful as adjuvant antidepressant therapies when there is a complaint of insomnia or a phase delay syndrome (Geoffroy et al. 2015a).

Agomelatine has a special place in these antidepressant strategies as, in addition to being a selective melatonin receptor agonist (MT1 and MT2), it acts as a serotonin receptor antagonist (5-HT2B and 5-HT2C) (Millan et al. 2003). Agomelatine, at doses of 25–50 mg, demonstrated a chronobiotic effect (almost similar to melatonin) but also clinically significant antidepressant and anxiolytic effects in humans (Hickie and Rogers 2011; Dubovsky and Warren 2009; de Bodinat et al. 2010; Lôo et al. 2002). A recent meta-analysis confirmed these effects by analyzing 20 published and unpublished studies demonstrating that agomelatine in MDD treatment is more effective than placebo and equivalent to other pharmacological antidepressants (Taylor et al. 2014). This antidepressant effect of agomelatine appears to be sustained over the long term. However, it should be highlighted that there are few studies with often weak methodological qualities (Guaiana et al. 2013). Agomelatine appears to have less side effects than conventional pharmacological antidepressants because it does not stimulate the 5HT-2A serotonergic receptor, which is responsible for sexual dysfunction and

gastrointestinal disturbances. However, it is important to note that there is a possible hepatotoxicity of agomelatine (Gahr et al. 2013, 2014). This hepatotoxicity resulted in the abandonment of its use in the United States.

In conclusion, melatonin has (at least) an interest as an adjuvant treatment for unipolar or bipolar MDD when there are sleep disorders (in particular insomnia) or a phase delay syndrome. Agomelatine also induces a resynchronization of circadian rhythms and an improvement in sleep parameters, with an antidepressant effect equivalent to other pharmacological antidepressants. Also the possible hepatotoxicity of agomelatine requires close monitoring.

## 9.4 Sleep Deprivation

As BLT, sleep deprivation or more commonly called "wake therapy" is part of chronobiological interventions that are not used yet in clinical practice. Currently, sleep deprivation appears in international guidelines for MDD treatments (Ravindran and da Silva 2013; Ravindran et al. 2009) as an alternative treatment, in combination with the recommended pharmacological therapies and psychotherapies. While it may seem paradoxical to prevent a patient from sleeping during a major depressive episode, this therapy is one of the most interesting chronobiological interventions for practitioners, and its immediate antidepressant effect has now been recognized for over 30 years (Schulte 1959; Wehr et al. 1979; Wirz-Justice and Terman 2012).

Sleep deprivation is indicated in the treatment of MDD. This therapy consists in keeping the patient awake for periods ranging from 3 to 4 h in the second part of the night (partial deprivation) to more than 40 h (total deprivation) (Giedke et al. 2003). This method has shown surprising positive results with rapid mood improvement (in 24–48 h) in 50–60% of patients in a MDD, independently of the subtype of depression (Benedetti et al. 2007). Sleep deprivation has shown an interest in MDD among unipolar disorder, bipolar disorder, postpartum depressive episode, schizoaffective disorder, or in major depressive episode in elder patients (Wehr 1990; Wu and Bunney 1990; Cole and Muller 1976; Leibenluft and Wehr 1992; Wirz-Justice and Van den Hoofdakker 1999; Parry et al. 2000). Predictors of clinical response to sleep deprivation have been identified and appear to be similar to the predictive clinical and biological clues of a good response to antidepressant treatments. They include the presence of high daytime mood variability (Haug 1992), "endogenous" type of depression (Vogel et al. 1975) (i.e., absence of identified triggering factor, but this endogenous characteristic is no longer used: studies have shown that no clinical or para-clinical marker actually differentiates "endogenous" depressions from "exogenous" depressions), an abnormal response to the dexamethasone test (King et al. 1982), or decreased levels of inflammatory markers (Francesco Benedetti et al. 2002). Underlying genetic variations also contribute to this response variability to sleep deprivation (Benedetti et al. 1999b, 2010).

The only contraindication to sleep deprivation is the existence of underlying epilepsy (Nakken et al. 2005). Furthermore, patients having this therapy should generally undergo a particularly careful medical examination; stress sometimes felt before or during this therapy may indeed be at risk of decompensating of chronic diseases, especially cardiovascular. Precautions regarding certain activities (e.g., such as driving) are also to be taken into account (risk of excessive daytime sleepiness caused by sleep deprivation).

One of the main obstacles to the implementation of this therapy in current clinical practice is probably the short and ephemeral nature of the improvement: 80% of patients' relapse after sleeping the next night or even after naps during the night of sleep deprivation (Svestka 2008). In order to limit the risk of relapse and extend this ephemeral antidepressant effect, several strategies have been proposed (Monteleone et al. 2011). The one that appears to be the more efficient is the sleep phase advance method. This treatment involves advancing bedtime at 5 p.m. in the afternoon, after a complete deprivation of sleep, and then keep advancing progressively bedtime 1 h per day (6 p.m., then 7 p.m., etc.),

this over a total duration of 7 days. This method would prevent relapse in 60–80% of patients who responded to sleep deprivation (Vollmann and Berger 1993; Riemann et al. 1996; Albert et al. 1998; Benedetti et al. 2001a). Moreover, the phase advance over a period of 3 days, more simple in clinical practice, would be as effective as a period of 7 days (Voderholzer et al. 2003). Another strategy was to consider sleep deprivation as a sequential treatment but with inconsistent results. A cycle would be defined as each period of sleep deprivation followed by restarting sleep. This treatment was carried out from one to six cycles over a period of about 4 weeks (Wirz-Justice 2003).

There is also growing evidence in the literature of the interest of combining sleep deprivation with drug therapy. Two open studies have shown that the combination of antidepressant therapy with antidepressant therapy was more effective than treatment alone (Caliyurt and Guducu 2005; Wiegand et al. 2001). Reynolds et al. showed that sleep deprivation was more effective than selective serotonin reuptake inhibitors and the combination of both (Reynolds et al. 2005). Some randomized studies are also in favor of the positive impact of this association: the addition of treatments such as lithium salts (Szuba et al. 1994; Benedetti et al. 2001a, 2014) or the 5-HT1A pindolol antagonist (Smeraldi et al. 1999) would allow to maintain this antidepressant effect of sleep deprivation. Its association with non-pharmacological therapies such as morning BLT, without or with concomitant pharmacological treatment (see Sect. 9.6), would also have shown positive results in maintaining this antidepressant effect (Neumeister et al. 1996; Colombo et al. 2000; Loving et al. 2002; Echizenya et al. 2013). A randomized study also suggested the combination of partial sleep deprivation with repetitive transcranial magnetic stimulation (rTMS) and showed maintenance of the antidepressant effect of sleep deprivation at 4 days in the group with active rTMS (Eichhammer et al. 2002). This finding was not replicated in a recent study (Kreuzer et al. 2012).

Most studies have shown rapid and sustained thymic improvement in patients with MDD in unipolar disorders, but such results are also found with bipolar depressions. For patients with BD, the switch rates to (hypo)manic episodes were not greater than those observed with antidepressants (Colombo et al. 2000). Overall, chronobiological interventions seem to be even more appropriate for these patients with BD. We know indeed that anomalies of the circadian rhythms constitute a fundamental component of the disorder (Bellivier et al. 2015). Benedetti et al. showed a significant efficacy in bipolar depression of the combination of sleep deprivation, phase advance, and concomitant lithium treatment (Benedetti et al. 2001a, 2014), as well as encouraging results for the combination of sleep deprivation with light therapy (Benedetti et al. 2005). The recent study by Wu et al. (2009) included a sample of 49 bipolar patients treated with mood stabilizers and antidepressants in combination of three sequences of chronobiological treatments (sleep deprivation, light therapy, and phase advance). Patients showed a more rapid and sustained improvement (decreasing depression scores) than patients treated with drug treatments alone on Day 2 of the procedure and up to 7 weeks. Finally, a study suggests a link between chronotype and antidepressant effect of sleep deprivation: in healthy volunteers, sleep deprivation would be beneficial in subjects with a vesperal profile (so-called evening/night owls), whereas it would be rather deleterious in terms of mood for those said morning type (Selvi et al. 2007). This result seems interesting to take into account in the case of euthymic bipolar patients, who, as we know, present their own circadian characteristics compared to healthy subjects, with a chronotype rather of the vesperal type (Giglio et al. 2010). Up to date, we do not have long-term studies, since patients already have major difficulties in tolerating even partial sleep deprivation. The effect of this therapy has also been evaluated in acute thymic episodes, but we do not yet know what the benefit would be for periods of remission. The data in terms of security also remain insufficient.

Thus, according to current scientific data, treatment with sleep deprivation shows a level 2 of evidence, as an adjunct treatment, in the acute management of MDD characterized by mild to

moderate intensity, and some data are in favor of its benefit in MDD with seasonal pattern, as well as depressive episodes in ante- and postpartum. The guidelines recommend it only as a third line of treatment, because of practical difficulties and tolerability in the medium and long term (Wirz-Justice and Terman 2012; Echizenya et al. 2013; Ravindran and da Silva 2013). Nevertheless, it seems important to emphasize that non-pharmacological therapies such as BLT and sleep deprivation have strong advantages as adjuvants, in terms of flexibility and patient acceptability. The side effects reported remain rare, and minimal, and can be controlled by simple and close monitoring. These therapeutic strategies also have the advantage of their rapid delay in action and can make it possible to considerably reduce the length of hospitalization and thus cost.

Future studies are needed to identify factors of individual variability in response to this therapy (age, gender, light sensitivity, severity of the disorder, sleep characteristics such as sleep quality and architecture) and the most effective modalities of application (right time of intervention in the course of the disorder, combinations of treatments, etc.).

## 9.5 Psychotherapies Focused on Circadian Rhythms and Sleep

To date, there is a large body of scientific evidence highlighting the value of psychotherapies in combination with pharmacological treatments in depressive episodes management (Vieta et al. 2009). They all have common goals, including improved adherence, acceptance of the disease, and overall a better quality of life for patients. Several types of psychosocial therapies exist, and they differentiate by their underlying theoretical models, their modalities, and their delay in the course of the disorder (during an acute episode or in a period of euthymia). Nevertheless, the stabilization of social rhythms is part of most psychosocial interventions' objectives used in mood disorders.

### 9.5.1 Interpersonal and Social Rhythm Therapy (IPSRT)

Interpersonal and social rhythm therapy (IPSRT) was developed by Ellen Frank 15 years ago (Frank et al. 2000). This approach is based on some preliminary scientific evidence, including the already well-established efficacy of interpersonal therapies (TIP) for depressive episodes in unipolar disorder (Cuijpers et al. 2014), as well as in circadian rhythm anomalies in patients with bipolar disorders (Murray and Harvey 2010). This type of intervention particularly targets the regulation and stability of social and circadian rhythms (control of daily routines and sleep) and integrates a behavioral approach as well as strategies for managing interpersonal relationships and stressful life events (Swartz et al. 2009).

IPSRT includes three types of interventions, interpersonal therapy, social rhythm therapy, and psychoeducation, with a focus on accepting long-term pathology. It begins with the principles of interpersonal therapy and its modalities. It is contracted and limited in time and allows to work on the links between life events, interpersonal relationships, social rhythms, and depressive symptoms. IPSRT comprises three phases: an initial phase, an intermediate phase, and a final phase (Bottai et al. 2010).

The initial phase should be started as soon as possible or even during an acute episode. It sums up the course of the disease, biographical elements, to have an overview of his interpersonal relationships and the different life events that have marked the patient's journey. It is also a time for initiating measures of psychoeducation, with informations given about bipolar disorder, its symptoms, comorbidities, as well as the treatments. The assessment of the patient's circadian and social rhythms is also carried out with evaluation of synchronizers and desynchronizers (substance abuse, jet lag, work, and family obligations). This evaluation is based on a tool called the Social Rhythm Metric (SRM), which can be compared to a valuable weekly agenda for the patient and the psychiatrist. This way, it is possible to collect important informations on a weekly basis: time of day, time of first contact

with a person, time of first activity, and mood and level of energy, self-assessed by the patient. Life events are also specified. This tool has the advantage of allowing the patient to appropriate this evaluation phase and to promote the awareness of the disorder and of his own rhythms.

The intermediate phase has several objectives: to work on the acceptance of the disease, the organization of social rhythms, and interpersonal therapy (problem-solving, evaluation of interpersonal dysfunctions). The development of social rhythms is of particular interest to us and represents one of the most important axes of this therapy. The objective is to look with the patient the disruptors of daily routines and circadian rhythms, such as cultural events, vacations, professional obligations (shift work), family, or the use of psychoactive substances. The therapist then establishes with the patient achievable objectives to regulate his rhythms, such as gradually adjusting his sleeping/waking schedules, in order to ensure a good sleep hygiene. Careful attention is given about linking social rhythms, sleep, and mood swings.

Finally, the final phase takes stock of the objectives previously established and worked, to consider a possible maintenance phase (consolidation of acquired knowledge and long-term patient support).

Scientific literature supports the efficacy of IPRST in combination with drug therapy for prevention of depressive relapses, extension of free intervals between episodes, and the better overall functioning of patients who have had these interventions (Miklowitz et al. 2007). The randomized trial (Frank et al. 2005) compared a sample of 175 bipolar I-type patients who followed for 2 years two types of psychotherapy: first, an acute phase where patients receive IPRST or intensive clinical management (ICM) and then, during the maintenance phase, either the patients having the same type of therapy or alternated with the other. This study showed faster remission following a depressive episode in IPRST patients compared to the control group, regardless of maintenance therapy. These patients also had a better stabilization of their daily rhythms, correlated with the quality and duration of remission. Two controlled studies (Frank et al. 2007, 2008) followed, confirming the interest of IPRST and proposing a comprehensive good practice manual for IPRST in bipolar disorder (Frank 2005).

A recent randomized controlled study also showed efficacy of IPRST combined with pharmacological treatment in a 49 younger group of patients with BD (aged 15–36 years and mostly with bipolar I-type disorder): a decrease in depressive and manic symptoms was observed but appeared to be no different from the control group of patients receiving another type of specialist supportive care, combining psychoeducation and supportive psychotherapy (Inder et al. 2015). Finally, some studies (but including small samples) have specifically focused on the efficacy of IPRST in bipolar depression (Swartz et al. 2012; Hoberg et al. 2013). Swartz et al. were the first to compare IPRST as monotherapy versus drug therapy (here, quetiapine) as monotherapy (Swartz et al. 2012). This randomized pilot study involved a sample of 25 patients with type II bipolar disorder and did not show any difference between the two groups, although both had a decrease in depressive symptoms at 12 weeks of follow-up. All these results, although preliminary, suggest the potential benefit of IPRST on the improvement of depressive symptoms and in the prevention of relapses. Here again, additional studies will be essential to identify the most effective methods of application of this therapy (duration, frequency, target population of patients who can benefit from it, etc.).

### 9.5.2 Cognitive Behavioral Therapies (CBT)

Common cognitive behavioral therapies (CBT) have demonstrated their efficacy in combination with drug therapy in the management of mood disorders. They include psychoeducational measures (see Table 9.2), as well as common CBT techniques, particularly targeting dysfunctional patterns of thinking for each patient, and problem-solving and stress management strategies. Whether in the form of short interventions (integrated into daily clinical practice or in a few

**Table 9.2** Tips for good sleep habits

| |
|---|
| – When it's bedtime: |
| Generally: create a comfortable place and atmosphere for sleeping |
| • Wear comfortable clothing/pajamas |
| • Organize your bed and bedroom in the most pleasant way possible: clean sheets and pillows, comfortable and rather firm mattresses |
| • Aerate your bedroom before bedtime |
| • The ideal room temperature for a good quality of sleep is 18 °C |
| • Regarding baths or showers: avoid the hot bath just before going to bed if it wakes you up (*but* there is no absolute rule as it can promote falling asleep in others; nevertheless, it makes frequently increased body temperature and does not promote falling asleep) |
| • Noise and light: be sure to isolate yourself as much as possible from noise, from outside light, or from the standby lights of electrical appliances, e.g., laptops, diodes, alarm clocks, television, etc. |
| • Do not allow pets in your room |
| • Dine light and avoid protein foods |
| – When you wake up: |
| • Wake up at a fixed time every day; this promotes good sleep/wake cycles |
| • Get out of bed when you are awake |
| • Do not work in bed |
| • Expose yourself to the light as soon as you are awake. Natural light in summer or artificial light in winter |
| • The body temperature has cooled overnight: Dress, have a breakfast with a hot drink and a hot shower in order to raise the body temperature |
| • Promote physical activity during the day (but avoid sport at the end of the day or in the evening); this improves the quality of sleep |

sessions), or conventional CBT over several months, data from the scientific literature support a reduction in the recurrence of depressive and manic episodes, with longer euthymic phases, better social functioning, and better adherence to treatment (Vieta et al. 2009).

A more specific approach to insomnia, called cognitive behavior therapy for insomnia (CBT-I), has been identified by the American Academy of Sleep Medicine as the first-line treatment in insomnia (Morgenthaler et al. 2006). This therapy includes several interventions: a step of psychoeducation ensuring a good sleep hygiene with learning to control the stimuli related to sleep, a short sleep deprivation step, and finally specific cognitive and behavioral work, focusing particularly on (false) beliefs and perceptions about sleep and its mechanisms (beliefs about optimal sleep duration, consequences of insomnia, etc.). Sleep hygiene education also includes a briefing time on the effects of caffeine, alcohol or other psychoactive substances, as well as physical exercise, on sleep. Advice is also given on sleep conditions, including light, noise, and room temperature. A summary of sleep hygiene rules is provided in the following table. Control of sleep-related stimuli typically includes four objectives to be achieved for the patient: (1) use the bed and bedroom only for sleep or sexual activity (do not read or watch TV in bed); (2) go to bed only when he is sleepy; (3) leave the room if he can't fall asleep, and return to bed within 15–20 min only if he is sleepy; (4) get up at the same time every morning. Other strict measures on time spent in bed are also applied. Excessive time spent in bed is indeed a factor in maintenance of sleep disorders and leads to more nocturnal awakenings and anxious ruminations. A time spent in bed is thus decided with the patient, called "sleep window" according to the duration of sleep per night. The goal is to improve the sleep efficiency to 85–90%, defined by the total sleep time divided by the time spent in bed.

The efficacy of CBT-I in insomnia has long been well demonstrated in randomized controlled trials (Hofmann et al. 2012; Morin et al. 2006; Riemann et al. 2015). It has thus shown an equivalent or even greater efficacy to short- and long-

term pharmacological treatment, with a decrease in nocturnal awakenings, a better sleep efficiency, and an improvement in the subjective feeling of sleep quality. In addition, there is increasing scientific evidence for its efficacy in the treatment of sleep disorders in various psychiatric disorders (mood disorders, addictions, anxiety disorders) (Soehner et al. 2013; Swanson et al. 2013; Talbot et al. 2014; Myers et al. 2011) and nonpsychiatric disorders (cancer, chronic pain, HIV infection) (Smith et al. 2005; Kamath et al. 2015). In addition, several variants of CBT-I have recently developed, including shorter therapies (Shimodera et al. 2014; Troxel et al. 2012), electronic versions on the Internet (Babson et al. 2015; Blom et al. 2015; Gosling et al. 2014; Cockayne et al. 2015), or "step-by-step" therapy ranging from more autonomous techniques such as personal development to more individualized and personalized psychotherapies (Ho et al. 2015; Espie 2009).

Regarding MDD, insomnia may be one of the symptoms of an acute episode or be comorbid of a mood disorder. In the case of associated depressive symptoms, available studies support the efficacy of CBT-I with improved sleep and mood (Perlis et al. 2000; Taylor et al. 2007; Manber et al. 2008, 2011). The study by Bei et al. suggests a possible role of the chronotype in the response to CBT, vesperal-type patients showing less improvement on depressive symptoms (Bei et al. 2015). Finally, very few studies have focused on the efficacy of CBT-I in bipolar disorders (Kaplan and Harvey 2013; Harvey et al. 2015; Steinan et al. 2014). The Kaplan and collaborators study showed an improvement in insomnia symptoms and quality of sleep (via subjective measures) after 8 weeks of CBT-I on a sample of 15 bipolar I-type patients (Kaplan and Harvey 2013). This improvement was already present after the first stage of general psychoeducation on sleep hygiene. Two patients presented symptoms of hypomania after control of environmental stimuli sessions, as well as two of the five patients having achieved sleep deprivation, however following an independent life event. Finally, Harvey et al. compared 30 patients with bipolar disorder undergoing CBT-I and 28 patients with bipolar I disorder with psychoeducation (control group) for 8 weeks and with a 6-month evaluation (Harvey et al. 2015). The authors proposed a CBT-I specific for bipolar disorder (CBTI-BP). It was characterized by the combination of IPSRT elements (see above), motivational interviews, reduction of the duration of sleep to 6.5 h maximum (in order to limit the risks of mood shift during sleep deprivation), and special attention to exposure to light (decreased light and stopping stimulating activities 30–60 min before bedtime, if necessary light therapy in the morning in case of depressive symptoms). This study showed encouraging results with improved sleep and mood in both groups and for patients in the CBTI-BP group, higher rates of remission, and especially a lower risk of thymic relapse (relapse rate of 13.6% versus 42.2% in the control group). These preliminary data are in favor of a positive impact of CBT on sleep disorders, thymic symptoms, and the course of mood disorders. However, more randomized controlled studies with larger samples are needed. These will help in answering the questions of feasibility and tolerance and to define the place of this therapy in the overall care of the patient with MDD.

## 9.6 Combination Strategies

Four types of chronotherapies have thus been shown to be effective in the treatment of MDD: BLT, agomelatine, sleep deprivation, and phase advance. All of them have shown a rapid antidepressant effect, but for some do not stay on the long-term, especially for sleep deprivation and phase advance. In addition of these four chronotherapies, psychoeducation measures focused on sleep and rhythms are also effective and should be proposed.

First, combining chronotherapies with pharmacological antidepressants would allow benefiting both from a rapid antidepressant effect (not possible with conventional antidepressants with a typical delay of action of 2–3 weeks) that could subsequently be maintained by the pharmacological treatment already prescribed. BLT combined with an antidepressant (SSRIs) demonstrated a greater synergistic effect than antidepressant

monotherapy or BLT alone in seasonal and non-seasonal unipolar MDD (Loving et al. 2002; Lam et al. 2016). Sleep deprivation has also shown a superior effect when combined with an antidepressant with a long-lasting effect (Loving et al. 2002). Its association with different types of antidepressants has been studied: serotonergic antidepressants (Smeraldi et al. 1999; Benedetti et al. 1997; Martiny 2004), noradrenergic (Shelton and Loosen 1993), serotonergic and noradrenergic (Wirz-Justice et al. 1976; Elsenga and van den Hoofdakker 1982; Kuhs et al. 1996), and dopaminergic (Benedetti et al. 2001b). However, it is demonstrated that the risk of manic switch is also increased with these two strategies of combination. Thus, if these strategies are considered, they should be used with extremely cautious, especially in individuals with BD (close monitoring or even hospitalization). Lithium therapy remains the first-line treatment in case of BD but also in the long-term maintenance of the action of chronotherapies such as sleep deprivation alone or in combination with light therapy and/or phase advance (see below) (Szuba et al. 1994; Colombo et al. 2000; Benedetti et al. 1999a, 2001a, 2005). Indeed, lithium is a well-known chronobiologic agent, and its therapeutic action has been related to its ability to alter circadian rhythms, including an improvement of day-to-day rhythmicity (Moreira and Geoffroy 2016; Geoffroy et al. 2016).

A bi-chronotherapy combining sleep deprivation with BLT demonstrated a synergistic effect and so can be considered in cases of severe or resistant MDD (Benedetti and Colombo 2011). The advantage of combining sleep deprivation with BLT is also to benefit from a rapid and powerful antidepressant action in 24–48 h of sleep deprivation and to maintain this effect by BLT (Neumeister et al. 1996). The team of Benedetti and collaborators, pioneers in the therapeutic use of sleep deprivation, propose for this combination a schema of a night of total sleep deprivation followed by a night of sleep recovery, this repeated three times. Nevertheless, in some cases partial sleep deprivation may be preferred. The main side effects are daytime sleepiness and manic switch (Benedetti and Colombo 2011). Thus, sleep deprivation should only be used in BD with close monitoring of side effects. Sleep deprivation has thus been associated with BLT in several studies with promising results when including individuals with BD nonseasonal MDD and then associated with lithium and antidepressants (Colombo et al. 2000; Loving et al. 2002; Benedetti et al. 2005, 2014). It should be emphasized that the meta-analysis of Tuunainen and collaborators indicated that there was an efficacy of this bi-chronotherapy only in patients that respond first to sleep deprivation (Tuunainen et al. 2004).

Finally, several studies have shown encouraging results in favor of the association of sleep deprivation followed by a phase advance in patients with unipolar MDD (Berger et al. 1997; Voderholzer et al. 2003) and bipolar MDD in combination with lithium (Benedetti et al. 2001a; Wu et al. 2009). The study of Wu and collaborators also included a BLT procedure, so the combination of the three chronotherapies (tri-chronotherapies) in addition to the lithium treatment. They showed that sleep deprivation supported by BLT and phase advance was superior in efficacy for improving depressive symptoms compared to pharmacological treatment alone, as soon as the second day of tri-chronotherapies, with an effect maintained for 7 weeks. In this model proposed, the intervention began with a night of sleep deprivation from 11 p.m. until 6 p.m. the following day (33 h of awakening). The BLT started the day after the end of the sleep deprivation session. Exposure to light was during 2 h at 5000 lux per day for 3 days. The phase advance began on the first night after sleep deprivation, with the first night that started at 6 p.m. (until 1 a.m.), then at 8 p.m. on the second night (until 3 a.m.), and on the third night at 10 p.m. (until 5 a.m.).

These strategies of combination of therapies thus seem to show interesting results to potentiate their effectiveness and facilitate their place in the current MDD treatment strategies.

Table 9.3 is summarizing the different types of interventions and their expected response.

**Table 9.3** Chronotherapies that are effective in the treatment of major depressive disorders (Adapted and modified from Benedetti et al. 2007)

| Type of intervention | Therapeutic response | |
|---|---|---|
| *Monotherapy* | *Latency* | *Duration* |
| Bright light therapy | A few days | Weeks/months |
| Agomelatine | Weeks (2 weeks min) | Weeks/months |
| Sleep deprivation | A few hours | Short (just after sleep recovery) |
| Phase advance | 1–2 days | Tolerance after 2 weeks |
| *Combination* | *Latency* | *Duration* |
| Bright light therapy + pharmacological treatment | A few days | Months |
| Sleep deprivation + phase advance | A few hours | Decreasing efficacy after stopping (1 week) |
| Sleep deprivation + pharmacological treatment | A few hours | Months |
| Repeated sleep deprivation | A few hours | Decreasing efficacy after stopping (1 week) |
| Bright light therapy + sleep deprivation + phase advance + pharmacological treatment | A few hours | Months |

**Conclusion**

Four types of chronotherapies have shown efficacy in the treatment of MDD both in unipolar or bipolar disorders and seasonal or non-seasonal subtypes: BLT, agomelatine, sleep deprivation, and phase advance. Melatonin and its agonists have efficacy as an adjuvant treatment in unipolar or bipolar MDD, especially when insomnia or delayed phase syndrome are associated. Psychotherapies focused on sleep or rhythms (IPSRT, CBT-I) are effective on sleep disorders, depressive symptoms, and the prevention of depressive relapses. The combination of several chronotherapies is possible and allows to potentiate the effects of each, with the relevant combination of rapid action chronotherapies to longer action chronotherapies (such as BLT + sleep deprivation). The risk of manic switch must be monitored in individuals with BD or at risk. These strategies of antidepressant chronotherapies in individuals with BD are to be carried out with a mood stabilizer, where lithium seems to have interesting interactions.

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# Suicidal Behavior in Depression: A Severe Form of Depression or a Distinct Psychobiology?

10

Subin Park and Jin Pyo Hong

## 10.1 Introduction

There is compelling evidence about the strong association of depressive disorder with suicidal behavior and suicidal death. Over 90% of suicide victims had at least 1 psychiatric disorder, and in particular, about 60% of victims had affective disorders including depression (Cavanagh et al. 2003; Henriksson et al. 1993; Robins et al. 1959). Given the strong association between suicidal behaviors and depression, it is important to identify risk factors for suicidal behaviors in depression.

Recently, suicidal behavior disorder has been included as an independent clinical diagnostic entity in Sect. 3 of DSM-5 (American Psychiatric Association 2013). This change is distinctive from current nosology in which suicidal ideation and attempts were perceived as the complication of psychiatric disorders rather than an independent disorder and accordingly were included as one of the symptoms of major depressive disorder (MDD) or borderline personality disorder (Oquendo and Baca-Garcia 2014). This change has been demanded to address suicidal behavior as a distinct condition of research to identify its specific psychological and neurobiological mechanisms and also as an independent treatment option (Aleman and Denys 2014). This change reflects the perception of suicidal behavior as an independent clinical disorder from other psychiatric disorders.

In the same vein, suicidal behavior in depression may not just be a severe form of depression, given that the severity of depressive symptoms does not distinguish suicidal and non-suicidal depressive patients (Malone et al. 1995; Mann et al. 1999). In addition, although MDD is one of the strongest risk factors of suicidal behavior (Kessler et al. 1999), only a small fraction of people with MDD get engaged in suicidal behaviors: the lifetime suicide risk is estimated about 3.4% (Blair-West et al. 1999). Then why some depressed patients are engaged in suicidal behavior, while many others are not? To answer this question, distinct predispositions to suicidal behaviors in depression should be understood (Mann 2003).

The stress-diathesis model was regarded as the most widely accepted hypothesis for understanding suicidal behavior. It describes suicidal behavior as the interplay between a stressor (e.g., an acute psychiatric crisis or a negative life event) and an individual vulnerability to suicide, perhaps resulting from a genetic predisposition and

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epigenetic alterations related to early-life stressful events (Salloum 2017). In this part, we will review previous research findings about suicidal disposition among patients with depression.

## 10.2 Psychological Dispositions

Pessimism and hopelessness increase the risk of suicidal behavior in depression (Beck et al. 1989; Hawton et al. 2013; Schneider et al. 2001). Beck et al. (1985) noted that only the extent of hopelessness among other variables predicted the eventual suicide of hospitalized patients with suicidal ideation after 10 years. This predictive validity of hopelessness was replicated to outpatients as well (Beck et al. 1989): more than 90% of suicide completers were from a high-risk group identified by cutoff scores of hopelessness 6 years ago, suggesting that hopelessness may be a sensitive indicator of prospective suicide completion. In particular, a high level of hopelessness remaining even after the remission of depression was associated with suicide attempts (Hind et al. 1994).

Accumulated evidence has shown a greater level of impulsivity and aggressiveness among suicide attempters or suicide victims (Brent et al. 1994; Dumais et al. 2005; Mann et al. 1999; Perroud et al. 2011). When comparing suicide attempter and non-attempter among depressed patients, there was no significant difference in the severity of depression and other general psychiatric symptoms between two groups, but suicide attempters had a higher level of impulsivity both before and after antidepressant treatment (Corruble et al. 1999). Impulsivity and aggressiveness were the key differences in the comparison between suicide completers and living depressed patients as well: the suicide completers with MDD had a higher level of lifetime impulsive and aggressive behaviors compared to living depressed patients (Dumais et al. 2005). Furthermore, Stein et al. (1998) found that a high level of aggressiveness was predictive of repetitive suicide attempts, which may increase the risk of suicide completion. This converging evidence demonstrates that impulsive and aggressive traits are the key markers for suicidal behaviors in depression. However, this association between suicidal behaviors and impulsivity and aggression may be significant only among younger adults (Conner et al. 2004; Dumais et al. 2005; Perroud et al. 2011).

This association of impulsive and aggressive traits with suicidal behavior may explain the high comorbidity with Cluster B personality disorder and substance abuse among depressive suicide attempters or completers (Dumais et al. 2005; Mann 2003). Dumais et al. (2005) noted that higher impulsivity and aggression among suicide completers with MDD were linked to the comorbidity with Cluster B personality disorders and alcohol abuse and dependence. Furthermore, Brodsky et al. (1997) examined the association of suicide attempts with specific traits of BPD and found that impulsivity was the only characteristic of BPD that was related to the increased number of suicide attempts.

Hostility is another temperament associated with suicide attempt (Weissman et al. 1973). When comparing temperament traits between suicide attempters and non-attempters with major depression, hostility was strongly associated with suicidal behavior in patients with major depression (Christodoulou et al. 2016; Paykel and Dienelt 1971; Pendse et al. 1999) and other psychiatric disorders (Brezo et al. 2006; Ferraz et al. 2013; Michaelis et al. 2004).

Cognitive rigidity has been identified as a predictor for suicidal behaviors in depression (Richard-Devantoy et al. 2012). According to cognitive rigidity hypothesis, mental inflexibility evidenced by diminished executive functioning is associated with suicide ideation and attempts among depressed patients (Dombrovski et al. 2008; Keilp et al. 2001; Marzuk et al. 2005; Patsiokas et al. 1979). By comparing depressive patients with and without suicide attempt history and non-depressive participants, Keilp et al. (2001) noted that the discriminating cognitive function between suicidal and non-suicidal depressed patients was executive functioning, while general cognitive functioning, such as memory and attention, discriminated two depressive groups from non-depressive control group.

The results suggest that suicide lethality in depression may be linked with more extensive cognitive impairment than general cognitive impairment of depressive patients. The findings for suicide attempt were replicated to suicide ideation as well (Marzuk et al. 2005). Cognitive rigidity may hamper generating alternative solutions for effective problem-solving under stressful situation and, therefore, might cause hopelessness that increases their risk for suicidal behavior (Marzuk et al. 2005). The deficits of executive functioning among suicidal depressive patients suggest their impairment in the prefrontal cortex (PFC) (Mann 2003).

## 10.3 Neurochemical Factors

Given the reduction of serotonergic function increases aggressive behavior and impulsivity (Coccaro 1989), serotonin has been linked to the neurobiological mechanism of suicide (Oquendo et al. 2014). Alteration of serotonin system, specifically hypofunction of serotonin system, has been found in suicide victims (Mann 2003). Lower level of 5-HIAA in cerebrospinal fluid (CSF), which indicates decreased serotonergic activity, was related to the incidence of previous suicide attempts among depressed patients (Mann et al. 1996). Importantly, the alteration was related to suicide attempts, independently of the history of MDD (Arias et al. 2001; Mann et al. 2000). In contrast, suicide victims were found to have increased tryptophan hydroxylase 2, decreased serotonin transporter binding affinity, and increased serotonin concentrations in the brain. These alterations may compensate the decreased serotonergic activity (Oquendo et al. 2014). In a prospective cohort study, the increased 5-HT1A autoreceptor binding affinity in the dorsal raphe nucleus of patients with depression, which leads to decreased serotonin firing, predicted more lethal suicidal behaviors (Oquendo et al. 2016). In a postmortem study, the changes in serotonin in the particular area were found among suicide victims: both the increase of 5-HT1A receptor binding (postsynaptic in the cortex) and decrease of serotonin transporter binding (presynaptic in the cortex) were localized to ventrolateral prefrontal cortex (VLPFC) (Arango et al. 1995). Considering the involvement of VLPFC in cognitive inhibition, low serotonergic input in this area may contribute to an impaired inhibition of suicidal depressive patients (Mann 2003).

Postmortem studies of suicide found abnormalities in noradrenergic system among suicide victims. Increased α2-adrenoceptor densities were found in the locus ceruleus of victims—the site for brain synthesis of noradrenaline—suggesting the decreased noradrenaline level (Ordway et al. 1994b). The inconsistent findings about the changes in tyrosine hydroxylase (TH) showed that TH immunoreactivity either increased (Ordway et al. 1994a) or decreased (Biegon and Fieldust 1992). Given that TH increases to compensate the decreased levels of noradrenaline, increased TH may result from the noradrenergic depletion after its increased release. In addition, increased level of noradrenaline and decreased α-adrenergic binding in the prefrontal cortex of were found in suicide victims (Arango et al. 1993). The findings suggest noradrenergic overactivity in the cortical region. Psychic anxiety is one of the clinical features associated with suicide in depression (Fawcett et al. 1990). Taken together, Mann (2003) suggested that pathological anxiety of suicidal people may cause the sensitive sympathetic response to stressors accompanying an excessive release of noradrenaline, which in turn deplete noradrenaline function. Then the depletion of noradrenaline may increase their hopelessness and pessimism that increase the risk of suicidal behavior.

Owing to its major role in the stress response system, the hypothalamic-pituitary-adrenal (HPA) axis has been heavily involved in the neurobiological mechanism of suicide. Measuring hyperactivity of HPA axis with dexamethasone suppression test (DST), in which failure to suppress cortisol indicates a hyperactive HPA axis, several studies have found associations between DST non-suppression and attempted or completed suicides among depressive patients (Coryell and Schlesser 1981, 2001; Jokinen and

Nordstrom 2009; Yerevanian et al. 2004). DST non-suppression increased the likelihood of eventual suicide 14-fold in a 15-year follow-up study of patients with MDD (Coryell and Schlesser 2001). With regard to cortisol levels, a proxy measure for HPA axis activity, both increased and decreased levels have been associated with suicide attempts (Mann and Currier 2007). A recent meta-analysis concluded that these inconsistent associations may be related to age, with elevated levels in samples with a mean age under 40 and blunted levels in samples with a mean age over 40 (O'Connor et al. 2016). The hyperactivity of HPA may underlie the aforementioned alterations in serotonergic and adrenergic system and PFC dysfunction (Mann 2002, 2003).

## 10.4 Neuroinflammation and Kynurenine Pathway

Inflammation is thought to contribute to suicidal behavior since inflammatory mediators, such as cytokines, reciprocally interact with the HPA axis and serotonin system (Bryleva and Brundin 2017). Elevated pro-inflammatory IL-6 level in blood and postmortem brain samples were found in suicidal patients compared with non-suicidal patients and healthy controls (Black and Miller 2015; Gananca et al. 2016). Inflammation in the brain is characterized by activation of glial cells. In one study, increased microglial priming and macrophage recruitment were observed in the dorsal anterior cingulate white matter of postmortem brain samples of depressed suicides compared with matched nonpsychiatric deaths (Torres-Platas et al. 2014).

Inflammation also causes activation of the kynurenine pathway, the main pathway for the degradation of tryptophan. Pro-inflammatory cytokines such as interferon-r, interleukin-1ß, and IL-6 can induce indoleamine 2,3-dioxygenase 1 (IDO-1) and tryptophan 2,3-dioxygenase (TDO), the key enzyme for degradation of tryptophan, and thus activate the kynurenine pathway (Bryleva and Brundin 2017). Since tryptophan is a precursor for serotonin, activation of the kynurenine pathway may reduce the availability of tryptophan and thus decrease serotonin synthesis. Sublette et al. (2011) found elevated plasma kynurenine levels in suicide attempters with MDD, compared to non-attempters with MDD. A more recent study found decreased tryptophan level and elevated kynurenine/tryptophan ratio in suicidal adolescents with MDD compared to non-suicidal adolescents with MDD and healthy controls (Bradley et al. 2015).

Quinolinic acid, one of the main metabolites of kynurenine, is known for its neurotoxic property through *N*-methyl-D-aspartate (NMDA) receptor agonism, leading to glutamatergic neurotransmission hyperactivation. Kynurenic acid, another main metabolite of kynurenine, is considered neuroprotective due to its NMDA and alpha-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) receptor antagonism (Bryleva and Brundin 2017; Salloum 2017). The quinolinic acid levels in the CSF of suicide attempters significantly elevated by around 300% of the levels in the CSF of healthy controls (Erhardt et al. 2013). In addition, CSF quinolinic acid levels remain significantly elevated by around 150% even after 2 years after a suicide attempt (Bay-Richter et al. 2015). The CSF quinolinic acid/kynurenic acid ratio, referred to as the neurotoxic ratio, was twofold higher in suicide attempters compared to healthy controls, suggesting the role of net positive NMDAR agonism on suicidal behaviors (Erhardt et al. 2013). These findings are in line with the facts that antisuicidal effect is produced by intravenous injection of ketamine, an NMDA receptor antagonist (Bryleva and Brundin 2017).

## 10.5 Genetic Factors

Results from studies of families, twins, and adoption support a substantial genetic component of suicidality. People who commit or attempt suicide have a higher familial history of suicidal acts (Brent and Mann 2005). Concordance rates for suicide and suicide attempts are higher in monozygotic twins compared to dizygotic twins (Voracek and Loibl 2007). The biological parents

of adoptees who commit suicide show a higher rate of suicide compared to the biological parents of control adoptees (Voracek 2007). The genetic components of suicidal behavior are estimated to be around 40% (McGuffin et al. 2010).

The serotonin transporter plays an important role in regulating serotogenic signaling at synapses. The gene of serotonin transporter (SLC6A4) has a common functional polymorphism in the promoter region (5-HTTLPR), which consists of long insertion (L) or deletion (S) polymorphism. Clayden et al. (2012) conducted a meta-analysis of 5-HTTLPR and found the significant association for the 5-HTTLPR S allele and attempted suicide, but not for completed suicide. A meta-analysis of the genetic polymorphisms of the gene coding for tryptophan hydroxylase 1 (TPH1), the rate-limiting enzyme in the biosynthesis of serotonin, also found the significant association of the polymorphism A218C with attempted suicide, but not with completed suicide (Clayden et al. 2012). In a recent meta-analysis by Gonzalez-Castro et al. (2014), the polymorphisms A218C and A779C have been associated with suicidal behavior on both Asian and Caucasian populations. For the neuronal isoform of TPH, tryptophan hydroxylase 2 (TPH2), a meta-analysis by Gonzalez-Castro et al. (2014) did not detect any significant association with suicidal behavior. In contrast, other meta-analytic study by Choong et al. (2014) found the association of two polymorphisms, rs7305115 and 1386486, with suicidal behavior, although the included studies were highly heterogeneous.

The genetic polymorphisms of the gene coding for catechol-o-methyltransferase (COMT), the key enzyme for degradation of catecholamines, were investigated in few meta-analyses (Mirkovic et al. 2016). A meta-analysis by Kia-Keating et al. (2007) found an association between the COMT 158Met polymorphism and suicidal behavior, but more recent meta-analytic studies failed to confirm the association (Calati et al. 2011; Clayden et al. 2012).

Monoamine oxidase A (MAOA) is a mitochondrial outer membrane enzyme that is responsible for the degradation of monoamine neurotransmitters including norepinephrine, dopamine, and serotonin. Although abnormalities in monoamine neurotransmission have been implicated in the molecular pathogenesis of suicidal behavior, the meta-analysis on the most extensively studied polymorphism in the promoter region, uVNTR, did not confirm the association with suicide attempts in both gender and violent suicide attempts (Hung et al. 2012).

## Conclusion

In this chapter, we reviewed previous research examining the risk factors of suicidal behaviors among depressive patients. Interplay between interconnected neural systems contributes to suicidal behaviors in depression, and neurobiological changes in suicidal depression appear to underlie the psychological vulnerability of suicidal behavior (Fig. 10.1; Mann 2003).

Personal state of hopelessness and pessimism predicts future suicide attempt and completion of depressive patients. The depletion of noradrenaline may underlie this hopelessness. Depressive patients with pathological anxiety may respond to stressors overly sensitively, and it may cause depletion of noradrenaline after its excessive release. Therefore it is plausible that severe psychic anxiety might be linked to hopelessness and pessimism over time, which eventually increase the risk of suicide.

In addition, impulsive and aggressive behavior has been identified as key predictor of repetitive suicide attempts. Impulsive and aggressive traits of suicidal patients may be linked with the hypofunctioning of their serotonin system. These two traits may also be associated with comorbidities with other psychiatric disorders such as BPD that increase suicide risk.

Cognitive rigidity may also increase the risk of suicidal behavior, by inhibiting an effective coping to stressors and heightening hopeless and pessimistic thinking and emotion as the outcome. This impairment in executive functioning may result from dysfunction of PFC, perhaps associated with the alterations in serotonergic and adrenergic system.

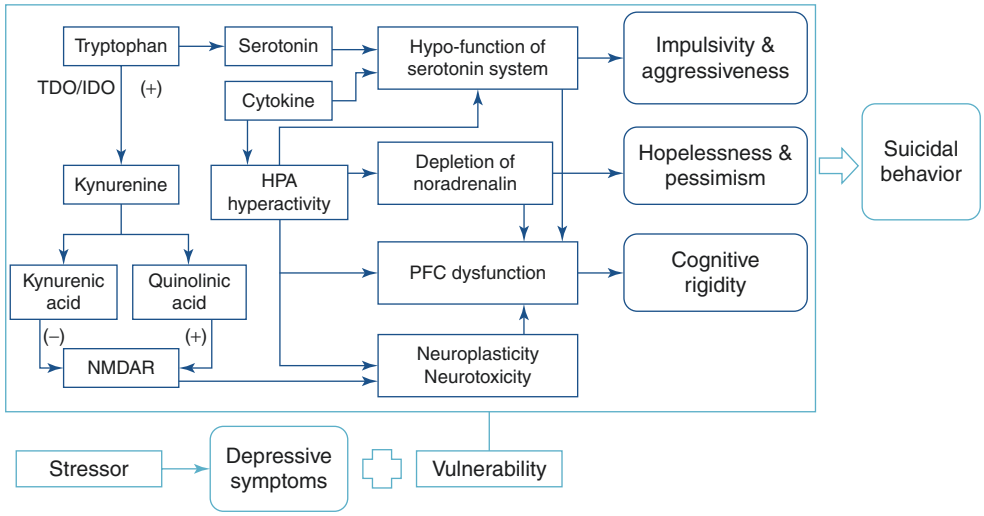


**Fig. 10.1** A stress-diathesis model of suicidal behavior in depression, modified from Mann (2003). *TDO* tryptophan 2,3-dioxygenase, *IDO* indoleamine 2,3-deoxygenase, *HPA* hypothalamic-pituitary-adrenal, *NMDAR* *N*-methyl-D-aspartate receptor

Depressive patients with the aforementioned predispositions may be highly vulnerable to suicide risk. Therefore, the assessment and treatment for suicidal behaviors in depressive patients should carefully consider these predispositions. Suicidal behaviors of depressive patients may not be merely severe depressive symptoms. Notably, suicidal behavior satisfies the criteria for diagnostic validity and has been demonstrated to be a reliable diagnosis (Oquendo and Baca-Garcia 2014). Reconceptualization of suicidal behavior as a distinct disorder may improve suicide risk screening and detection in clinical practice and also help expand suicide research by using a well-defined phenotype. With the advances in molecular genetics and neuroimaging technology, a better understanding of suicidal behavior as a distinct psychobiology is expected in the future.

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# 11 Cognitive Dimensions of Depression: Assessment, Neurobiology, and Treatment

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## 11.1 Cognitive Impairment in Depression

Although reduced concentration is one of the diagnostic criteria of depression, there are other cognitive impairments in patients with depression. Although some patients do not experience cognitive decline, most studies reported that depressed patients underperformed on various neurocognitive function tests compared to a control group (Zakzanis et al. 1998). Key aspects of cognitive impairment in depressed patients include attention, memory, and psychomotor speed. Although language, perception, and spatial perception are typically well maintained in depressed patients, impairments to these can occur due to the secondary effects of lack of concentration, motivation, or ability to structure tasks (Mayberg et al. 2002). According to previous studies, consistently observed cognitive issues in depressed patients were memory deterioration due to reduced concentration and reduced executive function due to rigidity of thought that prevented patients from changing focus easily (Marazziti et al. 2010). Other studies have reported that processing speed (Nebes et al. 2000), selective attention, response inhibition, executive function (Beats et al. 1996), and episodic memory (Austin et al. 1999) were consistently observed areas of cognitive decline in depressed patients. In a study that utilized functional magnetic resonance imaging (fMRI), when a depressed patient group and a control group were asked to perform the same working memory task, activation of additional neural circuits was required for the depressed patient group (Harvey et al. 2005).

The characteristics of cognitive impairment in depressed patients are clearer when compared to Alzheimer's disease (AD), which is a representative neurocognitive disorder. There are some distinguishable points between patients with depression and patients with AD in terms of cognitive impairment (Olin et al. 2002; Steffens and Potter 2008) (Table 11.1). First, depressed patients tend to experience greater subjective cognitive dysfunction relative to AD patients. Second, cognitive impairment in depressed patients is usually more rapid and mood congruent, while patients with AD experience more steady and progressive cognitive impairment. Third, cognitive impairment is more pronounced in effortful jobs among depressed patients, unlike with AD patients, who experience cognitive impairment in phasic or gnostic processes or apraxia. Fourth, information processing speed or psychomotor speed is often maintained in AD

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**Table 11.1** Typical clinical and cognitive presentations of depression versus Alzheimer's disease

| Feature | Depression | Alzheimer's disease |
|---|---|---|
| Subjective memory complaints | Overestimate level of cognitive impairment | Underestimate level of cognitive impairment |
| Rate of cognitive change | Acute | Insidious |
| Course of cognitive change | Mood-congruent fluctuations in cognition | Progressive cognitive decline |
| Memory | Improvement with repeated exposure; recall improves with retrieval cues | No improvement despite repeated exposure; cueing does not help recall performance |
| Aphasia/apraxia/agnosia | Uncommon | Emergence after memory impairment |
| Information processing speed | Slowed | Normal in early stage |
| Psychomotor speed | Slowed | Normal in early stage |

patients at early stages; a reduction in these speeds is more pronounced in depressed patients, even at early stages. Fifth, depressed patients show much poorer memory function in early stages and recover with repeated assessment; retrieval cues are often helpful for recall. However, AD patients show poor performance, even with repeated assessment, and retrieval cues are not helpful for recall.

## 11.2 Model to Explain Cognitive Impairment in Depression

One of the models to explain cognitive impairment in depression states that depressed patients cannot efficiently distribute and utilize cognitive resources (Anacker and Hen 2017). This hypothesis assumes that cognitive impairment in depressed patients is not a disorder of a specific area of cognitive function, but is due to lack of energy required to perform cognitive functions in general. Unlike AD patients that have impaired semantic recall, depressed patients have well-maintained semantic memory. Many studies have revealed that explicit memory for recent information is impaired in both AD and depressed patients and that implicit memory is only impaired in AD patients, but not in depressed patients. These results demonstrate how cognitive impairment is often observed during the performance of effortful tasks in patients with depression.

Another model hypothesized about the correlation between specific cognitive functions and specific neuroanatomical locations. This model is based on the observation that the pattern of memory impairment in depressed patients is similar to that of patients with prefrontal cortical dysfunction. In a study that compared patients with primary depression and patients with neurological disorders (i.e., Parkinson's disease), the pattern of cognitive impairment was similar. Both groups had reduced concentration, working memory, psychomotor speed, planning, strategic searching, and flexibility of goal-directed thought processes (Flint et al. 1993).

## 11.3 Cognitive Impairment and Depression Severity, Age Group, and Remission

In a meta-analysis that assessed the correlation between the severity of depression and the level of cognitive impairment, significant correlations were observed between the severity of depression and some aspects of cognitive impairment (i.e., episodic memory, executive function, and processing speed), while there was no significant correlation between severity of depression and semantic memory or visual-spatial memory (McDermott and Ebmeier 2009). Other studies have reported worsened processing speed and executive function with increased severity of depression, more specifically, with increased apathy (Boone et al. 1995; Feil et al. 2003).

Many studies have reported that different patterns of cognitive impairment are observed in different age groups of depressed patients. Relatively younger patients exhibit impairments in concen-

tration, short-term memory, and working memory, while language- or learning-associated functions remain normal (Mormont 1984; Savard et al. 1980). In contrast, older depressed patients report impaired memory as their chief complaint and can present similar to AD patients. Impairment in executive function in older depressed patients was associated with planning, ordering, structuring, and abstract thinking. Sometimes, these impairments were associated with a recurrence or relapse of depression (Pisljar et al. 2008). One study suggested that different cognitive impairments were observed for different ages of onset of depression. Individuals with early-onset depression often exhibit impairment in episodic memory, while later-onset depression is often associated with impaired executive function and processing speed (Herrmann et al. 2007).

Previously, researchers believed cognitive impairment in patients with depression was associated with the severity of depression and therefore thought that cognitive impairment should disappear after the remission of depression (Basso and Bornstein 1999). However, some recent studies report cases of persistent cognitive impairment, even after the remission of depression. Some studies found that even after a significant improvement in depressive symptoms, there were many cases of persistent cognitive impairment for over 6 months and that impairment was more pronounced in effortful task performance than in automatic performance (Hammar et al. 2003). Thus, some claimed that cognitive impairment should be regarded as a trait marker of depression (Marazziti et al. 2010). This is the key reason why cognitive impairment in depression should not be considered as a mere symptom, but a possible prognostic marker of progression into neurocognitive disorder (i.e., Alzheimer's disease).

## 11.4 Association Between Early-Onset Depression and Cognitive Disorders

Most studies that established a relationship between depression and neurocognitive disorders focused on the relationship between late-onset depression (LOD) in patients over 60 years old and AD. However, considering that LOD is mostly premonitory or an early symptom of AD, it is difficult to validate depression as a true risk factor for AD. In contrast, early-onset depression (EOD) often occurs in younger or middle-aged patients and has a long disease duration until the onset of AD. Therefore, this allows us to validate whether depression is a true risk factor for AD.

There are five published studies investigating the relationship between EOD and AD, including four prospective cohort studies and one case-control study. All of these studies found that EOD played a key role in the pathogenesis of AD, reporting a two- to fourfold increase in risk of AD onset (Barnes et al. 2012; Dal Forno et al. 2005; Dotson et al. 2010; Geerlings et al. 2000; Green et al. 2003). One of these studies reported that, although the risk of AD increased by fourfold in EOD patients, there was no association between LOD and the onset of AD (Geerlings et al. 2000). Another study reported that depression increased AD risk twofold and that value increased to fivefold at 1 year prior to the onset of AD. In conclusion, EOD is considered an important risk factor for AD, but whether it is a direct cause or if there is a third factor mediating the association between depression and AD remains unclear. Furthermore, the relationship between LOD and AD is still very unclear.

## 11.5 Neurocognitive Function Tests for Patients with Depression

To date, there have been few specially designed tools for measuring cognitive function within depression. For depression, typical neurocognitive function tests are used. The selection of a particular neurocognitive function test is based on various factors, and a differential diagnosis is the most important factor to be considered. For example, to assess whether impaired memory is due to AD, depression, or aging, general neurocognitive function, including various cognitive dimensions, should be assessed for potential impairment. Furthermore, test levels of difficulty should vary from easy to difficult to reveal the deterioration of cognitive function regardless of

the severity of depression. The following are basic dimensions of neurocognitive function tests to assess overall cognitive function (Table 11.2).

## 11.6 Cognitive Biological Model of Depression

The amygdala in depressed patients has greatly enhanced resting metabolism, and exposure to aversive stimulation results in a greater increase in activation of the amygdala (Seminowicz et al. 2004; Siegle et al. 2007). In contrast, resting metabolism of the prefrontal cortex (PFC) is greatly reduced in patients with depression (Mayberg et al. 1999). In a fMRI study, depressed patients exhibited increased amygdala reactivity while performing emotion-processing tasks and decreased dorsolateral prefrontal cortex (DLPFC) activation while performing cognitive tasks (Mayberg et al. 1999; Seminowicz et al. 2004; Siegle et al. 2007). Moreover, depressed patients showed decreased functional connectivity between the amygdala and the DLPFC. The corticolimbic dysregulation model is a neurobiological mechanism that utilizes these observations to explain cognitive impairment in depression (Comte et al. 2016).

First, cognitive impairment in depression occurs through bottom-up processing. The pro-

**Table 11.2** Neurocognitive function tests, according to cognitive function dimension

1. Consciousness, attention, orientation
   - (a) Consciousness
     - Glasgow Coma Scale
   - (b) Concentration
     - Digit span
     - Reverse digit span
     - Reverse sequence
     - Serial 7s
     - Continuous performance
   - (c) Orientation: time, person, place
2. Memory
   - (a) Verbal
     - 4 unrelated word test
     - Paired associated learning test
     - Story recall test
     - Rey auditory verbal leaning test
     - California verbal learning test
     - Hopkins verbal learning test
   - (b) Visual
     - Visual reproduction
     - Visual paired associates
     - Rey-Osterrieth complex figure test
   - (c) Wechsler Memory Scale (WMS)
3. Language
   - (a) Spontaneous speech
     - Fluency, articulation, prosody, grammar, paraphasia
   - (b) Verbal fluency test
     - animal naming test
   - (c) Naming and word finding
     - Boston naming test
   - (d) Comprehension
     - Follow simple commands
     - Follow commands, using objects
     - Answer yes-no questions
     - Reading comprehension
   - (e) Repetition
   - (f) Reading
   - (g) Writing
4. Visuospatial skills
   - (a) Copy drawings (interlocking pentagon, a clock face, a house, or a person)
   - (b) Rey-Osterrieth complex figure test
5. Executive function and higher cortical functions
   - (a) Calculation
   - (b) Similarity proverb
   - (c) Judgment
   - (d) Multiple loop
   - (e) MN sequence
   - (f) Go-no-go test
   - (g) Fist-edge-palm test
   - (h) Trail making test
   - (i) Stroop test
   - (j) Praxis
     - Ideomotor praxis
     - Ideational praxis
6. Others
   - (a) Agnosia
     - Visual agnosia, prosopagnosia, environmental agnosia, stereognosis
   - (b) Right-left disorientation
   - (c) Neglect
     - Line bisection test
     - Star cancelation test

cess begins with hyperactivity of the limbic system, represented by the amygdala, followed by hyper-activation of the PFC, frontal cortex, ACC, hippocampus, and subgenual cingulate cortex. These hyperactivities cause problems with redistribution of cerebral blood flow. The brain controls oxygen distribution through redistribution of cerebral blood flow (Disner et al. 2011), and problems in oxygen distribution can affect cognitive function in various regions of the brain.

Second, weakened top-down processing causes cognitive impairment in depression. Weakened top-down processing results in difficulties with controlling emotions. Structures associated with top-down processing include the DLPFC, medial prefrontal cortex (MPFC), ventrolateral prefrontal cortex (VLPFC), and, from the subcortical region, anterior cingulate gyrus (ACC) and thalamus. The DLPFC is associated with rumination and processing of bias, the MPFC is associated with self-referential schemas, and the VLPFC is associated with attention to bias. When top-down regulation is weakened, the cognitive controlling ability of the PFC is weakened, while the emotional reactivity of the amygdala is enhanced. Unstable connections between the PFC and subcortical areas result in an inability to react and judge properly against stimulation and eventually result in a decline in cognitive function (Roiser et al. 2012).

In summary, the brain of depressed patients is characterized by increased bottom-up emotional reactivity (by activation of the amygdala) and decreased top-down emotional regulation (by deactivation of the DLPFC). In other words, depressed patients have weakened top-down cognitive control and enhanced bottom-up emotional activation and therefore have abnormal cognitive function. In conclusion, impaired cognitive function in patients with depression causes problems in the neurofunctional network.

## 11.7 Amyloid Positron Emission Tomography (PET) Scans

Some studies suggest that depression occurs as a way to express neurodegeneration (Baldwin et al. 2005). They suggest that, due to neurodegeneration, not only cognitive function but also emotional controlling function is impaired. Therefore, recent studies on cognitive function in depression highlight the use of amyloid positron emission tomography (PET) scans.

One of the most important tasks when diagnosing neurocognitive disorders, especially AD, is to identify the histopathology of the brain. The characteristic pathological finding of AD is a neurofibrillary tangle (NFT), composed of tau proteins, within the cell and amyloid plaques outside the cell. Amyloid plaques are composed of peptides called amyloid-β (Aβ), and amyloid cascade theory hypothesizes that the accumulation of Aβ induces pathology through neurotoxins and NFT, eventually resulting in impaired cognitive function (Hardy and Higgins 1992). Recently, advances in nuclear medicine allowed for radiological assessment of amyloid accumulation. Amyloid positron emission tomography (PET) can identify Aβ accumulation levels in the brain by injecting a tracer to detect Aβ (Herholz and Ebmeier 2011; Villemagne et al. 2011). Based on this, amyloid PET is expected to become a useful diagnostic tool for the differential diagnosis of depression and AD. In fact, there are studies currently being performed to predict the progression from depression to AD in depressed patients with concurrently impaired cognitive function utilizing amyloid PET (Chung et al. 2016; Harrington et al. 2015; Tateno et al. 2015). Moreover, there is a high chance of amyloid PET being used to biologically assess the level of cognitive dysfunction in patients with depression.

## 11.8 Utilization of Amyloid PET in Depression

In a study published in 2008 (Butters et al. 2008), the authors performed amyloid PET on eight depressed patients (composed of six individuals with mild cognitive impairment [MCI] and two cognitive normal [CN] individuals) and eight control subjects. The results showed similar levels of amyloid accumulation for the CN depressed patients and the control group. Among the six patients with MCI and depression, three showed similar levels of amyloid accumulation as the AD

patient group, and the remaining three showed varying levels. They suggested, based on these results, that amyloid accumulation has the potential to diagnose cognitive impairment in patients with depression. Furthermore, they reported that the frontal lobe and precuneus were the significant regions of amyloid accumulation associated with depression.

In a study published in 2009 (Lavretsky et al. 2009), the authors performed amyloid PET and tests to assess depressive and anxiety symptoms in 23 MCI and 20 CN subjects. The results showed that for the MCI group, depression scores and anxiety scores were associated with amyloid accumulation in the lateral temporal lobe and posterior cingulate cortex, respectively. For the CN group, depression scores and anxiety scores were associated with amyloid accumulation in the medial temporal and frontal lobes, respectively. The authors suggested that the presence of MCI made a significant difference in the pathophysiological mechanism of emotional conditions and anxiety.

In a study published in 2012 (Madsen et al. 2012), the authors compared amyloid accumulation between 28 elderly subjects (mean age = 61 years old) who once had depression and remitted and 18 healthy control subjects. They reported no significant relationship between depression and increased amyloid accumulation and suggested that depression should not be considered a risk factor for AD. However, results from more recent studies showed a significant association between depression and AD. In a study published in 2014 (Wu et al. 2014), the authors compared amyloid PET scan results between 25 subjects with depression and 11 CN subjects (>60 years old). The results showed that, relative to CN patients, depressed patients had significantly increased amyloid accumulation in the parietal lobe and precuneus. This result supports the findings of the 2008 study, which found a significant accumulation of Aβ in the same region.

Some previous animal studies identified an association between depression and amyloid pathology. Depression is associated with failure to control the hypothalamic-pituitary-adrenal axis due to hypercortisolemia. One of the studies (Green et al. 2006) found increased amyloid production when dexamethasone was injected in mice, which was due to increased expression of amyloid precursor protein (APP) and β-APP secretase. In a mouse model of depression induced by sudden restraint or chronic isolation, amyloid levels increased in the hippocampus (Kang et al. 2007). This was activated by an injection of corticotropin-releasing hormone (CRH) into the hippocampus and was suppressed by pretreatment with a CRH antagonist.

A study published in 2015 (Tateno et al. 2015) reported that later onset of depression was correlated with significantly increased accumulation of Aβ. Moreover, among elderly depressed patients, the amyloid-positive group was significantly older, and the period between the onset of depression and the time when patients received the amyloid PET scan was significantly shorter. The authors concluded that amyloid pathology had a greater impact on the onset of depression in the case of late-onset depression.

Another study published in 2016 (Chung et al. 2016) performed amyloid PET scans on 39 MCI patients with a history of depression and 39 MCI patients with no history of depression. When they compared the results, the depression group had significantly higher levels of Aβ accumulation in bilateral frontal lobes, and the authors suggested that this region could be a biomarker for depression in MCI patients. Another study (Brendel et al. 2015) divided 371 MCI patients into 2 groups (with and without depression). From the entire cohort, 206 were amyloid positive and 165 were amyloid negative, and Aβ accumulation was increased in the frontotemporal lobes and insula in depressed patients in the amyloid-positive group.

There are continuous studies using amyloid PET to identify the correlation between depression and cognitive function, as well as to identify whether depression is a risk factor for AD. Meaningful results are being published, and the accumulation of results from more prospective studies with larger sample sizes will allow us to better understand the pathophysiology behind depression-induced cognitive impairment.

## 11.9 Vascular Pathology in Depression with Cognitive Impairment

Cerebrovascular risk factors have great effects on depression and cognition. Subjects with more than two cerebrovascular risk factors had more severe symptoms of depression compared with those without cerebrovascular risk factors, and the outcomes of cognitive function tests were poorer (Barch et al. 2012). In other words, more cerebrovascular risk factors cause a higher chance of structural changes in the brain, and individuals with more cerebrovascular risk factors have a higher chance of developing depression with cognitive impairment. Frequent observation of deep white matter hyperintensities on MRI was associated with poorer outcomes on neurocognitive tests. More specifically, there was a close relationship with executive function and memory tests. Looking at MRI studies published to date, subcortical ischemic change appears to play a key role in the onset of depression (Geerlings et al. 2012; Saavedra Perez et al. 2013). Furthermore, these vascular factors have a relatively strong relationship with cognitive function. Therefore, vascular physiology could be a common cause for both depression and reduced cognitive function.

## 11.10 Drug Treatment of Depression with Cognitive Impairment

The pathophysiology of cognitive impairment in depression is not yet known, and this could also be a multifactorial disorder. Therefore, there is no clear theoretical guideline for treatment of depression with cognitive impairment, and treatment is not simple. In addition, there is a dearth of large-scale prospective studies on this issue.

The effects of antidepressants on cognitive function vary between different studies. In sertraline (Lyketsos et al. 2000, 2003) and fluoxetine studies (Tariot et al. 1998), there was no significant correlation between antidepressant use and cognitive function. Another study (Munro et al. 2004), however, showed that although there was no change in cognitive function in the sertraline treatment group, post hoc analyses showed improvement in cognitive function for female subjects, while no cognitive changes or worsening cognition were observed for male subjects. In a double-blind study comparing moclobemide and a placebo, treatment provided improvement for not only depression but also for cognitive function (Roth et al. 1996). Tricyclic antidepressants (TCAs) were found to worsen cognitive function in some patients (Petracca et al. 1996; Reifler et al. 1989).

The biggest issue for medication treatment of depression with cognitive impairment is that no large-scale prospective study has been performed. When analyzing 11 different randomized placebo-controlled studies, 5 studies showed significant effects over placebo (sertraline (Lyketsos et al. 2003), clomipramine (Petracca et al. 1996), maprotiline (Fuchs et al. 1993), moclobemide (Roth et al. 1996), citalopram (Nyth and Gottfries 1990)), while 6 studies showed no significant effect over placebo (sertraline (Banerjee et al. 2011; Rosenberg et al. 2010), mirtazapine (Banerjee et al. 2011), venlafaxine (de Vasconcelos Cunha et al. 2007), imipramine (Reifler et al. 1989), fluoxetine (Reifler et al. 1989)). A recent double-blind placebo-controlled study showed significant improvement for all three groups (sertraline-, mirtazapine-, and placebo-treated groups) after 13 weeks (Banerjee et al. 2011). In contrast, medication treatment groups showed more side effects compared to control groups. In other words, this study found that representative antidepressants, such as sertraline or mirtazapine, did not have a significant effect on improving cognitive function. A recent meta-analysis showed similar results. Both response rates and remission rates were not significantly better than those of the placebo group (Nelson and Devanand 2011).

Once it is decided to use antidepressants to treat depression with cognitive impairment, it is recommended to use selective serotonin reuptake inhibitors (SSRIs) rather than TCAs. Treatment should continue regardless of initial improvement. Cognitive deficits can be persistent even

after depression is remitted, and in such cases, the condition can progress into neurocognitive disorders such as AD. If the patient does not respond to antidepressants, additional medications can be given. However, augmented treatment for depression with cognitive impairment patients is not established, and treatment plans should be decided after regular monitoring of patient conditions.

The effects of cholinesterase inhibitors against depression are not clear. In a galantamine study monitored for 21 weeks, overall Neuropsychiatric Inventory (NPI) scores were improved over a placebo group, but there was no significant effect on depression (Cummings et al. 2004). In a double-blind study of donepezil treatment for 24 weeks, overall NPI scores significantly improved—and more specifically, improvements were significant for anxiety, lack of inspiration, or hypersensitivity—but no effect was observed for depression (Gauthier et al. 2002). Anticonvulsants (carbamazepine, valproic acid, lamotrigine, gabapentin, and topiramate) showed no clear effect against either depression or cognitive dysfunction (Pinheiro 2008). Similarly, patients taking atypical antipsychotics (olanzapine, quetiapine, and risperidone) showed no significant improvement in depression or cognitive function, and olanzapine can sometimes worsen the symptoms of depression (Sultzer et al. 2008).

### Conclusion

When comparing depression and AD, section-specific differences are observed under neurocognitive tests. These differentiating points are clear, but commonalities—such as the high risk of progression into neurocognitive disorder in EOD patients with cognitive impairment—are also emphasized. Severity of depression and level of cognitive decline are correlated in certain neurocognitive dimensions. There are models to explain cognitive impairment under depression. A psychological hypothesis states that depression patients cannot effectively distribute and utilize cognitive resources. A biological hypothesis states that weakened top-down cognitive control and enhanced bottom-up emotion activation result in cognitive impairment. To assess cognitive function in depression, typical neurocognitive function tests to assess overall cognitive function are preferred over specific examination tools. Recently, amyloid PET is being highlighted for its usefulness in patients with depression and cognitive impairment, and many studies are being done on this topic. Since the effects of antidepressants on cognitive function are not completely established, regular monitoring of patients is required to provide best treatment.

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# Part III

# Complicated Clinical Manifestations of Depression

# 12 Overlapping Chronic Pain and Depression: Pathophysiology and Management

Jan Jaracz

## 12.1 Introduction

Epidemiological studies convincingly point to the frequent comorbidity of depression and chronic pain. Bair et al. (2003) who reviewed 14 studies published between 1957 and 2003 demonstrated that 65% (range 15–100%) of depressed patients reported pain. The same authors identified 42 papers investigating the occurrence of depression in people suffering from chronic pain of different etiology. Symptoms of depression were detected in 52% (range 1.5–100%) of patients in pain clinics. This observation may inspire to formulate a hypothesis that both conditions may share common pathophysiological mechanisms.

## 12.2 Pathophysiology

The first assumption refers to neurotransmitters, i.e., serotonin, noradrenaline dopamine, and glutamate as well as pro-inflammatory cytokines, substance P, and brain-derived neurotrophic factor (BDNF). The second conjecture relates to brain structures involved in the pathogenesis of both depression and the processing of pain.

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### 12.2.1 Cytokines

Pro-inflammatory cytokines represent a class of proteins which play a central role in the immune system and in the inflammatory response. Interleukin-1β (IL-1β), interleukin2 (IL-2), interleukin-6 (IL-6), interleukin-8 (IL-8), and tumor necrosis factor-α (TNF-α) are involved in activation of lymphocyte, macrophage, and neutrophil as well as the regulation of immunoglobulin by production B cells.

Cytokines exert a modulatory effect on several aspects of brain functioning. IL-1 and, to a lesser extent, Il-6 and TNF-α activate the hypothalamo-pituitary-adrenocortical (HPA) axis leading to glucocorticoid receptor resistance and hypercortisolemia. Hyperactivity of HPA axis is a well-documented biological marker of major depression (Zunszain et al. 2011).

Cytokines produce a modulatory impact on neurotransmitter systems. First of all they reduce availability of tryptophan, which is a precursor of 5-HT. This in turn leads to deregulation of both monoamine synthesis and reuptake, causing reduced monoamine availability, and, according to monoamine hypothesis, induces symptoms of depression (Miller et al. 2009; Müller 2014). Moreover, inflammation increases the activity of kynurenine pathway of tryptophan metabolism by induction of indoleamine 2,3-dioxygenase (IDO). This metabolic switch increases the production of quinolinic acid, which agonizes NMDA receptors (NMDA-R)



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and finally leads to reduced neuroplasticity (Jeon and Kim 2016). Cytokines also have a significant negative impact on dopamine synthesis, packaging, and release which may cause symptoms of depression (Felger 2017). Pro-inflammatory cytokines have an impact on neuroplasticity by affecting important aspects of neuronal functioning particularly apoptosis, oxidative stress, and metabolic derangement, as well as by impairing axonal and dendritic branching (Hayley et al. 2005). It has been shown that IL-1β refrains long-term potentiation, a form of neuronal plasticity which is a neural substrate of learning and memory (Hayley et al. 2005; Pickering and O'Connor 2007). Data suggest that these cognitive functions are commonly affected in major depression (MD).

It has been postulated that cytokines and chemokines excessively produced in different diseases can sensitize neurons of the first pain synapse and, in this way, cause central sensitization which eventually results in the activation of neurons by innoxious signals (Schaible 2014; Clark et al. 2013). These changes promote long-term maladaptive plasticity, resulting in persistent neuropathic pain (Ellis and Bennett 2013; Maes et al. 2012).

Four lines of evidence indicate a relationship between elevated levels of pro-inflammatory cytokines, chronic pain, and depression. First, several studies have shown elevation of pro-inflammatory cytokines in neuropathic pain and other pain conditions, such as arthritis. The neutralization of cytokines seems to have an analgesic effect (Schaible 2014; Shubayev et al. 2010). Second, depression is commonly reported in somatic disorders related to activation of inflammatory mechanisms including asthma (Goodwin et al. 2004), rheumatoid arthritis (Murphy et al. 2012), inflammatory bowel disease (Walker et al. 2008), and coronary heart disease (Celano and Huffman 2011). Third, depression is a common side effect in patients treated with cytokine therapies due to cancer and hepatitis (Capuron et al. 2000; Musselman et al. 2001). Fourth, results of meta-analyses have provided strong data that serum levels of the pro-inflammatory cytokines IL-1, IL-6, and TNF-α in major depression are elevated (Dowlati et al. 2010; Liu et al. 2012; Young et al. 2014).

The causes of increased levels of pro-inflammatory cytokines in depression have not been precisely elucidated so far. Recently, Slavich and Irwin (2014) have proposed a "social signal transduction theory of depression." The basic assumption of this theory is that stress upregulates immune mechanisms involved in the inflammatory response. A secondary effect is dysregulation of neuroendocrine and neurotransmitter systems which disturb brain functioning. The final result of these dysfunctions is the appearance of symptoms of depression.

Bai et al. (2014) investigated the relationship between pro-inflammatory cytokine levels and pain symptoms in patients with major depressive disorder (MDD) and minor depressive disorder. The level of soluble P-selectin, but not of other pro-inflammatory cytokines, appeared to be a significant predictor for the presence of both somatic and pain symptoms in depression. An association between increased pain sensitivity and increased TNF-α concentration was found in depressed female patients (Euteneuer et al. 2011). However, the association of normalization of cytokines levels with an improvement in painful symptoms in depressed patients has not been studied so far.

### 12.2.2 Brain-Derived Neurotrophic Factor (BDNF)

BDNF plays a role in the formation of neural proliferation, growth, and survival. Opposite abnormalities of BDNF secretion have been found in depression and chronic pain. A decreased level of BDNF in major depression was reported in several studies and confirmed in meta-analysis conducted by Molendijk et al. (2014). However, higher than normal serum levels of BDNF were detected in chronic pain conditions like fibromyalgia (Haas et al. 2010) and in irritable bowel syndrome (Yu et al. 2012). Interestingly, in patients with fibromyalgia, BDNF levels correlated with severity of symptoms of depression (Nugraha et al. 2013).

Data reviewed recently by Nijs et al. (2015) confirmed that the BDNF's upregulation leads to sensitization of peripheral nociceptors, dorsal root ganglia, spinal dorsal horn neurons, and brain descending inhibitory and facilitatory pathways. It has been also found that the BDNF val-66met polymorphism marks vulnerability for chronic multisite musculoskeletal pain compared to val66val carriers (Generaal et al. 2016). BDNF in turn modulates fast excitatory (glutamatergic) and inhibitory (GABAergic/glycinergic) signals.

### 12.2.3 Glutamate

Glutamate is considered as a primary excitatory neurotransmitter in the human central nervous system. Receptors which transduce glutamate signaling fall into two categories: ionotropic (NMDA, AMPA, and kainite receptors) and metabotropic receptors (mGLU). Three groups (I–III) of mGLU receptors have been identified on the basis of their location, impact on $K^+$ and $Ca^{++}$ channels, and the role in excitatory and inhibitory processes.

mGLU receptors, particularly from group I, are localized in brain structures involved in pain processing. Increased expression of mGLU 1/5 receptors was identified in animal models of pain. There is growing evidence suggesting the potential role of mGLU receptor agonists in treatment of acute and chronic pain (see Golubeva et al. 2016 for review).

In depression, numerous studies have demonstrated higher serum and cerebrospinal fluid (CSF) levels of glutamate, suggesting enhanced glutamatergic neurotransmission. Also postmortem studies showed alterations in glutamate receptors in MDD (Hashimoto 2009).

Indirect evidence pointing to the role of the glutamate system in major depression arise from studies demonstrating the antidepressant effect of drugs which modulate glutamatergic neurotransmission. Memantine blocks current flow through channels of *N*-methyl-D-aspartate (NMDA) receptors. Results of the recent study imply that in patients with MDD treatment with memantine, add-on to sertraline was more effective than treatment with sertraline plus placebo (Amidfar et al. 2016). Ketamine noncompetitively antagonizes the NMDA receptors. Meta-analysis of nine clinical studies confirmed a significant reduction of symptoms of depression after a single-dose infusion of ketamine (Kishimoto et al. 2016). Preclinical studies indicate that metabotropic glutamate receptor 5 (mGlu5) negative allosteric modulator (NAM)—basimglurant—causes disinhibition of discrete glutamate neuronal networks in brain circuits involved in mood and emotion regulation. Therefore it has been postulated that this agent is a promising antidepressant (Fuxe and Borroto-Escuela 2015). Some data suggest that pharmacologically induced inhibition of mGlu5 receptors and amplification of mGlu2/3 and mGlu4/7/8 receptors may cause reduction of symptoms intensity in both depression and chronic pain (Golubeva et al. 2016).

### 12.2.4 Substance P

Neuropeptide substance P acts by binding to the neurokinin-1 receptor (NK-1R). Both substance P and NK-1R are widely distributed in the central nervous system, particularly in the amygdala, hypothalamus, periaqueductal gray matter, locus coeruleus, and parabrachial nucleus, and are colocalized with serotoninergic and noradrenergic neurons. Originally, it has been hypothesized that substance P plays a role as nociceptive transmitter in afferent sensory fibers. The presence of substance P and NK-1R receptors in limbic regions implied their role in the regulation of emotion processing and in responses to stress (Bittencourt et al. 1991).

In major depression, an elevated level of substance P in serum (Bondy et al. 2003) and in cerebrospinal fluid (Geracioti et al. 2006) has been demonstrated. In patients who responded to treatment with antidepressants, a level of substance P gradually decreased (Bondy et al. 2003). Some experimental studies indicate that the effect on the serotonin and noradrenaline systems caused by NK-1R antagonists is similar to that caused by antidepressants (Blier et al. 2004). However, results of clinical studies led to ambiguous conclusions.

Amelioration of symptoms of major depression was reported in two studies using orvepitant (Ratti et al. 2013) and aprepitant (Kramer et al. 1998) agents which block central NK-1R. Contrary to these results, the study by Keller et al. (2006) did not demonstrate the efficacy of aprepitant in MDD.

### 12.2.5 Neurotransmitters: Serotonin (5-HT) and Noradrenaline (NA) and Dopamine (DA)

The monoamine hypothesis of depression was formulated 50 years ago. It posits that depletion of concentrations of 5-HT, NA, and DA has a causative role in pathogenesis of depression (Delgado 2000). A reduction of signaling in ascending serotonin neurons, projecting from midbrain raphe and noradrenaline neurons—projecting from locus coeruleus pathways to limbic system and frontal cortex—is responsible for "psychological" symptoms of depression.

It has been postulated that the malfunction of descending 5-HT and NA neurons may modify perception of pain and cause painful physical symptoms in depression (Stahl 2002). These neurons have an inhibitory role in pain perception. Two reciprocally connected anatomic structures play a key role in the inhibition of pain. The first, the periaqueductal gray (PAG), receives fibers from the amygdala, hypothalamus, and frontal cortex. The second, the rostral ventromedial medulla (RVM), receives inputs from the thalamus, parabrachial regions, and noradrenergic neurons from the locus coeruleus. Descending projections from the RVM increase the release of 5-HT in the dorsal horn leading to the antinociceptive effect. The RVM contains "on cells" which facilitate pain transmission as well as "off cells" which inhibit pain perception. Moreover, stimulation of the PAG and RVM can release NA into the spinal dorsal horn. The final antinociceptive effect is mediated by its NA binding to alpha-2 receptors (Ossipov et al. 2014).

Ascending dopaminergic transmission from the ventral tegmental area to the NAc and prefrontal cortex plays a key role in the regulation of mood, salience, motivation, and reward. Aberrant functioning of this system may cause such symptoms of depression as anhedonia and lack of motivation. The dopaminergic system also exerts a modulatory effect on the perception of nociceptive signals. This effect is illustrated by frequent comorbidity of Parkinson's disease and chronic pain (Jarcho et al. 2012; Mitsi and Zachariou 2016).

These data imply that in the pathogenesis of both depression and chronic pain, an interaction of immune, endocrine, and neurotransmitter systems play a central role. These abnormalities probably cause dysregulation of brain structures involved in the regulation of emotion and processing of pain.

### 12.2.6 Brain Networks of Depression and Pain

Functional neuroimaging enables identification of cortical and subcortical structures involved in the perception of different aspects of pain, also referred to as "pain matrix." Primary and secondary somatosensory cortices and the IC are responsible for encoding the sensory aspects of pain, its location, and duration. The emotional and motivational aspects of pain perception are processed in the ACC, IC, amygdala, and NAc. The prefrontal cortex plays a role in the regulation of pain perception (Apkarian et al. 2005; Bushnell et al. 2013).

Structures involved in processing the affective component of pain are also relevant to understanding a neural basis of depression. In short, emotion and reward processing are regulated by the amygdala and ventral striatum. The medial prefrontal cortex and ACC regulate the processing of emotion and the autonomic regulation of emotion. Both the dorsolateral (DLPFC) and the ventrolateral (VPFC) prefrontal cortex, by their connections to the limbic region, are involved in the cognitive control of emotions. Disturbances of these structures and connecting pathways account for affective, motor, and cognitive symptoms of depression (Kupfer et al. 2012) and also chronic pain (Lee and Tracey 2010). Neuroimaging studies have demonstrated modest structural and functional abnormalities in the

frontal-limbic regions of depressed patients (Apkarian et al. 2004; Arnone et al. 2012; Busatto 2013) and in chronic pain conditions like fibromyalgia and chronic back pain (Kuchinad et al. 2007; Burgmer et al. 2009; Robinson et al. 2011; Ivo et al. 2013; McCrae et al. 2015).

The prefrontal cortex is implicated in continuous monitoring of the external world and the maintenance of information in short-term memory and in governing efficient performance control in the presence of interfering stimuli, as well as in the regulation of perception and the behavioral expression of pain. In the context of pain perception, Lorenz et al. (2003) argue that the DLPFC plays a role in "keeping pain out of mind."

Results of functional brain imaging studies in patients with depression and chronic pain also indicate to abnormal function of common brain structures. Early PET studies of depressed patients provided evidence that brain glucose metabolism in the prefrontal cortex is decreased (Mayberg et al. 1999; Kimbrell et al. 2002) These observations were confirmed by more recent reports (Li et al. 2015). The second neuroimaging marker of major depression, confirmed in a meta-analysis of functional imaging studies, is increased activity in the medial and inferior prefrontal cortex, the basal ganglia, and in the amygdala—neural systems supporting the regulation of both pain and emotion (Fitzgerald et al. 2008). Interestingly, dysfunction of the prefrontal cortex was also demonstrated in patients with rheumatoid arthritis (PET study) (Jones and Derbyshire 1997) and in fibromyalgia (fMRI study) (Loggia et al. 2015).

Evidence suggests that in patients with MDD, modulatory mechanisms of pain perception are ineffective. During painful stimulation in unmediated depressed patients exposed to painful heat stimulation, activation in periaqueductal gray, rostral anterior cingulate, and prefrontal cortices was decreased in comparison to non-painful stimuli. These structures are responsible for pain and emotion modulation. Moreover, increased activation in the right amygdala, anterior IC, and ACC may suggest a bias toward affective processing of pain which was also observed during anticipation of pain (Strigo et al. 2008). The aim of the study by López-Solà et al. (2010) was to investigate whether brain responses to painful stimuli in depressed patients normalize after 1 and 8 weeks of treatment with duloxetine. The results imply that the clinical improvement in the course of treatment with duloxetine was related to a significant reduction of activation in, i.e., the pregenual ACC, right prefrontal cortex, and pons, regions overactivated at baseline.

Results of several studies indicate dysfunction of IC in the regulation of pain perception in depression. IC possesses an extensive connection with frontal-limbic structures (Graff-Guerrero et al. 2008; Strigo et al. 2010). Neuroimaging studies provided evidence for the functional reorganization of the IC in major depression. In depressed patients, emotional processing was shifted to the dorsal anterior insula—regions normally activated in response to physical pain. This phenomenon seems to explain why depressed individuals perceive pain in response to non-painful stimuli (Mutschler et al. 2012).

A wealth of experimental and clinical data shows that mesolimbic dopaminergic neurons have the modulatory role in the perception of pain. Dysfunction of the NAc and the ventral tegmental area were documented to induce excessive pain in animal models (Saadé et al. 1997). Then PET studies showed abnormalities in the striatal dopaminergic system in patients with atypical facial pain (Hagelberg et al. 2003a, b) and burning mouth syndrome (Hagelberg et al. 2003a).

Deficits of dopamine are also linked with the common comorbidity of pain and depression in Parkinson's disease. However, dysfunction of the reward dopamine reward system is postulated as a cause of core symptoms of depression anhedonia, reduced motivation, and decreased energy levels (Nestler and Carlezon 2006).

## 12.3 Management

The first tricyclic antidepressant (TCA)—imipramine—was introduced in the 1960s. Somewhat later, the effectiveness of this class of drugs in the management of chronic pain was discovered. In the last decade of the twentieth century, several new classes of antidepressants, namely, selective

serotonin reuptake inhibitors (SSRIs) and SNRIs, were accepted for treatment of depression and other psychiatric disorders. Subsequently, these drugs turned out to be useful in the treatment of chronic pain syndromes. As a consequence, in the WHO three-step ladder of management of chronic pain, antidepressants are recommended as adjuvant treatment to nonopioid and opioid analgesics (Kapur et al. 2014). Clinical evidence suggests that antidepressants are effective in the management of chronic pain conditions (i.e., neuropathies, back pain) and functional somatic syndromes (i.e., fibromyalgia and irritable bowel syndrome) and in the treatment of PPS in the course of major depression.

In recommendations regarding pharmacological treatment of neuropathic pain, Dworkin et al. (2010) argue that TCA, SNRIs, gabapentin, and pregabalin, as well as topical lidocaine, are methods of first-line management. These recommendations were supported by two subsequently published meta-analyses, confirming the efficacy of TCA and SNRIs in the treatment of neuropathic pain (Griebeler et al. 2014; Finnerup et al. 2015). These two groups of antidepressants appeared also to be useful in the management of non-neuropathic chronic pain in the course of rheumatoid conditions, lower back pain, and headaches, whereas studies with SSRIs provided inconsistent results (Dharmshaktu et al. 2012).

Functional somatic syndromes—fibromyalgia (FM) and irritable bowel syndrome (IBS)—manifest among other symptoms by unexplained pain and commonly co-occur with depression. Results of clinical studies and their meta-analyses consistently confirm the efficacy of amitriptyline and SNRIs (duloxetine, milnacipran, and venlafaxine) in reducing pain and other symptoms of FM (Arnold et al. 2013; Chappell et al. 2008; Häuser et al. 2012; VanderWeide et al. 2015), whereas Walitt et al. (2015) did not find convincing evidence for SSRIs' efficacy in treating pain, fatigue, and sleep problems in patients with FM. Studies examining the usefulness of antidepressants in the treatment of IBS have provided inconsistent conclusions. Results of a 12-week double-blind study in constipation-predominant IBS showed a better response in patients treated with fluoxetine in comparison to a placebo group (Vahedi et al. 2005). Good efficacy of citalopram (Tack et al. 2006), but not paroxetine (Masand et al. 2009), was also reported. Furthermore, in an open-labeled study, the treatment with duloxetine caused an improvement in gastrointestinal symptoms (Brennan et al. 2009). Ford et al. (2009) in their systematic review and meta-analysis found evidence for the efficacy of TCAs or SSRIs in the treatment of distension, pain, and stool consistency in patients with IBS. In a more recent meta-analysis, Xie et al. (2015) concluded that TCAs may also ameliorate symptoms of IBS, whereas the authors did not find strong evidence supporting the efficacy of SSRIs for the treatment of IBS.

These data suggest that in the aforementioned painful conditions, dual-action antidepressants possibly have a superior effect on pain in comparison to SSRIs. PPS in depression are likely to have a different neurobiological basis than neuropathic pain, painful functional syndromes. Hence, one may presume that extrapolation of results from studies of patients with primary pain conditions to recommendations for patients with depression and PPS is not justified.

The efficacy of antidepressants with different mechanisms of action for reducing severity of pain in psychiatric disorders was the aim of several studies. Two randomized, double-blind studies demonstrated that fluoxetine (Luo et al. 2009) and citalopram, but not reboxetine (Aragona et al. 2005), alleviated symptoms of somatoform pain disorder. The efficacy of SNRIs in treatment of PPS in depression was widely investigated. The advantageous impact of venlafaxine on both symptoms of depression and chronic pain was found in an observational study of 505 patients treated in primary care (Begré et al. 2008) and in an 8-week study of patients with first-episode depression with painful symptoms (Huang et al. 2013), whereas a 6-week investigation of patients with depression and co-occurring chronic lower back pain showed a modest therapeutic effect on pain of 150 mg of venlafaxine. At the final point of the study, only 26.4% of participants responded in both conditions (Rej et al. 2014).

Duloxetine is another potent, dual-reuptake inhibitor of 5-HT and NA. This medication has

been studied in several placebo-controlled, randomized trials which showed that duloxetine is effective in reducing pain in depressed patients (Brannan et al. 2005; Fava et al. 2004; Raskin et al. 2007). The results of a meta-analysis of 11 randomized, placebo-controlled studies conducted by Ball et al. (2011) confirmed these findings.

The issue of whether serotonergic drugs are as effective as noradrenergic agents in the treatment of PPS in depression was the aim of our study. We found that during 8-week treatment, both serotonergic (escitalopram) and noradrenergic (nortriptyline) antidepressants were equally efficacious in the alleviation of PPS in depression (Jaracz et al. 2015).

In clinical practice, SSRIs are recommended as a first-line treatment of depression. So a relevant question arises as to whether SSRIs are as effective as SNRIs in patients with depression and PPS. A multicenter, randomized, non-blinded, parallel group 12-week trial conducted by Martinez et al. (2012) showed that, in terms of depression remission rate, the efficacy of duloxetine was similar to that of generic SSRIs (citalopram, fluoxetine, paroxetine, or sertraline), whereas the impact of duloxetine on PPS was substantially better. These findings are contradictory to the results, published earlier, of a pooled analysis of eight studies comparing the efficacy of duloxetine (40–120 mg/day) and paroxetine (20 mg/day) in depressed patients. Both drugs appeared to be comparably effective in the reduction of painful symptoms assessed by visual analog scale (VAS) (Krebs et al. 2008). Taken these findings into account, the authors conclude that there is no clear evidence to suggest the superiority of SNRIs over SSRIs in the treatment of MDD with accompanying pain. This assumption corroborates the results of a recent meta-analysis conducted by Gebhardt et al. (2016). The authors included 19 studies investigating the efficacy of different classes of antidepressants in the treatment of primary depressive disorder with pain symptoms and found no relevant differences among SNRIs and SSRIs in the alleviation of PPS.

In patients with depression with inadequate response to treatment with SSRIs switching to another antidepressant, preferably different mechanism of action is recommended. The rationale for this strategy was investigated in patients with MDD with considerable pain, who did not respond or partially responded during 6 weeks of treatment with SSRIs (Perahia et al. 2009). After switching to duloxetine, significant diminution of pain severity, time in pain, and interference with functioning due to pain was noted. The authors of another study found that in patients with moderate to severe pain in the course of MDD initially treated with escitalopram and who did not improve after 4 weeks, a switch to duloxetine at this point of the study led to earlier alleviation of pain intensity and better response in terms of functional remission than in a group of patients were change to duloxetine took place after 8 weeks (Romera et al. 2012).

The relationship between improvement of painful symptoms and basic symptoms of depression seems to be an interesting theoretical and practical problem. In this regard, two hypotheses should be considered. The first of these is that the reduction of pain is secondary to an improvement of core depressive symptoms, and the second is that antidepressive drugs have a direct impact on PPS. The view prevails that there is a bidirectional relationship between reduction of severity of depression and intensity of pain (Kroenke et al. 2011). Moreover, a significant pain reduction between weeks 2 and 4 appeared to be a good predictor of a positive response to treatment with duloxetine (Schneider et al. 2011). The relationship between PPS and efficacy of treatment was also investigated by Robinson et al. (2013) in a post hoc analysis of two 8-week studies comparing duloxetine 60 mg/day and a placebo. Applying a path analysis, the authors found that the probability of obtaining remission in patients treated with duloxetine is dependent on improvement in pain and functional impairment. Moreover, the alleviation of pain and mood severity was related to functional improvement in patients with PPS associated with MD.

A path analysis carried out in two studies of MD patients showed that, at least 50% of the duloxetine impact on pain was independent of the improvement in the psychological symptoms of

depression (Fava et al. 2004; Mallinckrodt et al. 2003). These results indicate that in patients with MD, antidepressants convey both direct and indirect analgesic effects.

It has been well documented that cognitive and emotional factors play a modulatory role in pain perception (Bushnell et al. 2013). In the group of cognitive processes, attentional control, expectation, and reappraisal play an essential role in pain perception (Wiech et al. 2008). The results of several studies indicate that psychotherapeutic approach, including cognitive-behavioral techniques, are useful in the treatment of both chronic pain (Hoffman et al. 2007; Reese and Mittag 2013; Monticone et al. 2015) and depression (Cuijpers et al. 2013). The alternative method, acceptance-based therapies, for example, mindfulness-based stress reduction programs and acceptance and commitment therapy, reveals beneficial effects on physical health and depression in patients suffering from chronic pain (Veehof et al. 2011). This becomes a premise for implementation of psychological methods in therapy of patients with depression and co-occurring pain. The aim of the Stepped Care for Affective Disorders and Musculoskeletal Pain (SCAMP) study was to evaluate the efficiency of antidepressant plus behavioral therapy in patients with musculoskeletal pain and comorbid depression. The results showed that optimized antidepressant therapy augmented with pain self-management program may result in amelioration of symptoms of depression and pain (Kroenke et al. 2009). Recently, Thielke et al. (2015) described the results of study of the Effectiveness of a Collaborative Approach to Pain (SEACAP). American veterans with chronic musculoskeletal pain were involved in this collaborative care intervention study. During a year-long study, assistants contacted patients to administer assessments of pain, disability, depression, and other health outcomes. Moreover, patients attended a four-session workshop that presented a brief activating approach to pain management and provided additional educational materials that focused on self-management. Pain intensity, pain interference, depression, and pain-related disability were monitored during the study. This intervention was more effective in terms of improvement of disability, depression, pain intensity, and pain interference in comparison to a group of patients treated "as usual."

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# 13 Clinical, Biological, and Therapeutic Characteristics Between Depression with and Without Medical Illness

Kiwon Kim and Hong Jin Jeon

## 13.1 Introduction

Interaction between depression and medical illnesses is well known by the impact of depression to medical illness with negative risk behaviors and psychobiological changes and by impact of medical illness to depression with biological changes and complications (Egede 2007; Katon et al. 2007; Katon 2011). More burdens of medical symptoms, functional disability, larger costs followed by significant increases in utilization, and poorer self-care coupled to increased morbidity and mortality would be related to comorbid depression (Narasimhan et al. 2008). Through pro-inflammatory interactions, hypothalamic pituitary axis dysfunctions, altered function in autonomic nervous system, and changed metabolic factors, accompanied with negative lifestyles, depression can worsen the progress of medical illnesses. Therefore, careful acknowledgment of depression in medically ill condition, following collaborative management on depression, would be effective dealing both with physical health and with mental health (Smith et al. 2016).

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## 13.2 Biological Mechanism Between Depression and Medical Illness and Chronic Stress

### 13.2.1 Biological Mechanism Related to the Hypothalamic-Pituitary-Adrenal (HPA) Axis

The bidirectional interaction between depression-related inflammation and inflammation induced from physical illness is a well-known theory suggesting novel antidepressant development and leading to the development of specialty of psychoneuroimmunology (Leonard 2017). Historically, stress-induced hypercortisolemia has been understood as a part of adaptive response which belonged to "fight-or-flight" response. But it can be applied to protective function only limited to acute situations, which in the prolonged stress response dissociated from the initiating stimulus; this component of adaptive mechanism can be harmful to the brain and peripheral organs (Segerstrom and Miller 2004).

The alteration coupled to chronic stress and cellular immunity brings alteration in the characteristics of glucocorticoid receptors consisted of their expression and sensitivity (Quan et al. 2003).



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The so-called glucocorticoid receptor desensitization, which is a combination of increased inactive alpha-glucocorticoid receptor isoform and decreased active beta-form of the receptors induced by pro-inflammatory cytokines, represents the declined response to the peripheral glucocorticoids (Pace and Miller 2009). Usually, in the acute stress reaction, glucocorticoids downregulate the expression of inflammation, but in the chronic stress reaction following chronic medical illness, glucocorticoid receptor desensitization leads to increased inflammatory state.

Chronic activation of the hypothalamic-pituitary-adrenal (HPA) axis accelerates this phenomenon bringing exaggerated release of glucocorticoids coupled with hindrance in the plasma binding capacity of corticosteroid binding globulin. These changes include both cellular reduction in the translocation of glucocorticoids receptors and reduction in the reactivity of receptor protein in immune cells, either in peripheral tissues or in the hippocampus, which was classified as essential region of negative feedback regulation of the HPA axis (De Kloet et al. 1998).

### 13.2.2 Biological Mechanism Related to the Immune System

Neuroinflammation includes implication of immune-related process occurring inside of the brain and spinal cord, which is a consequence of harm brought by infection, psychological stress, and physical stress. Followed by neuroinflammation, the innate immune cells including the microglia, astrocytes, and oligodendroglia, reacted by the stimulus, are encouraged to release cytokines, chemokines, and accessory inflammatory mediators, known as the prostaglandins. Such harmful and maladaptive inflammatory response in the brain system is clearly manifested in the major neurological disorders, embracing cerebrovascular events, multiple sclerosis, and neurodegenerative diseases like Alzheimer's disease or Huntington's disease (Lee et al. 2010).

Previously dividing the immune response into the innate and adaptive components, the brain has been considered to be a special region in regard of immune system. Triggered by the pathogen, the innate immune system initiates the release of the histamine, prostaglandins, bradykinin, serotonin, and leukotrienes, producing a localized inflammatory response including vasodilation and pain, gathering macrophages.

The adaptive immune response includes the functions of T cells and B cells, which are known to be lacking in the bran system. But T cells rooted from the periphery system also circulate to the brain and spinal cord through the meninges, choroid plexus, and cerebrospinal fluid. Blood-brain barrier, which has been known as physical barrier, conversely can work for the route of large molecules and cells depending on the region of the brain or of the choroid plexus regions and the degradation stage of the astrocyte-pericyte sheath (Leonard 2017).

The pro- and anti-inflammatory cytokines including IL-1β, IL-6, TNF-α, IFN-γ, IL-antagonist, and TGF-β boost the HPA axis, followed by upregulation of cortisol synthesis, and activate the tryptophan-kynurenine pathway (Galic et al. 2012). These phenomena, which can lead to the neurotoxic *N*-methyl-D-aspartate (NMDA) glutamate agonist quinolinic acid precipitating oxidative stress and neurodegeneration are highly observed features in late life depression (Myint and Kim 2003).

## 13.3 General Issues as Clinical Characteristics in Depression with and Without Physical Illness

In this section, clinical manifestations related to depression comorbid to medical illnesses will be described in crude way, which will be discussed in detail, lately. In endocrine disease classification, depression is quite common clinical characteristics in Cushing's syndrome manifested as major depression, often with melancholic subtype, commonly accompanied with irritability and emotional lability, vegetative symptoms, anhedonia, psychomotor retardation or agitation, decreased concentration, and suicidal thoughts (Kelly 1996; Sonino et al. 1993). People with hypothyroidism

show depression or anergia (Sternbach et al. 1983), while people with primary hyperparathyroidism accompany depression, tiredness, forgetfulness, decreased concentration, uneasiness, sleepless, and irritability (Tsukahara et al. 2008). Neurological disorders, which can be associated with dysfunctional regulation of chronic inflammation, including multiple sclerosis, meningioma, and Parkinson's disease contain major depressive disorder features and concomitant anxiety (Gonera et al. 1997; Kantorova et al. 2017).

In malignant disorders, loss of ambition, loss of motivation, or lack of energy to proceed accompanied with vegetative symptoms seems to be common in pancreatic cancer (Grassi et al. 2014). In lung cancer (Montazeri et al. 1998) and gastric cancer (Andersen et al. 2014), all depressive features can be manifested as related to its shared mechanisms or precipitated by paraneoplastic syndromes or concomitant medications and poorly controlled pain. Heart disease especially in myocardial infection, major depressive clinical features, demoralization, somatic and generalized anxiety, panic, and agoraphobia all can be understood as early manifestations of comorbid medical illnesses (Ottolini et al. 2005). AIDS patients also report somatic and nonsomatic symptoms of depression ranging from sadness to low mood and anhedonia usually 1.5 years before their diagnostic sentence and continue to report these symptoms thereafter (Lyketsos et al. 1996).

## 13.4 Depression with and Without Pain

Pain and depression commonly exist simultaneously, bringing 2.5–10 times increase in anxiety or depression in patients with pain (Cocksedge et al. 2014; Means-Christensen et al. 2008). Comorbid pain can blur the fine description of mood change and interfere with treating depression, which depressed patients frequently complain about pain than their low mood (Bair et al. 2003). Though clinician has detected depression comorbid with pain, clinicians are frequently apt to be focused on pain management than their psychological treatments, which can bring poor outcomes (Bair et al. 2003). Patients with both pain and depression showed larger number of general practice visits, more frequent tests, higher rate of antidepressant change, and more frequent referral to secondary care (Watson et al. 2009). More severe work dysfunction has been observed in patients with comorbid pain and depression mediated by both sickness absence and loss of productivity (Demyttenaere et al. 2010).

While assessing patient with pain, careful history taking related to current or past maltreatment or shock would be necessary. The clinician should show empathy on their medical illness and pain with structured interview. Acknowledging patient's behavior related to pain and illness would be an essential part of interview. Delicate approach on invasive test and on using medication which can bring addiction is necessary. Every time, careful consideration on psychiatric evaluation and related interview should be prepared. There are several fundamental rules for administrating opioid analgesics. First, make strong therapeutic relationship between clinician and the patient. Second, careful checkup for the psychiatric status such as comorbid depression or anxiety should be accompanied with therapeutic approach related to pain. Third, enough dose of pain killer with appropriate duration with regular phase should be administrated to the patient, not to make the patient crave for additional pain killer. Fourth, it would be better to use "around the clock" rather than with prn medication. Long-acting sustained-release dosage form of pain killer would be preferred to short-acting dosage form of injection type. Regular and quite frequent thorough evaluation for the pain itself would guide necessary approaches to the clinician.

## 13.5 Depression with and Without Autoimmune Disorders

Frequent comorbidity with depression and autoimmune disorders was discussed in previous section. However, few longitudinal studies have gone through to prove immune responses affecting the brain and leading increased risk of mood disorders. From a nationwide longitudinal follow-up study,

autoimmune disease and infections seemed to be risk factors for subsequent mood disorder diagnosis. Their associations seem to be in line with an immunologic hypothesis for incidence of mood disorders in these patients (Benros et al. 2013). Inside of autoimmune disease patient, systemic inflammation can induce a "sickness behavior," with symptoms of fatigue, loss of appetite, apathy, decreased social interaction, concentration difficulty, and sleep problems. These symptoms are similar to symptoms of depression, and studies have suggested that in vulnerable patients, prolonged sickness behavior can progress to depression.

Unrestrained acute and chronic inflammation has unintentional detrimental effects on cognition, mood, and fatigue. The chronic inflammatory state in systemic lupus erythematosus (SLE) with recurrent episodes of acute escalation brings the necessary cascade for altered CNS processes that govern cognition and mood. Clinically, central neuropsychiatric SLE (NPSLE) syndromes including cognitive impairment, mood disturbances, and fatigue are both transient and chronic, and neuronal damage alone from direct antibody or MMP-mediated toxicity or ischemia, embolic events, or atherosclerotic disease would not lead to transient phenomena. However, altered cytokine- and chemokine-mediated signaling through peripheral or central pathway may impact synaptic plasticity and LTP in a short time, bringing a result of transient cognitive impairment.

Both anti-NMDAR and anti-P antibodies have been shown to be associated with synaptic plasticity in region of hippocampus, in addition to their neurotoxic influences, suggesting additional results as transient cognitive impairment or mood disturbances. The same pro-inflammatory cytokines have been shown to promote oxidative stress resulting in DAMPS production and TLR engagement leading to extreme fatigue. For it is important in SLE pathogenesis and dose-dependent associations of therapeutic effect of itself on neuropsychological symptoms of fatigue, depression, and seizures, IFN-α is thought to be important clue on SLE.

Depression is one of the most commonly reported symptoms in SLE with debilitating effects on quality of life, and the ultimate goal is to develop appropriate therapeutic strategies. Interestingly, not all therapies need to be immunosuppressive as evidenced by the success of fish oil for antioxidant properties in fatigue (Arriens et al. 2015). Otherwise, anticytokine therapies, targeting IFN-α and its receptors, may bring benefit independently unaffecting peripheral organs.

Inflammatory bowel disease (IBD), one of the well-known autoimmune disorders, also frequently seems to be accompanied with depression. Recent reconceptualization of depression as clinical phenomenon representing activated immune-inflammatory, oxidative, and nitrosative stress pathways consisted of tryptophan catabolite, autoimmune, and gut-brain pathways. Oxidative and nitrosative pathways are combination of the pathogenesis in IBD. Usually lower quality of life and increased morbidity in IBD are associated with increased depression prevalence, suggesting the depression role with modulation on IBD. Increased oxidative and nitrosative stress processes in depression coincide with the biological underlying mechanisms of IBD, suggesting increased comorbidity of both disorders (Martin-Subero et al. 2016).

In some patients, depressive symptoms remit with aggressive medical treatment of underlying IBD progression, while others need additional behavioral interventions or symptom-targeted medication because of their functional impairment or persistence of depression. Not all patients with IBD show depression, especially when observed during the IBD remission phase (Greenley et al. 2010; Reed-Knight et al. 2014). More thorough longitudinal studies discriminate depressive phenotypes and different mechanisms related to concomitant depression in Crohn's disease (CD) and ulcerative colitis (UC). Comprehensive evaluation of both neurobiological and psychosocial aspects related to depression will help clinician intervene in patient's health-related quality of life.

## 13.6 Depression with and Without Endocrine Disorders

Excessive or lack of thyroid hormones can cause depression but also can be fixed by suitable thyroid treatment (Hage and Azar 2012). Thorough thyroid function test, detecting subclinical

hypothyroidism, also can be helpful in nonresponse group of depression (Hage and Azar 2012), in which, in case of confirmation of subclinical hypothyroidism, prescription of thyroid hormone in modest levels would be helpful. In thyroid hormone augmentation regimen, triiodothyronine with dose between 25 and 50 microgram per day is preferred to thyroxine for its biological activity in the brain (Orsi et al. 2014). Contraindication of using triiodothyronine in coronary artery disease or chronic heart failure and precaution in diabetic patients should be noted. Patients with polymorphism which means lower conversion activity of thyroid hormone were more likely to react to triiodothyronine augmentation (Cooper-Kazaz et al. 2009). Even if assessment of thyroid dysfunction is not the primary step for depressive patients, when patients are not responding to treatment either accompanying history of thyroid disease or concomitant signs and symptoms of thyroid dysfunction, thyroid evaluation should be considered for screening.

The most common psychiatric representation of Cushing's syndrome is mood disorders. Depression occurs in approximately 25% of the patients in the prodromal phase of Cushing's syndrome (Sonino et al. 1993). The incidence, type of mood disorders, and response to treatment are not related to the etiology of Cushing's syndrome (Sonino and Fava 2001). The potential risk factors related to depression are old age, being female, high levels of cortisol in the urine before treatment, and more severe clinical condition (Sonino et al. 1998). Still clear conclusion whether depressive disorders result from direct effect of hypothalamic-pituitary-adrenal axis disorders or indirect effect of disfigurement, pain, and a lack of self-appearance is not existing. Functional hypercortisolism in major depression (Carroll et al. 2012; Tirabassi et al. 2014) was suggested in a ground of animal models, and the hippocampus is particularly sensitive to hypercortisolism brought by exposure to exogenous glucocorticoids or heavy stress as hippocampal neurons have a high density of glucocorticoid receptors, which in the case of chronic hypercortisolism may lead to a selective shrinkage of the hippocampus. Individuals with Cushing's syndrome are observed to have difficulties in distinguishing emotional states and have impaired activation of brain structures responsible for perception, processing, and regulation of emotions similar to those found in major depression (Langenecker et al. 2012). Normalizing level of cortisol through appropriate treatment can bring treatment effect to the comorbid depression, decreasing accompanied percent of patients' (Lau et al. 2015; Osswald et al. 2014).

Relationship between diabetes and depression has been discussed for many years for their similar mechanisms and impacts. Fetal or maternal stress, consistent low socioeconomic status, and poor health behaviors in individuals accompanying genetic predisposition might promote dysfunctional HPA axis, circadian rhythm shifts, and precipitation in the innate inflammatory response. Altered regulation of these biological pathways might bring insulin resistance and type 2 diabetes, depression, dementia, and cardiovascular disease. Excess pro-inflammatory cytokines in the brain resulting in increased neuroactive metabolites coming from decomposition of tryptophan and reduced serotonin would lead to depression.

Also close association between type 1 diabetes and depression is striking, during adjustment to diagnosis of type 1 diabetes and treatment course with increasing vulnerability to depression. It may be related to more sensitive brain which leads to quick end effects of these biological pathways or first environmental stress impact bringing central dysregulation of metabolism (Moulton et al. 2015).

Even though screening and treatment for depression in diabetes are still incomplete, detecting depression in diabetes with validated instruments can be effective if there are subsequent treatment pathways. To prevent negative interaction between diabetes and depression, all three approaches should focus on remission of depression, improvement of depressive symptoms, and fine glucose control. Through collaborative care and stepped approaches, numerous psychological and medical interventions could lead to depression treatment in diabetes. However, further evidence should be proposed for treatment evaluation for depression subtypes in diabetic individuals,

the cost-effectiveness of treatments, healthcare service use, accompanying cultural impacts, and new treatment approaches including preventive interventions (Petrak et al. 2015).

## 13.7 Depression with and Without Cancer

Depression is common in individuals with cancer (Currier and Nemeroff 2014), supported by recent major meta-analysis (Mitchell et al. 2011) reporting 16% prevalence of major depression in oncology and hematology inpatient and outpatient individuals. Elderly patients with metastases showed 2.2 times increased ration of depression, while individuals with cognitive impairment showed 3.6 times increased likelihood (Mystakidou et al. 2013). However, differential diagnosing between pathological and normal bereaving reactions to cancer is major challenging step. Though hardship on this assessment, depression even in subthreshold condition should be alarmed for its negative influence on quality of life, treatment compliance, suicidality and mortality rate. From these backgrounds, all individuals with cancer should be screened for depressive symptoms from the initial visit, with appropriate interval follow-ups correlated to clinical progress, including post-treatment, at the time of recur, progressed phase, and transition period considering palliative care. Valid and reliable assessments with phased screening and assessment should be applied, with full identification of the pertinent history of depression risk factors. About 25–30% of individuals usually fully report depressive mood and anhedonia, which should complete the full version of the Personal Health Questionnaire (PHQ-9) (Kroenke et al. 2001). Even though the usual cutoff score for PHQ-9 is ten, for individuals with cancer, PHQ-9 cutoff score is applied as eight (Manea et al. 2012). And applying assessment with consideration of culture, tailoring assessment, and treatment option for learning disabilities or cognitive impairments and careful approach with differentiating depression in elderly patients are necessary.

Appropriate referral to a psychiatrist, psychologist, physician, or other trained professionals is essential in situation such as risk of self-injury or others' injury, severe depression or agitation, or the psychotic state or delirious state. Such careful assessments should be applied with collaborative team approach, accompanying clear identification of signs and symptoms in depression, cancer symptoms, stressors, risk factors, and vulnerability. Before starting antidepressant medication especially including administration of interferon, medical cause or substance problem related to depression must be considered and managed.

## 13.8 Depression with and Without Major Organ Failures

### 13.8.1 Depression with and Without Myocardial Disease and Congestive Heart Failure

Both an increase in coronary heart disease (CHD) in individuals with depression and increased morbidity and mortality in CHD patients who become depressed are well-known interaction. One large prospective study found that depressive symptoms had more great likelihood of CHD events in late life, especially sudden cardiac death, with a specific relationship between this outcome and antidepressant use (Manea et al. 2012). Fifteen to twenty percent of individuals with myocardial infarction or angina are reported to have major depressive disorder (MDD) (Mavrides and Nemeroff 2013). And these individuals were reported to be associated with increased mortality and decreased cardiovascular outcome. Between close relationship with coronary artery disease and depression, few mechanisms including inactivity, decreased heart rate variability (Whooley et al. 2008), platelet hyperactivation (Morel-Kopp et al. 2009), and increased inflammatory markers or HPA activity are thought to be existed. Speaking of chronic heart failure, 21.5% of individuals with heart failure were reported to have depression, higher in more severe heart failure, which leads to higher mortality rate and following cardiac events (Diez-Quevedo et al. 2013).

### 13.8.2 Depression with and Without Chronic Obstructive Pulmonary Disease (COPD)

Forty-one percent of patients with COPD were observed to accompany with mild to moderate depressive symptoms, and the most severe depressed individuals seemed to be more hospitalized (Fan et al. 2007). The most severe depressive patients were reported to have significantly increased 3-year mortality rate as odds ratio of 2.7 increased tendency of dyspnea and decreased body weight (Janssen et al. 2010).

### 13.8.3 Depression with and Without Chronic Renal Failure (CRF)

Through subjective report-based depression screening in chronic kidney disease (CKD), 20% of individuals with CKD were estimated to have depression, while 23% of individuals with dialysis were estimated to have depression (Palmer et al. 2013). Both social and biological risk factors and the consequence of renal failure and dialysis on loss of control in life and quality of life make this comorbid depression in CKD higher (Bautovich et al. 2014). Multiple poor outcomes such as frequent and long hospitalizations, poor compliance to treatment, and high mortality rate can be associated with depression in CKD. Although these consequences, rated of diagnosis and followed appropriate management in depression co morbid to CKD remain unclear and low (Hedayati and Finkelstein 2009).

## 13.9 Depression with and Without Neurological Disorder

### 13.9.1 Depression with and Without Cerebrovascular Disease

The prevalence of comorbid depression in inpatients with cerebrovascular disease (CVD) is approximately 20%, and prevalence in outpatients with CVD is about 23% (Robinson 2003). Individuals with both CVD and active phase of depression were reported to have higher 5-year mortality rate than those with stroke alone. Previously, the location of a stroke was suggested to be an important mediating factor to poststroke depression, which now has been found no evidence, compromised with other consistent predictors, including sequelae of stroke such as physical disability, cognitive impairment, and severity of stroke (Carson et al. 2000; Hackett and Anderson 2005).

### 13.9.2 Depression with and Without Parkinson's Disease

Approximately 8–17% of Parkinson's disease patients are reported to have major depression, but differential diagnosis between comorbid major depression and Parkinson's disease and patients with sole Parkinson's disease is difficult because of similar symptoms such as psychomotor retardation and restricted facial expression. Although detecting comorbid depression is difficult, prevalence of depression in Parkinson's disease has been reported to be positively associated with severity of Parkinson's disease and accompanied dementia (Aarsland et al. 2011).

### 13.9.3 Depression with and Without Dementia

The prevalence of depression in dementia is estimated at approximately 25% (Enache et al. 2011; Orgeta et al. 2014). Individuals with dementia are recommended to go through evaluation and follow-up evaluation for depression over time (Ihl et al. 2011; Sorbi et al. 2012). Ruling out for secondary causes of depression also should be assessed. The application of a valid tool for screening depression in dementia includes the Geriatric Depression Scale (GDS), Cornell Scale for Depression in Dementia (CSDD), or Dementia Mood Assessment Scale (DMAS) (Hort et al. 2010; Sorbi et al. 2012). Among these instruments, the CSDD, clinician rating tool which can cover caregivers' depression with high sensitivity, was more commonly recommended (Callahan

et al. 2006; Hort et al. 2010). Sophisticated assessment is essential to find cognitive disorders in geriatric population with depression through fine neuropsychological investigations. The lack of generalization in feasible Alzheimer's disease neuroimaging and neurochemical CSF biomarkers and low rate application of this assessment in late-life depression make this correct diagnosis harder.

Even though psychological interventions have been proved for their beneficial results, recent antidepressant use in individuals with both dementia and depression has still been questioned. Further studies should focus on clinical and biological features to predict cognitive impairment in both early- and late-life depression. Devotion to find neurobiology of depression comorbid to cognitive impairment is also necessary, involving networks or neurotransmitter systems for precise diagnosis in depression alone and concomitant neurodegenerative disorders with depression. More large-scale, collaborative researches on late-life depression are needed, covering clinical, neuroimaging, neuropsychological, genetic, neurochemical, and environmental perspective. Careful approaches to prevent cognitive decline in patients with late-life depression are also essential. Big data with full description of demographic, psychopathological, and genetic biomarker and imaging is necessary, considering heterogeneous features observed in depression group and pathological location of the brain in depression. These researches should be analyzed with both cross-sectional and longitudinal methods. Transfertilized form of researches such as the precision medicine paradigm (Collins and Varmus 2015) adopted from oncology can be a key to solve this ambiguity. Accepting that individuals with depression and neurodegenerative disorders could have complex genetic, epigenetic, and genomic patterns is necessary, bringing molecular and cellular pathways which can be tracked and also worked as targets for treatment. These conditions can precede far before clinical symptoms emerge in depression and degenerative disorders, bringing possibility of comprehensive exploratory biomarkers, supporting precision medicine.

## 13.10 Therapeutic Approaches in Depression with and Without Medical Illness

Clinicians must apply careful therapeutic interventions considering side effects and impairments already existing due to the medical illnesses or other concomitant prescriptions. Drug interactions and metabolism should be sophisticatedly managed especially with individuals with renal or hepatic dysfunction. Major issues related to drug interventions contain the effect of SSRIs on cytochrome P450 enzyme (CYP450) activity and controversial bleeding risk. Despite these sophisticated considerations needed for management, this medication found to have significant advantage over placebo in remission and/or response with similar efficacy between SSRIs and TCAs, in depression with chronic medical illnesses: CVA, COPD, cancer, Parkinson's disease, diabetes, and cardiovascular disease (Taylor et al. 2011). However, matter of this therapeutic intervention lies in poorer response to antidepressants and more adverse effects (Mitchell and Subramaniam 2005). Safe application of antidepressants in medically ill individuals also should be focused considerably. Such concern is like using antidepressants as tricyclic antidepressants (TCAs) in individuals with heart diseases. Individuals with arthritis, pain management, and osteoporosis should be managed with careful assessment in interaction with concomitant medication and antidepressants (Caughey et al. 2010). Antidepressants, psychosocial interventions, and other medications to treat depression should be accompanied with managing dysfunctional conditions including endocrine alterations, chronic pain, and altered inflammation. Integrated care for depression in full concept of comorbidity also can bring better prognosis related to depression but needs sophisticated forms targeting special comorbid medical illnesses. Recently, collaborative care or stepped care approaches have appeared to be promising in these situations (Miller et al. 2013; Woltmann et al. 2012). The collaborative care consisted of a medically supervised nurse, the general practitioner work-

ing as guidelines, and collaborative care management, to control risk factors associated with multiple illnesses. They work as stratified structures, comprised of structured evaluation, multidisciplinary treatment, and follow-up monitoring. With these interventions, clinicians can also focus on outcomes including mortality, morbidity, and risk factors for both physical illness and depression. Growing interest in the effect of psychological therapies is uprising, including cognitive behavioral therapy (CBT) and psychoeducation in individuals with both depression and medical illnesses, either as sole therapy or as augmentation to antidepressants. When it comes to individuals concomitant with neurodegenerative disorders, therapy should include various nonpharmacological approaches, like stimulation-oriented, cognitive-behavioral, reminiscence, exercise, or multisensory therapy (Nutt et al. 2010; Qaseem et al. 2016). Most guidelines, grounded from clinical experiences, recommend the use of SSRIs compared to side effect profile of TCAs (Dua et al. 2011; Sorbi et al. 2012). Major concern lying with TCAs is anticholinergic side effects followed by worsening cognitive function (Gauthier et al. 2012). Other antidepressants including mirtazapine, venlafaxine, and bupropion seemed to have benefit. Stimulants, cholinesterase inhibitors, and electrical convulsive treatment (ECT) also showed benefit on a case-by-case basis. Within treatment model for individuals with both depression and medical illness, clinicians and researchers would need careful selection of the specific components and outcomes providing big impact for their patients (Breland et al. 2015).

**Conclusion**

Depression with medical illnesses is a complicated situation which needs sophisticated assessment and interventions. Depressive symptoms can be easily affected by symptoms of accompanied physical illnesses, sometimes bringing difficulties to differentiate sole physical illness and comorbid depression, which comes from inflammatory pathways, alteration in HPA axis, dysfunctional regulation of hormones, and change in neurotransmitters. Considering significant prevalence of depression in medical illnesses and its impact on the prognosis of medical illnesses expressed as morbidity or mortality, careful assessment of depressive symptom screening and severity should be prepared with validated assessment. Grounded from previous researches, screening for depression must be followed by appropriate management for depression. Recent management is recommended as collaborative team emphasizing fine regulation in medication application considering interaction and metabolism, sophisticated management in pain, and intensive management for medical illness.

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# Burnout Syndrome and Depression

14

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> We cannot have a successful science if we let our data lie to us. To attain cumulative knowledge, we must detect and correct those lies. If we do this, we can successfully apply Occam's razor and uphold the important principle of scientific parsimony. We can discover the simplicity at the deep structure level that underlies the apparent and confusing complexity at the surface structure level.—Schmidt (2010, p. 240).

## 14.1 Introduction

The burnout syndrome has elicited growing interest among the psychology and the psychiatry community since it was first described in the mid-1970s (Freudenberger 1974, 1975; Maslach 1976; Maslach and Pines 1977). Generally viewed as a job-induced affliction (Maslach et al. 2001; Schaufeli and Taris 2005), burnout has become a hotspot of occupational health research (Schaufeli et al. 2009b; Schonfeld and Chang 2017; Weber and Jaekel-Reinhard 2000). The syndrome has been associated with a variety of negative occupational consequences—including impaired work performance, absenteeism, and job turnover (e.g., Schaufeli et al. 2009a; Swider and Zimmerman 2010)—and adverse health outcomes (e.g., Ahola et al. 2010; Toker et al. 2012). Relatedly, burnout research has resulted, in recent years, in various recommendations and calls for action regarding the management of job stress (e.g., Epstein and Privitera 2016; Shanafelt et al. 2017).

In this chapter, we provide an overview of the burnout syndrome. We start by depicting the pioneering phase of burnout research that led to the introduction of the burnout construct in the scientific literature. We then describe the shift from initial exploratory and mainly qualitative research on burnout to more systematic, quantitative research on the syndrome. Finally, we summarize the most recent findings pertaining to the characterization of the burnout syndrome. These findings compellingly suggest that the syndrome referred to as burnout is a depressive condition and not a distinct entity. The findings call for more conceptual parsimony and theoretical integration in psychology and psychiatry, in the interest of more effective treatment and prevention strategies and enhanced transdisciplinary communication.

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## 14.2 The Dawn of Burnout Research

The burnout syndrome was first described by Freudenberger (1974) as he was working as an unpaid clinical psychologist in an alternative healthcare agency based in New York City.[1] Freudenberger (1974) observed that some of the volunteer staff, which included the author himself, developed a constellation of symptoms in response to their daily struggle to look after their patients—mostly drug addicts. Based on his field observations, Freudenberger (1974, 1975) characterized burnout as a slowly installing syndrome involving, among other signs and symptoms, fatigue, physical weakness and susceptibility to illness, sleep disturbance, weight alteration, irritability and frustration, crying spells, cynical and suspicious attitudes, psycho-rigidity, and professional inefficacy. Freudenberger (1974) indicated that the burned-out individual "looks, acts and seems depressed" (p. 161). Freudenberger (1975) further noted: "In their negativism the burn-out seems to be expressing his own depressed state of mind" (p. 79). Etiologically speaking, the burnout syndrome has been viewed, from the outset, as the product of a long-term discrepancy between the expectations and resources of the individual on the one hand and the actual outcomes and demands of his/her activity on the other (Freudenberger 1974, 1975). Freudenberger and Richelson (1980) thus considered the burnout syndrome to be "brought about by devotion to a cause, way of life, or relationship that failed to produce the expected reward" (p. 13).

The emergence of the burnout construct was also stimulated by social psychological research conducted in California. Maslach (1976) came to use the term "burnout" as she was studying emotions and coping strategies among human services workers. In so doing, she observed that some workers experiencing unresolvable job stress (i.e., work overload) developed symptoms of exhaustion and counterproductive detachment—irritability, depersonalization, neglect, withdrawal from work, and derogatory and callous attitudes toward recipients—that undermined their professional efficacy. "Burnout" was used as an umbrella label for these symptoms (see also Maslach and Pines 1977; Pines and Maslach 1978).

The dawn of burnout research was thus marked by an empiricist (i.e., atheoretical and data-driven) approach to (occupational) health, relying on methods such as exploratory interviews, on-site observations, case-studies, and personal experiences (Leiter and Maslach 2016; Maslach et al. 2001). Importantly, the initial publications dedicated to the burnout syndrome did not include any review of already-described stress-related conditions (Bianchi et al. 2017d). Moreover, the burnout construct was elaborated independently of the research carried out in psychiatry and, more globally, in medicine. Controlled clinical investigations were not conducted. The symptom picture associated with burnout was not compared with the symptom pictures of stress-related conditions identified in the past.

In the next section of this chapter, we continue our examination of the history of the burnout construct by focusing on the development, from the 1980s, of methods designed to study the burnout syndrome more systematically.

## 14.3 Shifting from Exploratory to Systematic Research on Burnout

### 14.3.1 The Definition and Assessment of Burnout Symptoms

The first standardized measure of burnout symptoms, the Maslach Burnout Inventory, was designed in the early 1980s (Maslach and Jackson 1981; Maslach et al. 2016). On the basis of the data collected during the exploratory phase of burnout research, Maslach and Jackson (1981) created a pool of 47 items. The items were administered to a sample of workers from various

[1] Fifteen years earlier in France, Veil (1959) described states of job-related exhaustion within a psychiatric framework.

health and service occupations (e.g., teachers, nurses, social workers) and then subjected to a factor analysis. Ten factors emerged from this initial analysis, of which four accounted for over three-fourths of the variance. The application of diverse item selection criteria (e.g., a factor loading exceeding 0.40 on only one of the four factors, a "high" item-total correlation) and the conducting of additional factor analyses eventually resulted in a 22-item questionnaire involving three dimensions: emotional exhaustion (e.g., "Working with people all day is really a strain for me"), depersonalization (e.g., "I feel I treat some recipients as if they were impersonal 'objects'"), and a sense of (reduced) personal accomplishment (e.g., "I deal very effectively with the problems of my recipients"). Emotional exhaustion refers to feelings of being emotionally drained and exhausted by one's work. Depersonalization involves a cynical attitude toward one's job and an unfeeling and impersonal way of responding to people one is working with (e.g., clients or colleagues). Reduced personal accomplishment defines a tendency to evaluate oneself negatively and to feel incompetent and dissatisfied with one's achievement on the job. The MBI assesses burnout symptoms within a 1-year time window, based on a 7-point scale (from 0 for "never" to 6 for "everyday").

Importantly, while the developers of the MBI conceptualized burnout as a three-component syndrome *combining* emotional exhaustion, depersonalization, and a sense of reduced personal accomplishment, they formally recommended, in contravention of this conceptualization, that the three components of burnout be examined *separately*, "given our limited knowledge about the relationships between the three aspects of burnout" (Maslach et al. 1996, p. 5). This recommendation has been criticized because it implies that individuals who suffer *only* from emotional exhaustion, *only* from depersonalization, or *only* from reduced personal accomplishment will be considered as suffering from the same condition, "burnout," although they present with symptom profiles that are, by definition, different and potentially call for different management strategies (Bianchi et al. 2017b; Brisson and Bianchi 2017a, b; Kristensen et al. 2005; Shirom 2005; Shirom and Melamed 2006).

Five versions of the MBI are currently available: the MBI-Human Services Survey (MBI-HSS), the MBI-Educators Survey, the MBI-General Survey (MBI-GS), the MBI for Medical Personnel, and the MBI-GS for Students (Maslach et al. 2016). The MBI-GS has been designed to allow virtually any occupational group to be assessed for burnout (Maslach et al. 1996). The MBI-GS contains 16 items phrased in generic ways. In the MBI-GS, the three dimensions of burnout have been relabeled exhaustion (e.g., "Working all day is really a strain for me"), cynicism (e.g., "I doubt the significance of my work"),[2] and (loss of) professional efficacy (e.g., "I can effectively solve the problems that arise in my work"). The three dimensions of the MBI-GS have been assumed to be equivalent to those of previous versions of the MBI. However, the validity of this assumption remains open to question (Larsen et al. 2017; Shirom 2003). For example, in a factor analytic study of the three subscales of the MBI-GS and the depersonalization subscale of the MBI-HSS, Salanova et al. (2005) found that a four-factor model of burnout with separate depersonalization and cynicism dimensions fit their data better than a three-factor model with depersonalization and cynicism collapsed into one factor.

The MBI has been the most widely used measure of burnout to date (Schaufeli et al. 2009b). The hegemonic status of the MBI in burnout research led some researchers to conclude that "*burnout is what the MBI measures*" (Schaufeli and Enzmann 1998, p. 188; Schaufeli 2003, p. 3). However, alternative measures, associated with slightly different conceptualizations of the burnout

[2] While cynicism has generally been characterized in burnout research as a negative, to-be-treated symptom (cynicism without caring, indifference), it is worth underlining that cynicism is multifaceted and can also be considered a "strategic virtue" (healthy cynicism) reflecting the enactment of a "realistic" and pragmatic, rather than "idealistic" and romanticized, view of one's work (e.g., in terms of personal expectations and aspirations). As noted by Rose et al. (2017), "tempered cynicism can protect the inner core of care and good practice" (p. 693).

construct, have been developed over time. For instance, the Burnout Measure (Pines and Aronson 1988; Pines et al. 1981) is intended to assess burnout as a combination of physical, emotional, and mental exhaustion. The Shirom-Melamed Burnout Measure (SMBM) operationalizes burnout as a syndrome combining physical fatigue, cognitive weariness, and emotional exhaustion (Shirom 2003; Shirom and Melamed 2006). The Oldenburg Burnout Inventory features only two subscales, exhaustion and disengagement (Demerouti et al. 2001; Halbesl eben and Demerouti 2005). The Copenhagen Burnout Inventory distinguishes between personal, work-related, and client-related burnout (Kristensen et al. 2005). Despite their differences, the main conceptualizations of burnout share the assumption that exhaustion is the core of the syndrome (Cox et al. 2005; Schaufeli and Enzmann 1998; Seidler et al. 2014). As put by Maslach et al. (2001), "exhaustion is the central quality of burnout and the most obvious manifestation of this complex syndrome" (p. 402).[3] "Exhaustion-only" conceptualizations of burnout (e.g., Kristensen et al. 2005; Shirom and Melamed 2006) reflect the view that depersonalization/cynicism and loss of personal accomplishment/professional efficacy do not need to be included in the syndrome because such constructs respectively refer to possible strategies to cope with (emotional) exhaustion and possible long-term consequences of (emotional) exhaustion (Kristensen et al. 2005, p. 194; Shirom and Melamed 2006, pp. 179–180).

[3]Maslach and Leiter (2016) recently seemed to change their mind regarding the centrality of exhaustion in the burnout syndrome, indicating that "the experience of cynicism may be more of a core part of burnout than exhaustion" (p. 109). This turnaround is intriguing given (a) the inconsistent findings on which it is based (Leiter and Maslach 2016, p. 97), (b) the fact that "exhaustion is… more predictive of stress-related health outcomes than the other two components [of burnout]" (Maslach and Leiter 2010, p. 726), and (c) the conclusions of meta-analytic reviews suggesting that exhaustion is the dimension of burnout that is "the most responsive to the nature and intensity of work-related stress" (Shirom 2003, p. 249). Moreover, in a meta-analytic review of 16 studies (Taris 2006), only emotional exhaustion (not depersonalization or reduced personal accomplishment) was found to be associated with decreased job performance.

### 14.3.2 The Unresolved Problem of Burnout Diagnosis

Although standardized measures of burnout symptoms are available, it is worth noting that no binding or consensual criteria for (differentially) diagnosing burnout have been established in more than 40 years of research (Bianchi et al. 2017d; Doulougeri et al. 2016; Weber and Jaekel-Reinhard 2000). As an illustration, burnout is not recognized as a nosological category in the latest versions of the *Diagnostic and Statistical Manual of Mental Disorders* [DSM-5; American Psychiatric Association (APA) 2013] and *International Classification of Diseases* (ICD-10; World Health Organization 2016).[4] The absence of a diagnosis for burnout is fundamentally problematic in that it undermines the ability of occupational health specialists to treat and prevent burnout. A key, yet overlooked, corollary of the impossibility of identifying "cases" of burnout is that the prevalence of the syndrome cannot be estimated (Bianchi et al. 2015a, 2016a, b, 2017c; Brisson and Bianchi 2017b). This state of affairs questions the validity of dozens of studies dedicated to estimating the prevalence of burnout and drains the recurrent claims about the "burnout epidemic" of their substance (Bianchi et al. 2017b, d; West et al. 2016).

Among other authors (e.g., Bianchi et al. 2015a, 2016a, b), Brisson and Bianchi (2017b) lamented "the widespread tendency among burnout researchers to put the cart before the horse by trying to estimate the prevalence of a syndrome that cannot be formally diagnosed" and pointed

[4]In the ICD-10, burnout is only briefly mentioned among the factors influencing health status and contact with health services. Interestingly, in The Netherlands, burnout has sometimes been equated with (job-related) neurasthenia (e.g., Schaufeli et al. 2001). Neurasthenia is indexed as a disorder in the ICD-10. Long considered to be part of *melancholia* (see Gamma et al. 2007), neurasthenia was first viewed as a distinct entity in the nineteenth century (Beard 1869; van Deusen 1869). Within the "neurasthenic approach" to burnout, burnout thus overlaps with a disorder isolated about 150 years ago. Other Dutch researchers (e.g., Kleijweg et al. 2013) have equated burnout with undifferentiated somatoform disorder, a derivative of neurasthenia that has been removed from the DSM-5 because of its lack of distinctiveness (APA 2013, p. 812).

out the worrying use of clinically and theoretically arbitrary identification criteria in burnout research (e.g., cutoff scores reflecting mere tercile-based splits).[5] It should be noted that the criteria used for identifying "cases" of burnout have not only been arbitrary. They have also shown considerable heterogeneity from one study to another (Bianchi 2015; Doulougeri et al. 2016), thereby jeopardizing between-study comparability. All in all, it must be acknowledged that the research dedicated to estimating the prevalence of burnout has been conspicuous by its vacuity. As a consequence, the findings derived from that research have been confusing for occupational health researchers and practitioners and have not offered public health decision-makers valid grounds on which to base their policies.

## 14.4 The Realization that Burnout Is a Depressive Condition

### 14.4.1 Early Clues

From the outset, burnout has been described in ways that were strongly evocative of depression. The overlap of burnout with depression is explicit in the initial descriptions of burnout proposed by Freudenberger (1974, 1975). Indeed, symptoms such as fatigue, sleep disturbance, weight alteration, or dysphoric mood constitute diagnostic criteria for major depression (APA 2013). Symptoms such as irritability and frustration, although not diagnostic criteria for major depression, are frequently observed in depressed individuals, especially in male and/or young patients (APA 2013; Judd et al. 2013). Judd et al. (2013) found that irritability/anger during major depressive episodes was a clinical marker of a more severe, chronic, and complex depressive illness. The overlap of burnout with depression is also detectable in the very dimensions of the MBI (emotional exhaustion, depersonalization, and reduced personal accomplishment; Maslach et al. 1996, 2016), as highlighted by Schonfeld (1991) and Bianchi et al. (2017a). To take but one example, emotional exhaustion has been shown to overlap with fatigue and loss of energy on the one hand and depressed mood on the other hand (Bianchi et al. 2017a), two diagnostic criteria for major depression (APA 2013). After having examined each dimension of the MBI in relation to depression, Bianchi et al. (2017a) concluded that emotional exhaustion, depersonalization, and reduced personal accomplishment refer to depressive signs and symptoms under nonpsychiatric terms.

More recent descriptions of burnout have been similarly suggestive of depression. For example, Maslach and Leiter (1997) wrote that burnout is not only about the "presence of negative emotions" but also about the "absence of positive ones" (p. 28), a picture that is reminiscent of depressed mood and anhedonia—the two core symptoms of depression (APA 2013). Maslach et al. (2001) asserted that there is "a predominance of dysphoric symptoms" in burnout (p. 404). Schaufeli and Buunk (2004) indicated that "first and foremost, burnt-out individuals feel helpless, hopeless and powerless" (p. 399), three feelings that are hallmarks of depression (Abramson et al. 1989; APA 2013; Laborit 1986; Peterson et al. 1993; Pryce et al. 2011).

Another source of concern regarding the distinctiveness of burnout has lain in the (presumed) etiology of the syndrome. In effect, unresolvable stress, which is thought to play a causative role in the development of burnout (Maslach et al. 2001; Shirom 2003), has been shown to be at the center of the etiology of depression (Laborit 1993; McEwen 2004; Pizzagalli 2014; Willner et al. 2013).[6] There is robust evidence, from research conducted in psychiatry, behavioral psychology,

[5] Diagnostic criteria for burnout would have required a clear specification of (a) the symptoms to be considered in clinical assessments, (b) the minimal duration and frequency of the exhibited symptoms, (c) the expected impact of the exhibited symptoms on the patient's (work) life, and (d) differential diagnosis procedures. The identification of distinctive biological correlates would have also been helpful.

[6] As emphasized by Sapolsky (2004), "it is impossible to understand either the biology or psychology of major depressions without recognizing the critical role played in the disease by stress" (p. 271) and "genes that predispose to depression only do so in a stressful environment" (p. 345).

and neurobiology, that depressive symptoms constitute basic responses to unresolvable stress in *Homo sapiens*, as in many other species (see Bianchi et al. 2017d). It is worth noting that the depressive feelings of helplessness and powerlessness can be viewed as direct consequences of the experience of unresolvable stress. From this perspective, the individual feels helpless and powerless precisely because he/she cannot neutralize the encountered stressors through effective action. Put differently, the individual does not feel in control vis-à-vis the encountered stressors. Hopelessness can be viewed as the expectation that this absence of control will last, that is, that helplessness and powerlessness will be experienced again and again in the presence of the stressors. The individual anticipates that he/she will not be able to manage in the future what he/she could not manage thus far. Because, in the individual's eye, action has proven to be ineffective in neutralizing stressors, passivity (i.e., inaction) and resignation become the predominant responses in the face of adversity. From an evolutionary standpoint, passivity can be considered preferable when stressors cannot be neutralized because passivity at least prevents the waste of energy associated with the production of ineffective action (Klinger 1975; Laborit 1986, 1993; Nesse 2000).

Freudenberger and Richelson's (1980) early claim that burnout results from an investment (cost) that is devoid of the expected return on investment (benefit) is also relevant to burnout-depression overlap.[7] Indeed, depression has long been viewed as a pathology of loss of gratification (i.e., loss of pleasure, happiness, or satisfaction in life). As reported by Beck and Alford (2009), loss of gratification is the most frequent complaint among depressed patients (p. 19). Importantly, under stress, a gratifying action is an action that allows the individual to neutralize the stressor. Unresolvable stress is thus synonymous with a long-term impossibility of acting in a manner that is gratifying—neurobiologically, of activating one's reward system and shutting down one's punishment system. All in all, depression can be conceived of as the product of a deficit of positive, rewarding experiences (i.e., experiences that activate the brain reward system), and an excess of negative, punitive experiences (i.e., experiences that activate the brain punishment system), with depressed mood and anhedonia two key symptoms of this disequilibrium (e.g., Bogdan and Pizzagalli 2006; Dombrovski et al. 2013; Pryce et al. 2011; Rolls, 2016; Wu et al. 2017).[8] In view of the above, the putative etiology of burnout could thus be considered to mirror the etiology of depression.

### 14.4.2 Attempts to Distinguish Burnout from Depression

In spite of the aforementioned similarities between burnout and depression, many burnout researchers have hypothesized that their entity of

[7] The view that burnout is etiologically related to an imbalance between investments and outcomes has been recurrently expressed in the literature. As an illustration, Heifetz and Bersani (1983) wrote: "It is not the heavy emotional investment per se that drains the provider; rather it is an investment that has insufficient dividends" (p. 61). More recently, this mismatch has been described in terms of (lack of) reciprocity between what the job gives and what it takes (see Schaufeli 2006). The same logics is at the heart of several current models of occupational strain such as Siegrist's (1996) effort-reward imbalance model. Freudenberger and Richelson's (1980) early view that burnout results from an imbalance between investments and outcomes thus remains very lively among burnout researchers.

[8] The well-established link between depression and suicide (Chesney et al. 2014) suggests that survival is not an objective under any condition in human beings. Everything happens as if human beings struggled for survival only as long as they consider their life worth living (i.e., sufficiently gratifying). The specific relationship between anhedonia and suicide supports this view (Winer et al. 2014), as does the finding that (a) the brain reward system is hypoactive in depressed patient (Dombrovski et al. 2013) and (b) individuals with major depressive disorder report blunted levels of both anticipatory and consummatory pleasure and elevated levels of both anticipatory and consummatory displeasure for daily activities (Wu et al. 2017). As summarized by Dombrovski et al. (2013), "suicide can be viewed as an escape from unendurable punishment at the cost of any future rewards" (p. 1020). Following a similar line of reasoning, it can be suggested that suicide occurs when the perspective of dying has become definitely more rewarding than the perspective of going on living.

interest was a distinct entity (Iacovides et al. 2003; Maslach et al. 2001). Three arguments have been frequently advanced in support of the view that burnout is not merely "old wine in new bottles" (Schaufeli and Enzmann 1998).

Proponents of the burnout/depression distinction claimed that, in contrast to depression, burnout was a job-related and work-specific syndrome (e.g., Maslach et al. 2001, p. 404). This claim, however, has been shown to be problematic because (a) depression can also be job-related,[9] (b) the job-related character of a syndrome is not nosologically discriminant per se—a job-related depression remains a depression—and (c) the postulate that the burnout phenomenon is restricted to work is logically specious (Bianchi et al. 2015d; Kahn 2008; Niedhammer et al. 2015; Wang 2005). Taking the problem the other way round, the extent to which burnout can be considered a job-induced syndrome has remained unclear (Bianchi et al. 2017b; Weber and Jaekel-Reinhard 2000). While burnout has been found to be predicted by occupational factors (Schaufeli et al. 2009a), research on the variance in burnout explained by non-occupational factors has been scarce (Hakanen and Bakker 2017). Interestingly, in a recent study involving 468 Swiss health professionals, only 44% of the participants reporting burnout symptoms considered their job to be the main cause of these symptoms (Bianchi and Brisson 2017).

Another argument employed to distinguish burnout from depression has consisted in contrasting the so-called social focus of burnout research with a supposedly "individual focus" of depression research (e.g., Pines and Aronson 1988, p. 53). This argument has been found to be invalid, for at least two reasons. First, the argument is grounded in a false presupposition, namely, that depression would not have been studied from a social perspective. An explicitly social perspective was taken, for instance, by Brown and Harris (1978) in their classic study of "the social origins of depression" in women. Over the last decades, a large body of research has in fact been dedicated to the social determinants of depression (e.g., socioeconomic status and social network; Gilman et al. 2002; Lorant et al. 2007; Ritsher et al. 2001; Rosenquist et al. 2011; Sapolsky 2005).[10] Moreover, the stress-depression relationship evidently implicates the social environment, given that the social environment is a key contributor to stress (Gilbert 2006; Pizzagalli 2014). In a recent study that included 3021 medical interns, Fried et al. (2015) found that all nine symptoms of major depression (APA 2013) increased—on average by 173%—in response to the stress of medical internship over a 1-year period. Second, and more fundamentally, the "social focus argument" advanced by some burnout researchers is epistemologically spurious. Indeed, *a difference in the perspectives adopted on given syndromes (*e.g., *individual* versus *social) should not be confused with a difference between the syndromes themselves*. Burnout and depression can both be examined from an individual or a social perspective. Incidentally, we note that moving back and forth from an individual to a social level of observation is likely to be fruitful in the study of any (psycho)pathology.[11]

Finally, it has been asserted that burnout differs from depression because the symptoms of burnout are, in the early stages of the burnout process, rather circumscribed to work—they do not contaminate the whole life of the individual—whereas the symptoms of clinical depression are pervasive (see Pines and Aronson 1988, p. 53; Schaufeli and Enzmann 1998, p. 39). Such a comparison, unfortunately, is inconsistent (Bianchi et al. 2015b). In effect, when comparing the *early stages* of the burnout process with *clinical* depression, burnout researchers contrast the early stages of the burnout process with the *late stages* of the depressive process, while remaining

[9]Methods allowing the specific link between job stress and depression to be investigated are available, both in research and medical settings (Bianchi et al. 2017).

[10]In a meta-analysis, Lorant et al. (2003) found compelling evidence for socioeconomic inequality in depression (see also Adler and Stewart 2010).

[11]Even psychosis (including schizophrenia), the variance of which is thought to be strongly explained by the genetic makeup of the individual, has been fruitfully studied from a social-environmental standpoint (Shah et al. 2011; Wicks et al. 2010).

silent regarding what is supposed to distinguish "clinical burnout"[12] from clinical depression. The comparison thus appears to be underlain by a defective articulation of dimensional (i.e., continua-based, process-focused) and categorical (i.e., taxa-based, state-focused) approaches to burnout and depression (Bianchi et al. 2017d). The difficulty coordinating dimensional and categorical approaches to psychopathology has long been encountered in burnout research, as illustrated by the view that burnout could be a phase in the development of a depressive disorder (e.g., Ahola et al. 2005). This problem is well-summarized in the following excerpt:

> …there is the question of whether burnout is a continuous condition or a dichotomized state. Are there degrees of burnout that can be experienced or is one either burned out or not?—Cox et al. (2005, p. 190).

Because dimensions and categories constitute two ways of *describing* the properties of psychological phenomena (Pickles and Angold 2003), the question is not to determine whether burnout *is* a continuous condition or a dichotomized state. The description of burnout within a dimensional or a categorical approach depends on the perspective that the investigator chooses to adopt on burnout, as a function of his/her objectives. Burnout, just as depression, can be studied as a process or an end-state (Bianchi et al. 2017d). There can be degrees of severity in burnout as in depression; qualitative leaps can be considered in burnout as in depression. Assuming that burnout is per se a process and depression is per se an end-state would be confusing, once again, the phenomena of interest with the approaches adopted to study those phenomena. Such epistemological confusion leads the investigator to make superfluous, and misleading, distinctions. Such distinctions result in a counterproductive fragmentation of knowledge that threatens conceptual parsimony and impedes theory building (Cole et al. 2012; Le et al. 2010; Schmidt 2010).

[12] We use inverted commas here because there are no binding or consensual diagnostic criteria for "clinical burnout"; "clinical burnout" has remained uncharacterized. We follow the same rule in the rest of the chapter.

All in all, the arguments invoked in support of the burnout-depression distinction have not stood up to scrutiny. We now review recent empirical findings pertaining to the characterization of the burnout syndrome in relation to depression.

### 14.4.3 Recent Research on Burnout-Depression Overlap

#### 14.4.3.1 Associations Between Burnout and Depressive Symptoms

Burnout and depressive symptoms have long been found to be positively correlated (e.g., Meier 1984), with moderate to high correlations generally reported. It has often been suggested, however, that burnout and depressive symptoms should be distinguished because, although substantial, their correlation was not perfect. A new light has been shed on this assumption over the last years.

The assumption that burnout and depression cannot be viewed as a single entity because the two constructs share significant, but limited, variance (e.g., Schaufeli and Enzmann 1998) has been tested as such in a recent study. Bianchi et al. (2016c) examined the extent to which the correlation between burnout and depressive symptoms (respectively assessed with the SMBM and the PHQ-9) differed in strength from the correlation between the affective-cognitive and somatic symptoms of depression. The results of the study indicated that the correlation between burnout and depressive symptoms ($r$ = 0.73) was similar in strength to the correlation between the affective-cognitive and somatic symptoms of depression ($r$ = 0.68). Because the affective-cognitive and somatic symptoms of depression are considered to form a unified entity with a correlation of 0.68, the authors concluded that there was no apparent obstacle to viewing burnout and depression as one entity with a correlation of 0.73.

Furthermore, emotional exhaustion—the core of burnout—has been found to be more strongly associated with "classical" depressive symptoms than with the other two dimensions of burnout—depersonalization and reduced personal accom-

plishment—in many studies (see Bianchi et al. 2015b). In view of these findings, the claim that depersonalization and reduced personal accomplishment constitute more cardinal features of burnout than "classical" depressive symptoms appeared to proceed from an incoherent reasoning (Bianchi et al. 2015d). By definition, a syndrome refers to a group of *concomitant* signs and symptoms (Shirom 2005). If emotional exhaustion more often co-occurs with "classical" depressive symptoms than with depersonalization and reduced personal accomplishment, excluding "classical" depressive symptoms from the burnout syndrome while including depersonalization and reduced personal accomplishment in the burnout syndrome is unwarranted.

Recent research has additionally suggested that the magnitude of the association between burnout and depressive symptoms had been distorted downward in the past due to measurement artifacts. Indeed, burnout is most frequently assessed within a 1-year (with the MBI) or a 1-month (with the SMBM) time window, whereas depression is most frequently assessed over a 1- or a 2-week period (e.g., with the Center for Epidemiologic Studies Depression Scale [CES-D] and the PHQ-9). Such differences in response frames can reduce the magnitude of the obtained correlations in the absence of actual differences between the examined phenomena. In a study that standardized the time window of the assessment of burnout and depressive symptoms, Bianchi et al. (2016d) found a correlation of 0.83 between the two variables. When corrected for attenuation, the correlation reached 0.91, a magnitude that is suggestive of empirical redundancy between the constructs under scrutiny—as recalled by Le et al. (2010), "two supposedly distinct constructs should not correlate 1.00 or near 1.00" (p. 113). In support of this hypothesis, associations of such magnitudes (*r*s around 0.80 or 0.90) have been found when correlating two measures of depression (Kung et al. 2013; Luteijn and Bouman 1988) or two measures of burnout (Shirom and Melamed 2006) with one another (see also Wojciechowski et al. 2000).

The overlap of burnout with depression has also been examined categorically, with the aim of specifically focusing on workers scoring at the upper end of the burnout continuum. Bianchi et al. (2013) found evidence that individuals with relatively high frequencies of burnout symptoms (based on the MBI) reported as many depressive symptoms (based on the Beck Depression Inventory-II) as patients diagnosed in psychiatry for a major depressive episode. In a study of 5575 French schoolteachers (Bianchi et al. 2014), in which burnout was assessed with the MBI, about 90% of the individuals experiencing burnout symptoms at least *a few times a week* met criteria for a provisional diagnosis of depression, as established by the PHQ-9 (Kroenke and Spitzer 2002). Similar results were obtained in the USA (Schonfeld and Bianchi 2016) and New Zealand (Bianchi et al. 2016c) based on teacher samples and in Switzerland (Bianchi and Brisson 2017) based on health professional samples, in studies that used the SMBM to assess burnout. A strength of the abovementioned studies is that they relied on conservative cutoff scores for categorizing burnout. Because such cutoff scores correspond to relatively high frequencies of burnout symptoms, they show close adherence to the theoretical characterization of so-called clinical burnout. Schaufeli and Buunk (2004) signalled that full-blown burnout reflects "a final stage in a breakdown in adaptation that results from the long-term imbalance of demands and resources" (p. 389). According to Leiter and Maslach (2005), a "burned out" worker feels "constantly overwhelmed, stressed and exhausted" (p. 2). These descriptions imply that the use of liberal cutoff scores, associated with relatively low symptom frequencies, is unwarranted when burnout is examined as an end-state (see also Schaufeli and Enzmann 1998, p. 58).[13] Although suboptimal in a context where burnout remains nosologically undefined, the strategy that consisted in relying on conservative cutoff scores to categorize burnout at least had the advantage of being sustained by a clear rationale. Available descriptions have

[13]The use of liberal cutoff scores in some earlier studies (e.g., Ahola et al. 2005) is likely to account for the weaker evidence of burnout-depression overlap observed in those studies.

suggested that an individual with full-blown burnout experiences burnout symptoms on a daily basis, consistent with the fact that burnout symptoms, once they have fully developed, are stable over time—for instance, exhaustion is typically unrelieved by ordinary rest or sleep, and cynicism involves a deeply ingrained negative attitude toward one's work.

Other categorical investigations of burnout and depression have been conducted. In a three-wave, 7-year study, Ahola et al. (2014) examined both within- and between-individual variations in burnout and depressive symptoms (assessed with the MBI and the short form of the Beck Depression Inventory, respectively) based on a sample of 3255 Finnish dentists. The study showed that burnout and depressive symptoms clustered together and increased or decreased commensurately over time, with low, intermediate, and high levels of burnout symptoms being respectively accompanied by low, intermediate, and high levels of depressive symptoms. Similar results were found in another cluster-analytic study, involving a sample of French teachers and two waves of data collection (Bianchi et al. 2015c).

Consistent with these findings, in a study of 5897 Austrian physicians, Wurm et al. (2016) observed that the likelihood of meeting the criteria for a provisional diagnosis of depression (as established by the Major Depression Inventory) gradually increased with the severity of burnout symptoms (assessed with the Hamburg Burnout Inventory). Compared to participants with no noticeable symptoms of burnout, participants with the most elevated levels of burnout symptoms had a *93-fold* higher risk of being identified as clinically depressed.

Finally, we note that the research dedicated to the nomological network of burnout and depression has not resulted in fully consistent findings (Bianchi et al. 2015b). Most probably, this state of affairs is due to (a) the heterogeneity of the conceptualizations and operationalizations of burnout used in past research and (b) the previously mentioned methodological problems that affected research on burnout-depression overlap. This being underlined, burnout and depression have been found to be similarly associated with a number of variables such as depressive cognitive style (including ruminative responses and pessimistic attributions), self-rated health, physical activity, neuroticism, extraversion, job satisfaction, job adversity, workplace social support, stressful life events, and antecedents of anxiety or depressive disorders (Bianchi and Schonfeld 2016; Bianchi et al. 2016d; Faragher et al. 2005; Rössler et al. 2015; Schonfeld and Bianchi 2016; Toker and Biron 2012).

In sum, recent empirical research has consistently shown that burnout and depressive symptoms are inextricably linked (Bianchi et al. 2017d). This conclusion has been supported by both dimensional and categorical analyses of burnout and depression, conducted in the framework of both cross-sectional and longitudinal studies. The conclusion appeared to be viable not only when the MBI was used but also when alternative measures of burnout, such as the SMBM, were employed.

#### 14.4.3.2 Factor Analyses of Burnout and Depression Measures

The view that burnout is distinct from depression has strongly relied on the finding that burnout and depression loaded on different factors when self-reported measures of burnout and depression were submitted to factor analyses (Maslach et al. 2001). Thus, in one of the most influential studies linked to this research area, Leiter and Durup (1994) concluded that burnout and depression were best modeled as two second-order factors—while acknowledging the strong correlation (0.72) between these factors. The study, however, had a number of limitations, such as (a) the poor fit of the constructed models, (b) the exclusion of nearly half the depression items from the confirmatory factor analysis for reasons of skewness, and (c) the non-consideration of the different time windows attached to the measures of burnout and depressive symptoms.

More recent studies offered investigators a different view of the relationships between the factors underlying the measures of burnout and depressive symptoms. Bianchi et al. (2016d) used the SMBM and the PHQ-9 to assess burnout and

depression, respectively. As a reminder, the SMBM includes three subscales, physical fatigue, cognitive weariness, and emotional exhaustion. The factor analyses carried out by the authors revealed that the depression latent variable correlated more strongly with the physical fatigue, cognitive weariness, and emotional exhaustion latent variables than the latter three latent variables correlated with each other. Such results confirmed that depressive symptoms lie at the heart of the burnout syndrome.

In a study that aimed at overcoming the limitations of past factor analytic studies by using more sophisticated modeling techniques, Schonfeld et al. (2017) assessed burnout with the MBI and depression with both the 10-item version of the CES-D (CES-D-10) and the PHQ-9. The study sample comprised 734 US teachers. The results of an exploratory factor analysis indicated that the items of (a) the emotional exhaustion and depersonalization subscales of the MBI, (b) the CES-D-10, and (c) the PHQ-9 substantially loaded on one single factor. The items of the (reduced) personal accomplishment subscale of the MBI were found to load only partly on that factor. A confirmatory factor analysis that controlled for potential item overlap in the measures of depressive symptoms and emotional exhaustion established that there was a high correlation (0.85) between depressive symptoms and emotional exhaustion, suggestive of a unique underlying construct.

The results of the latest factor analytic studies of burnout and depression measures have consolidated the view that burnout and depressive symptoms form a unified structure. Put differently, these results have suggested that it would be misguided to isolate burnout from the spectrum of depression.

#### 14.4.3.3 Biological Research on Burnout and Depression

Over the last years, the overlap of burnout with depression has been increasingly investigated from a biological standpoint. Heterogeneous findings have emerged from this line of research. For instance, Toker et al. (2005) found that in women, burnout, but not depression, was positively associated with microinflammation (expressed by heightened concentrations of high-sensitivity C-reactive protein [hs-CRP] and fibrinogen) whereas in men, depression, but not burnout, was positively associated with hs-CRP and fibrinogen concentrations. By contrast, examining the question of whether burnout could be distinguished from depression based on heart rate variability, brain-derived neurotrophic factor, and hippocampal volume, Orosz et al. (2017) did not find conclusive evidence for burnout's distinctiveness. Beyond the specific limitations attached to one study or another, biological research on burnout and depression has been rendered fundamentally inconclusive by the non-consideration of depression subtypes in the conducted studies (Bianchi et al. 2015b).

Considering depression subtypes is central in biological research on burnout and depression because different depression subtypes have been associated with opposite neurovegetative, immune, and endocrine profiles. For instance, depression with melancholic features has been associated with insomnia, aphagia, sympathetic hyperactivity, decreased immune function, and hypercortisolism, whereas depression with atypical features[14] has been associated with hypersomnia, hyperphagia, sympathetic hypoactivity, increased immune function, and hypocortisolism (Gold and Chrousos 2002; Lamers et al. 2013). These differences directly bear on the status of variables such as microinflammation, heart rate variability, brain-derived neurotrophic factor, or hippocampal volume. Thus, the neglect of depression subtypes can result in misleading conclusions regarding burnout-depression overlap. Emblematically, the argument that burnout is distinct from depression because burnout involves hypocortisolism whereas depression involves hypercortisolism caves in as soon as atypical depression is taken into consideration (Bianchi et al. 2015b).

Because subtypes of depression have been ignored in biological research on burnout and

[14]The term atypical "does not connote an uncommon or unusual clinical presentation" (APA 2013, p. 186). Depression with atypical features is a frequently encountered form of depression.

depression, the studies conducted in this area could not inform us about burnout-depression overlap. Researchers should be more aware of, and careful about, the heterogeneity of depression in the future.

## Conclusion

In this chapter, we proposed an overview of burnout, from the introduction of the construct in the mid-1970s to the growing realization that the syndrome was better conceived of as a depressive condition. Long questioned, the distinction between burnout and depression has eventually been shown to be problematic, both logically and empirically. Recent studies helped clarify the issue of burnout-depression overlap at theoretical and epistemological levels and provided us with compelling evidence that the pathogenesis of burnout is depressive in nature.

The history of burnout research suggests that transdisciplinary communication and methodological standards should be strengthened to avoid the proliferation of constructs that, in fact, refer to the same phenomena. Construct proliferation—a transgression of the scientific canon of parsimony—is considered a major problem today (Cole et al. 2012; Le et al. 2010; Schmidt 2010). Construct proliferation undermines theory building and, consequently, slows research advance. As can be seen from the initial articles on the burnout syndrome, pioneers of burnout research, who were coming from the fields of clinical and social psychology, paid little attention to the work accomplished by their colleagues in other areas of psychology (e.g., behavioral psychology; see Peterson et al. 1993) and other disciplines such as psychiatry and (neuro)biology—(neuro) biology has constituted a highly productive discipline regarding stress-related syndromes (Goldstein and Kopin 2007). Because a new construct should not be introduced in the scientific literature without careful consideration of its added value vis-à-vis related, already-available constructs, such neglectfulness has been highly problematic.

Instead of multiplying "depression-like" constructs, we recommend that investigators concentrate their present and future efforts on (a) more harmoniously coordinating dimensional and categorical approaches to depression (Cuthbert and Insel 2013; Kotov et al. 2017), (b) further developing a flexible, multiscale (e.g., sub-individual, individual, interpersonal, social) framework for the study of depressive conditions, and (c) better understanding how the forms taken by depression can vary as a function of the duration and intensity of the unresolvable stress experienced by the individual and the developmental stage(s) at which the individual experiences unresolvable stress (Bale and Epperson 2015; Koenig et al. 2011). Such an agenda is in our estimation promising in terms of knowledge production and integration. The relationship between stress and depression, through the impossibility of effective/gratifying action, offers a privileged access to the general principles of human adaptation.

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# The Link Between Obesity and Depression: Exploring Shared Mechanisms

15

Young Sup Woo and Won-Myong Bahk

## 15.1 Introduction

Both obesity and depression are common problems, with major public health implications. The lifetime prevalence of major depression is 6.5–21.0%, and the World Health Organization (WHO) has ranked depression the fourth leading cause of disability and has anticipated it to be the second leading cause by 2020 (Kessler and Bromet 2013). The prevalence of obesity is high as well and has rapidly increased over the past three and a half decades, with 11% of men and 15% of women obese in 2014 (Arroyo-Johnson and Mincey 2016).

The potential association between depression and obesity has been proposed because of the high prevalence of both conditions and the fact that symptoms of depression include changes in appetite/weight, sleep, and psychomotor activity (Stunkard et al. 2003) and that psychological aspects such as negative body image and self-esteem, maladaptive schemas, and body image dissatisfaction in obese people could lead to depression (Gavin et al. 2010). A number of early studies have investigated the association between obesity and psychopathology, including depression, but these studies reported a negative association. These studies on the personality and psychopathology of obesity have compared groups of obese and nonobese individuals and reported no link between obesity and psychological correlates. For example, Moore et al. (1962) examined the relationship between obesity and mental health using data obtained from 1660 persons selected as representative of 110,000 inhabitants of a residential area of New York City. In mental health indices, obese individuals made more pathological scores on "immaturity," "rigidity," and "suspiciousness" than nonobese individuals, but there were no significant differences in anxiety and depression levels. Rather, some researchers reported less psychopathology in obese individuals than normal-weight individuals. Crisp and McGuiness (1976) reported that obese men have lower levels of depression than normal-weight men ("jolly fat" hypothesis). It is not surprising that negative or heterogeneous results were obtained from early studies because those studies had methodological limitations such as using a single measure and various and arbitrary definitions of obesity (Friedman and Brownell 1995).

However, results supportive of the "jolly fat" hypothesis have primarily been observed for older, male cohorts and were conducted two or

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more decades ago. Recent epidemiological studies demonstrated that obesity is associated with an increased risk of developing depression (Simon et al. 2006; Dong et al. 2004; Dearborn et al. 2016) although the precise mechanisms underlying the interaction between obesity and depression have not been elucidated. In this chapter, to better explicate the pathophysiological mechanisms underlying interaction between obesity and depression, we demonstrate the association between depression and obesity in recent literature. From a clinical point of view, this could imply the importance of monitoring obesity in depressed patients and, vice versa, paying attention to depressed mood in patients with obesity.

## 15.2 The Association Between Depression and Obesity: Recent Epidemiological Studies

Based on the strong probability that depression and obesity will occur together, a considerable number of studies in recent decades have studied the association between depression and obesity. Several cross-sectional studies with general population found a positive association between depression and obesity. Atlantis et al. reviewed 20 cross-sectional studies and reported that obesity and depression are positively associated in women, but not in men, in studies from the United States. However, the association was not found in studies from populations other than the United States (Atlantis and Baker 2008). A meta-analysis of 17 cross-sectional studies (de Wit et al. 2010) found that there was an overall positive association between depression and obesity, with an odds ratio (OR) of 1.18, and the association was significant for females but not significant for males in subgroup analysis. Overall, although cross-sectional studies support this association, evidence from cross-sectional studies does not provide a clear picture of the relationship between depression and obesity. Hence, longitudinal studies are necessary to examine the contextual relationship between depression and obesity.

### 15.2.1 Obesity Predicting Depression: Prospective Studies

In the Alameda County Study (Roberts et al. 2003), obese (BMI $\geq$ 30) adults over age 50 had elevated odds ratios of depression (2.09) 5 years later, and this was significant even after controlling for potential covariates. The increased future risk for developing depression/depressive symptoms in obese populations at baseline has been reported repeatedly in several subsequent longitudinal studies, with female subjects having an odds ratio of 5.25 (Kasen et al. 2008), elderly subjects having an odds ratio of 1.60 (Godin et al. 2012), and a large prospective cohort study of men and women subjects in which the odds ratio for depression per standard deviation increase in body mass index (BMI) was 1.11 (Bjerkeset et al. 2008). Recently, in a meta-analysis conducted by Luppino et al. (2010), an obese person was more likely to develop depression (unadjusted OR = 1.55).

Some studies suggest that the future risk of depression may be disproportionately affected by potential confounding factors. In a large longitudinal study, baseline obesity did not affect the risk of future depressive symptoms in overall subjects, but obesity was associated with increased risk of symptoms of depression in subjects of higher socioeconomic status (SES), with a relative risk of 1.97 (Fowler-Brown et al. 2012). In addition, the increased risk of depression in obese people could be attributed in part to physical inactivity. A study examining the prospective association of BMI and physical activity with depressive symptoms in young women (Ball et al. 2009) showed that physical activity seems to be protective against the onset of depressive symptoms, but the increased risk of depressive symptoms associated with weight gain is not alleviated. Moreover, recent studies suggest that metabolically unhealthy obesity and metabolically healthy obesity may have different effects on the risk of future depression. Hamer et al. (2012) reported that metabolically unhealthy obesity increased the risk of depressive symptoms at follow-up, with an OR of 1.5, compared

to the nonobese healthy control, whereas metabolically healthy obesity did not. Besides, in the aforementioned meta-analysis (Luppino et al. 2010), significant predictive effects of baseline obesity for future depression were observed in studies conducted in the United States (OR = 2.12), although this effect was not significant in studies conducted in Europe (OR = 1.33, nonsignificant).

### 15.2.2 Depression Predicting Obesity: Prospective Studies

The results from studies on the effects of depression on future obesity are a little more controversial compared to studies on the effect of obesity on later depression. In the late 1990s, Pine et al. (1997), Bardone et al. (1998), and Barefoot et al. (1998) reported results from longitudinal studies that investigated the effects of depression/depressive symptoms in adolescence on the risk of obesity in adulthood. In one study, depression in adolescence predicted obesity in early adulthood (Pine et al. 1997; Beydoun and Wang 2010). In another study (Barefoot et al. 1998), depressive symptoms in adolescence exaggerated pre-existing weight change tendencies; initially lean subjects with depressive symptoms gained less weight than the non-depressed control, and initially heavy subjects with depressive symptoms gained more. In the other study (Bardone et al. 1998), adolescent depression did not affect BMI at follow-up.

Whether depression/depressive symptoms may contribute to future obesity has been inconclusive in subsequent studies: some indicated that baseline depression can predict future obesity (Goodman and Whitaker 2002) or abdominal obesity (Vogelzangs et al. 2008), but others posited that depression did not increase the risk of future obesity (Roberts et al. 2003). Moreover, gender may be a mediating factor for the relationship between depression and future risk of obesity. The increased risk of developing obesity in depressed subjects has been observed only in females in some studies (Richardson et al. 2003; Hasler et al. 2005; Fowler-Brown et al. 2012). In a meta-analysis of 16 studies (Blaine 2008), depressed populations were significantly higher in risk of developing obesity compared to non-depressed, with an OR of 1.19. The risk of later obesity was particularly higher for adolescent females (OR = 2.57). In another meta-analysis (Luppino et al. 2010), baseline depression/depressive symptoms significantly increased the risk of later obesity (OR = 1.58). In this meta-analysis, there were no specific moderators of this association. Taken together, depression may increase the risk of future obesity, but some other factors, including gender, may moderate this association.

## 15.3 Moderators of the Relationship Between Depression and Obesity

Initial researches examining the bidirectional relationship between depression and obesity failed to consider the complexity and heterogeneity of the relationship. As noted by Friedman and Brownell, various moderators including biological, behavioral, cognitive, and social factors might be involved in the relationship between obesity and depression.

Among sociodemographic factors, being female and on a low income conferred risk of comorbid obesity and depression. The associations of age, ethnicity, marital status, and educational attainment with the relationship between depression and obesity were not consistent (Preiss et al. 2013). Psychological and social variables also moderate the relationship between depression and obesity. Anger, sadness, and excitement were associated with the relationship in female depression and obesity and low interpersonal effectiveness, loneliness, and ineffective conflict resolution in male (Musante et al. 1998). Negative body image, experience of weight-related stigma, and low social/interpersonal activity were associated with the relationship between depression and obesity across both genders as well (Gavin et al. 2010; Preiss et al. 2013).

As for behavioral factors, physical activity has an influence on the relationship between obesity and depression. Additionally, the relationship

could be differently influenced by physical activity by gender (Beydoun and Wang 2010; Siegel et al. 2000; Jorm et al. 2003). In one study, depression led to lower levels of physical activity, which led to a BMI increase in females, while it led to less physical activity, which led to lower BMI in males. Dysfunctional eating and dieting behavior also influence the relationship between obesity and depression. Stress and mood states such as depression and anxiety can have divergent effects on feeding behavior. While stress and negative mood decrease appetite and weight in some individuals, it can have an orexigenic and weight-increasing effect in others. Increased preference for palatable, calorically dense food is observed in stressed animals (Cottone et al. 2009) and depressed subjects (Macht 2008). Then, how do stress and emotions affect eating? One way is that sweet, fatty foods can improve mood (Gibson 2006). Moreover, consumption of palatable food can attenuate the stress response (Adam and Epel 2007). However, the relieving effect of palatable food consumption on negative emotions and mood states does not persist. The association between stress/negative emotional state and preference for palatable food is thought to be mediated by hypothalamic–pituitary–adrenal (HPA) activity and the opioidergic and dopaminergic reward system (Adam and Epel 2007; Gibson 2006). Repeated stimulation of these pathways induces adaptation and promotes the compulsive nature of overeating of energy-dense foods and consequent obesity (reward-based stress eating model) (Gibson 2006; Adam and Epel 2007). Stress also promotes secretion of glucocorticoids and insulin, which increases food intake and obesity (Dallman 2010). Increased adiposity, in turn, promotes vulnerability to depression (Novick et al. 2005; Sharma and Fulton 2013).

Recent evidence suggested that the type of food may have an impact on the risk of depression. The consumption of saturated/trans-fat-rich foods can increase the odds of depression via increase in overall and abdominal adiposity, while diets containing mostly unsaturated fats reduce the odds of depression and decrease depressive symptoms (Sanchez-Villegas and Martinez-Gonzalez 2013; Edwards et al. 1998; Lin and Su 2007). As will be discussed below, central adiposity may not only cause or exacerbate metabolic abnormalities but also incur neuropsychiatric impairments, including depression. Moreover, saturated fatty acids can disturb the leptin and insulin signaling pathway in the hypothalamus, by reducing their catabolic actions (Posey et al. 2009; Kleinridders et al. 2009). A high saturated fatty acid level in serum correlated with the severity of depression (Tsuboi et al. 2013). In conclusion, depression can induce an unhealthy diet, and a chronic unhealthy diet can promote aggravation of depressive symptoms via inducing central adiposity and increasing serum saturated fat concentration.

Another moderating variable is the severity of obesity. In studies which compare the class of obesity, subjects with class III obesity (BMI $\geq$ 40.0) had more than three times the risk of depression than the control group, after controlling for demographic and behavioral variables (Keddie 2011; Ma and Xiao 2010). One study found that a 20-unit increment in BMI increased the risk for depression, with an odds ratio of 1.8 (Dong et al. 2004). Studies which compared overweight with obesity reported that the obese group had more frequent depressive symptoms as well (Barry et al. 2008; Johnston et al. 2004). In sum, although the severity of obesity was measured differently among studies, most studies found a significant relationship between severity of obesity and risk of depression.

In their review, Markowitz and colleagues (Markowitz et al. 2008) proposed two causal behavioral paths from obesity to depression, the health concern pathway and appearance concern pathway, and two pathways that link depression to obesity, the direct physiological pathway and indirect psychosocial pathway, based on the moderators. The health concern pathway involves functional impairment and poor perceived health, which lead to depression. In the appearance concern pathway, negative psychological/behavioral aspects of obesity including stigma, body image dissatisfaction, and repeated dieting make people vulnerable to depression, especially in women and those of high SES. Factors which make it more difficult for depression patients to care for

themselves effectively, e.g., poor adherence, binge eating, negative thoughts, and reduced social support, constitute the indirect pathway from depression to obesity. The direct physiological pathway includes biological changes, which will be discussed later.

In conclusion, evidence suggests that the bidirectional association between depression and obesity is mediated by several variables including severity of obesity, gender, experience of stigma, psychological characteristics, eating and dieting behavior, and SES. The moderating variables between obesity and depression should be better understood, so that integrated prevention and intervention strategies could be developed.

## 15.4 Neurobiological Mechanisms Underlying the Association Between Depression and Obesity

Metabolic and endocrine disturbances linking depression with obesity and visceral adiposity include HPA axis dysfunction, insulin and leptin resistance, inflammatory signals, and oxidative stress (Fig. 15.1).

### 15.4.1 HPA Axis Dysfunction

Disturbance of the HPA axis and increased cortisol levels are involved in the pathophysiology of both depression and obesity. In abdominal obesity, the negative feedback mechanism mediated by cortisol is impaired and in turn leads to elevated cortisol levels and increased cortisol secretion in response to stress (Incollingo Rodriguez et al. 2015). In individuals with central obesity, a hyperactivated HPA axis results in a higher cortisol response to corticotrophin-releasing hormone (CRH) stimulation and increased response to stress (Pasquali 2012). In a recent systematic review, greater abdominal fat is associated with greater responsivity of the HPA axis, reflected in morning awakening and acute stress reactivity, especially in adipocytes (Incollingo Rodriguez et al. 2015). Increased cortisol concentrations have been causally linked to fat accumulation and weight gain, as glucocorticoids induce adipocyte hyperplasia by promoting conversion of preadipocytes to mature adipocytes (Incollingo Rodriguez et al. 2015). Especially, hypercortisolemia is associated with the accumulation of visceral fat (Brown et al. 2004; Kyrou and Tsigos 2009).

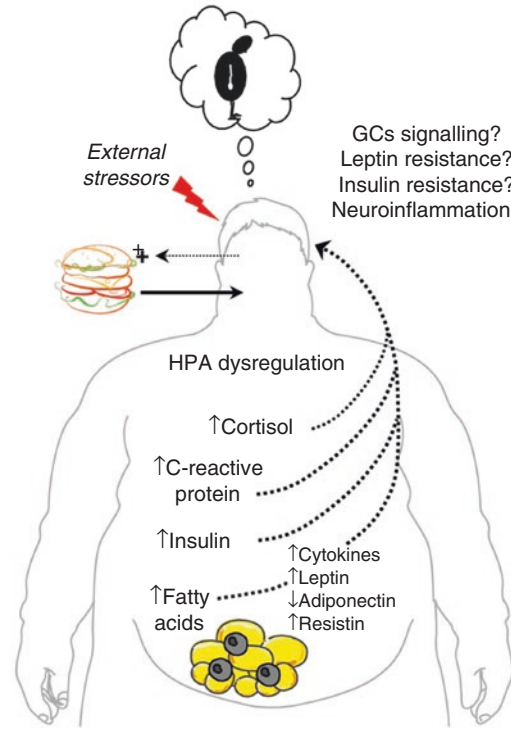


**Fig. 15.1** Disturbed metabolic signals which link obesity and depression. Changes in metabolic signals associated with central obesity correlate with depression. Consumption of energy-dense diets, especially those high in saturated fat, promote abdominal obesity which induces a variety of endocrine changes; function of the hypothalamic–pituitary–adrenal (HPA) axis is disturbed, and plasma levels of hormones involved in the regulation of energy metabolism and mood, such as cortisol, insulin, leptin, adiponectin, and resistin, are altered. Obesity is posited to link metabolic disturbance and depression via inducing impairments in brain glucocorticoids and leptin and insulin receptor signaling. Central fat accumulation results in increased levels of circulating inflammatory mediators, leading to neuroinflammatory responses and depression. Abbreviations and symbols: ↑ increased, ↓ decreased, *GC* glucocorticoid. Figure as originally published in Hryhorczuk C, Sharma S and Fulton SE (2013). Front Neurosci 7:177. doi: https://doi.org/10.3389/fnins.2013.00177

Dysregulation of the HPA axis is also present in depression. Glucocorticoids alter HPA activity and the glucocorticoid receptor-associated emotional/behavioral effects of stress in midbrain and limbic circuits, which regulate reward and emotion as well as exert effects on maintenance of energy homeostasis (Herman et al. 2003). In animal studies, chronic exposure to cortisol and overexpression of glucocorticoid receptors in the brain induce depressive-like behavior (Gregus et al. 2005). In human subjects, serum cortisol concentrations are increased in depression, especially in the melancholic subtype, while hypoactivity of the HPA axis is reported in the atypical subtype. In spite of these categorizations of depression subtypes, hypercortisolemic depression is suggested to be associated with increased visceral adiposity (Hryhorczuk et al. 2013).

The relationship among excessive glucocorticoid, visceral obesity, and depression can be speculated by the central impairments in the adipocyte cortisol metabolism by 11β-hydroxysteroid dehydrogenases (11βHSDs), which catalyze the interconversion of active cortisol and inert cortisone. While 11βHSD2 catalyzes rapid conversion of active cortisol to inactive cortisone, 11βHSD1 catalyzes the intracellular regeneration of cortisol from inactive cortisone (Seckl 2004). Overexpression of 11βHSD1 is well-implicated in visceral fat accumulation and affiliated peripheral metabolic abnormalities such as insulin resistance (Tchernof and Despres 2013). Hence, 11βHSD1 is widely localized in the brain, including the hippocampus and hypothalamus, which are associated with emotional regulation, and this enzyme plays a key role in the glucocorticoid theory of depression, numerous studies indirectly suggesting that 11βHSD1 may be involved in depression (Wyrwoll et al. 2011). A single-nucleotide polymorphism in the 11βHSD1 gene is associated with altered expression of 11βHSD1 at the central feedback sites of the HPA axis and is also associated with higher risk of depression (Dekker et al. 2012). Recently, an animal study demonstrated that ablation of the 11βHSD1 gene results in an antidepressant-like phenotype in mice (Slattery et al. 2016).

It is known that HPA axis disturbance serves as a common pathophysiology of both obesity and depression. However, as a high saturated fat diet and visceral fat accumulation are important mediators of HPA disturbances and depression associated with obesity, there is more to be explored regarding the contribution of HPA axis disturbances to depression elicited by diet-induced obesity.

## 15.4.2 Adipose-Derived Hormones

### 15.4.2.1 Leptin

Leptin is secreted by the adipocyte and its levels are correlated with percent body fat (Maffei et al. 1995). In obese people, high circulating levels of leptin are in proportion to their greater fat mass. Apart from its anorexigenic, anti-obesity effect, leptin is involved in mood regulation. In chronic stress animal models of depression, leptin levels are suppressed with reduced sucrose preference, which is regarded as an analog of anhedonia (Willner 2005). In studies with transgenic mice, leptin-deficient ob/ob mice or leptin receptor-deficit db/db mice showed increased behavioral depression (Yamada et al. 2011). Another aspect that should be considered is the antidepressant efficacy of leptin. In animal studies, leptin administration induced antidepressive behavior in normal mice and reverse depressive behavior in chronic stress model and leptin-deficient ob/ob mice (Yamada et al. 2011). These behavioral effects of leptin were accompanied by increased neuronal activation in the hippocampus, which is considered to be an important region for regulation of the depressive state (Lu et al. 2006).

However, the relationship between leptin and depression is unclear in human subjects. Several clinical studies suggest a link between depression and lower levels, or increased levels, of leptin, especially in women (Rubin et al. 2002; Zeman et al. 2009) and atypical depressive patients (Gecici et al. 2005). Moreover, antidepressant treatment either increased or did not change leptin levels (Schilling et al. 2013). In a recent meta-analysis, more conflicting results were reported (Carvalho et al. 2014): the peripheral

leptin level did not differ between depression patients and healthy controls, and between major depressive disorder individuals with severe depression versus healthy controls. However, its level was significantly higher for participants with mild/moderate major depressive disorder compared to controls. Leptin serum levels did not change after antidepressant treatment (Carvalho et al. 2014). The authors indicated that there was significant heterogeneity between studies included for the leptin diagnostic meta-analysis. Hence, they performed meta-regression analyses to verify the possible influence of moderator variables and reported that a higher overall sample BMI was associated with a significantly higher difference in leptin serum levels between major depressive disorder patients and healthy controls.

In the "leptin hypothesis of depression" (Lu 2007), these conflicting results from human studies could be explained by the complexity of leptin response in obese subjects who have high levels of leptin. In obese people, leptin resistance that is similar to the one that links type 2 diabetes and insulin resistance is caused, which blunts the central action of leptin, despite increasing concentrations (Munzberg and Myers 2005). It is well documented that leptin sensitivity is diminished owing to impaired transport of leptin into the central nervous system (CNS) and reduced function of the leptin receptor and defective leptin receptor long isoform (LepRb) signaling (Myers et al. 2012). In light of leptin's ability to inhibit depressive behaviors in animal models, it is possible that leptin resistance may contribute to the higher rate for depression in obese people. This could also help to interpret some of the conflicting results obtained in relation to circulating leptin levels in depressed patients (Lu 2007). Moreover, in a population-based study, increased risk for depression is associated with the interaction between leptin and abdominal obesity (Milaneschi et al. 2014). Based on these observations, it is supposed that low leptin signaling rather than leptin level per se is related to depression pathophysiology (Lu 2007).

An interesting question that remains to be addressed is how impaired leptin signaling affects mood. Leptin may affect mood via HPA axis functioning. The baseline concentrations of leptin are negatively correlated with mobilization of glucocorticoid (Komorowski et al. 2000), and chronic stress-induced HPA activation decreases circulating leptin concentrations (Ge et al. 2013). Moreover, administration of leptin lowers high corticosterone levels and prevents the induction of CRH synthesis in the paraventricular nucleus and the activation of the CRH neurons in food-deprived ob/ob mice (Huang et al. 1998). Leptin also plays a role in the pathogenesis of depression via the long form of its receptor (LepRb), which mediates the biological actions of leptin and leads to intracellular signal transduction in the midbrain and forebrain. Genetic deficiency of hippocampal LepRb results in leptin resistance and a depression-like behavior in mice, and loss of LepRb in glutamatergic neurons in the hippocampus and prefrontal cortex also induces a depressive phenotype (Guo et al. 2013). One of the other ways that leptin signaling affects mood is by regulation of the dopaminergic and serotonergic systems. Leptin can modulate the mesolimbic dopaminergic system by restoring tyrosine hydroxylase (the rate-limiting enzyme in dopamine production) expression in the ventral tegmental area via regulating LepRb-expressing inhibitory neurons in the lateral hypothalamus, which innervates the ventral tegmental area (Leinninger et al. 2009). Leptin also activates signal transducer and activator of transcription 3 (STAT3), a key downstream mediator of leptin receptor signaling, in dopaminergic neurons in the ventral tegmental area (Fulton et al. 2006). Leptin can regulate vesicular somatodendritic dopamine stores, dopamine transporter activity, and dopamine release as well (Liu et al. 2011). Although the role of serotonin–leptin interactions appears to be less clear, some studies report that leptin can increase serotonin content and metabolism in the forebrain, but not in the frontal cortex (Calapai et al. 1999; Harris et al. 1998). In line with these findings, hypothalamic 5-HT1A receptor expression was increased, and serotonin turnover in the hypothalamus and hippocampus was decreased in leptin-deficient ob/ob mice compared to lean control mice (Schellekens et al.

2012). However, a recent study on rats has shown that leptin directly influences serotonin metabolism by increasing serum serotonin levels, while serotonin in brain tissue (hypothalamus and hippocampus) seems to be decreased after leptin administration (Haleem et al. 2015). In summary, although there is not yet conclusive evidence explaining the relationship between leptin and obesity mood, leptin is one of the major contributing factors in the pathogenesis of depression comorbid with obesity in that leptin hypothesis explains the deficiency in depression and resistance in obesity.

#### 15.4.2.2 Adiponectin and Resistin

Adiponectin and resistin are other adipose-derived hormones considered to take part in the regulation of energy metabolism and insulin sensitivity. Adiponectin acts as an insulin-sensitizing adipokine. The plasma levels of adiponectin are thought to be changed secondary to metabolic disturbance in obesity because they are negatively correlated with obesity, waist circumference, visceral fat, and insulin resistance in humans while not changed in metabolically healthy obesity (Hryhorczuk et al. 2013). There are also evidences that the circulating level of adiponectin is correlated with depressive symptoms, although the direction of changes is not consistent; there are reports of both positive and negative correlation between depressive symptoms and adiponectin concentration, or no change in patients with depression (Hryhorczuk et al. 2013). Plasma resistin levels in relation to obesity are more complicated; some early studies reported that resistin levels are increased with obesity in animal models and humans, but other studies found that resistin is downregulated in obese animals and humans. In depressed patients, the resistin level was increased in atypical depression, but not in typical depression, and lowered in a remitted state (Lehto et al. 2010; Weber-Hamann et al. 2007). In a recent meta-analysis (Carvalho et al. 2014), peripheral adiponectin and resistin levels were significantly lower in depression patients compared to healthy controls. With antidepressant treatment, adiponectin and resistin levels in depression patients are not affected (Lehto et al. 2010). In summary, the link between peripheral adiponectin and resistin concentrations and depression in human subjects is still unclear. However, it deserves further explanation as to the potential role of adiponectin and resistin in the shared pathophysiology of depression and obesity.

### 15.4.3 Insulin

The link between the development of insulin resistance and obesity, especially visceral obesity (Hayashi et al. 2008), and between insulin resistance and depression (Kan et al. 2013) has been well documented. Prospective studies indicate that insulin resistance/metabolic syndrome with obesity is associated with significantly increased risk of developing depression (Hamer et al. 2012). A small but significant association between depression and insulin resistance was observed in a recent meta-analysis, despite the effect size attenuated in analyses adjusted for body weight and other confounders (Kan et al. 2013).

Several studies were performed to determine the role of insulin in mood. A growing body of evidence indicated that alteration in insulin signaling pathways including insulin availability and/or sensitivity or availability of insulin receptor is important to the underlying pathophysiology of depression (Cha et al. 2017). Insulin exerts its biological function mainly by binding its receptors distributed in the olfactory bulbs, cerebral cortex, hippocampus, cerebellum, and hypothalamus (Detka et al. 2015). The binding of the ligand to insulin receptors leads to the phosphorylation of insulin receptor substrate docking proteins (IRS), favoring the generation of intracellular signals. The two main intracellular signaling pathways are the IRS-phosphatidylinositol 3-kinase (PI3K)-Akt pathway and the Ras-mitogen-activated protein kinase (MAPK) (MEK/ERK) pathway, which are known to be involved in depression pathophysiology (Chaudhury et al. 2015). Moreover, insulin may be acting to regulate mood by modulating neurogenesis. As noted above, insulin receptor expression is high in the hippocampus

and olfactory bulb, which shows relatively high levels of adult neurogenesis (McNay and Recknagel 2011). Given that insulin serves as a growth factor and increases brain-derived neurotrophic factor (BDNF) and vascular endothelial growth factor (VEGF), which have trophic effects on the amygdala, hippocampus, and prefrontal cortex, and insulin-like growth factor 1 (IGF-1) is a potential regulator of hippocampal neurogenesis, then insulin resistance may lead to decreased central insulin levels leading to impaired neuroplasticity and function of key brain areas essential to regulation of mood (Rosenblat et al. 2015). In addition to these roles of the brain insulin receptor, recent studies demonstrated that altered insulin signaling pathways in the brain induce monoaminergic dysfunction. For instance, amphetamine-induced dopamine release is significantly reduced by insulin depletion, which suggests insulin signaling pathways may represent a mechanism for regulating dopaminergic neurotransmission (Williams et al. 2007). Along with this, circulating levels of insulin can influence the function of the norepinephrine and serotonin transporter, and in turn, extracellular levels of norepinephrine and serotonin (Kemp et al. 2012).

In clinical studies, intravenous insulin increased hippocampal neuronal activity and improved mood (Rotte et al. 2005), and intranasal insulin improved mood and cognition in healthy, obese, and Alzheimer's disease patients (Shemesh et al. 2012). Recent clinical and preclinical trials examined the repurposing of antidiabetic medications, including an insulin-sensitizing agent, pioglitazone (Colle et al. 2017), and glucagon-like peptide-1 (GLP-1) receptor agonists (Mansur et al. 2017; Sharma et al. 2015), in depression. The improvement of depressive symptoms by pioglitazone was positively correlated with attenuation of insulin resistance (Kemp et al. 2012). Positive correlations between insulin resistance and severity of depressive symptoms have also been reported in cross-sectional studies (Shomaker et al. 2010; Timonen et al. 2005). In sum, data points toward insulin resistance as one of the culprits in obesity-induced depression, while enhancing insulin signaling has an antidepressant effect.

### 15.4.4 Inflammatory Signals

Obesity is associated with systemic, low-grade chronic inflammation. Pro-inflammatory cytokines, including interleukin (IL)-1β, tumor necrosis factor (TNF)-α, IL-6, and C-reactive protein (CRP) levels and inflammatory signaling, have been reported to be increased in obesity (Gnacinska et al. 2009). Diverse mechanisms contribute to the development of inflammation associated with obesity. White adipose tissue, composed of adipocytes and stromavascular fractions including macrophages and lymphocytes (Langlet et al. 2012), is one of the main protagonists. Evidences suggest the positive association between visceral adiposity and circulating levels of cytokines (Park et al. 2005; Visser et al. 1999). Adipocytes, together with infiltrated macrophages and T cells that progressively accumulate in the white adipose tissue, have the ability to potently secrete inflammatory mediators (Capuron et al. 2017). In diet-induced obesity, the number and size of adipocytes increase and immune changes occur. Adipose tissue macrophages polarized into an M1 "classically activated" phenotype, which has enhanced pro-inflammatory cytokine production and generated reactive oxygen species. Moreover, obesity induces a Th1 dominant state which leads to a pro-inflammatory environment (Lee and Lee 2014). Obesity activates the innate immune system through Toll-like receptors (TLRs); binding of fatty acid to TLR4 activates transcription factors such as NF-κB and activator protein 1 (AP-1). These proteins upregulate the expression of pro-inflammatory cytokines and chemokines (Konner and Bruning 2011). Obesity-induced inflammation also affects many organs, including adipose tissue, liver, pancreas, and muscle. For example, the pro-inflammatory shift also involves hepatocytes to be altered in their metabolic function and Kupffer cells to be skewed toward a pro-inflammatory phenotype. Together, diet and alterations to hepatic homeostasis lead to the production of circulating pro-inflammatory mediators resulting in obesity-induced metabolic inflammation (Guillemot-Legris and Muccioli 2017).

Recently, the gut microbiota alteration was considered as one of the possible mechanisms contributing to the development of obesity, particularly with regard to modulation of inflammation, energy metabolism, and body weight homeostasis (Finelli et al. 2014; Flint 2011; Verdam et al. 2013). Altered gut microbiota composition induced by obesity—increase of the LPS-bearing species (*Firmicutes* and *Enterobacteriaceae*) with a proportional reduction in *Bacteroidetes* as well as bacterial richness—alters epithelial cells of the intestinal barrier while promoting the translocation of bacteria and their cell wall components, such as LPS, to activate macrophages that, in turn, will produce pro-inflammatory cytokines through induction of TLR4. Increased concentrations of systemic LPS, "metabolic endotoxemia," and other bacterial products or an increase in free fatty acid levels in the liver, adipose, and muscular tissues resulting in the recruitment of TNF-α- and IL-6-producing pro-inflammatory M1 macrophages and the role of inflammation in adipose tissue become more evident (Bleau et al. 2015).

A large body of evidence supports that the brain is a target of the systemic inflammatory process in obese individuals. One of the potential mechanisms through which inflammation affects the brain is altered bidirectional communication using inflammatory signals between periphery and brain as a result of obesity. The protective function against peripheral inflammatory changes of blood–brain barrier (BBB) could be disrupted by obesity (Stranahan et al. 2016). In addition, the blood–CSF barrier across the choroid plexus epithelium could be compromised by systemic inflammation (Balusu et al. 2016). In response to changes in levels of peripheral mediators, including leptin, insulin, fatty acids, or cytokines, phenotypic changes in brain cells occur. Microglia, resident immunocytes in the CNS which produce inflammatory mediators, are activated by saturated fatty acids and monounsaturated fatty acids via the TLR4/NF-κB pathway resulting in cytokine secretion and generation of reactive oxygen species in obesity conditions (Button et al. 2014). Astrocytes are also activated by saturated fatty acids to produce IL-6 or TNF-α (Gupta et al. 2012).

The hypothalamus is a structure that is particularly affected by the increased inflammatory process in the brain of obese individuals (Thaler et al. 2012). The hypothalamic arcuate nucleus plays a critical role in controlling energy homeostasis and body weight by integrating peripheral metabolic cues such as leptin, insulin, or ghrelin. This role of hypothalamic arcuate nucleus and subsequent neuronal response is disrupted by neuroinflammation induced by obesity (Thaler et al. 2012; Naznin et al. 2015). Exposure to a high-fat diet increased reactive gliosis within a week, and even one day of a high-fat diet feeding increased the number of microglia in the hypothalamus (Thaler et al. 2012; Waise et al. 2015). Obesity is also associated with increased hypothalamic expression of pro-inflammatory cytokines such as IL-6 and TNF-α and activation of IKKβ/NF-κB through elevated endoplasmic reticulum stress in the hypothalamus (Thaler et al. 2012; Zhang et al. 2008). The neuroinflammation derived from obesity affects structures beyond the hypothalamus (Thaler et al. 2013; Lu et al. 2011; Guillemot-Legris et al. 2016). Similar neuroinflammatory processes were observed in the hippocampus or cerebral cortex in animal models of obesity. Enhanced IKKβ/NF-κB-mediated inflammatory signaling, increased expression of pro-inflammatory cytokines (e.g., IL-1β, IL-6, and TNF-α), and activation of astrocytes and microglia were reported in the hippocampus and cerebral cortex of obese animal models (Lu et al. 2011; Carlin et al. 2016).

The changes in inflammatory biomarkers in depression have been extensively studied. It is well known that increased inflammatory cytokines can induce depression-like behavioral changes in animals and humans, as well as depressed patients showing an increased level of pro-inflammatory cytokines such as IL-1, IL-6, and TNF-α, in addition to increased concentrations of acute phase proteins including CRP, chemokines, and adhesion molecules (Pace and Miller 2009). The role of cytokine in inducing depressive symptoms could be explained by dysregulated monoaminergic neurotransmission, impaired neuronal growth and survival, and altered HPA axis function, described above (Kiecolt-Glaser et al. 2015). Cytokines

modulate production, transport, and metabolism of monoaminergic neurotransmitters, e.g., serotonin, dopamine, and glutamate, which affect mood (Capuron and Miller 2011) by stimulating enzymes including indoleamine 2,3-dioxygenase (IDO) and GTP-cyclohydrolase 1 (GTP-CH1). Cytokines enhance tryptophan catabolism by stimulating indolamine 2,3-dioxygenase, by which depression could be promoted by slowing serotonin production and enhancing potentially neurotoxic, glutamatergic kynurenine metabolites (Dantzer et al. 2011). By immune activation, GTP-CH1 which produces an essential cofactor for dopamine and serotonin biosynthesis, tetrahydrobiopterin (BH4) is activated to lead to production of neopterin at the expense of BH4 formation in activated brain immune cells (Capuron et al. 2017). Therefore, cytokine-induced GTP-CH1 activation reduces monoaminergic transmission (Castanon et al. 2015). Consistent with these findings, increased brain kynurenine neurotoxic metabolites, which are associated with impaired neurogenesis, are reported in depression (Campbell et al. 2014; Steiner et al. 2011; Savitz et al. 2015; Zunszain et al. 2012). Moreover, reduced BH4 levels are reported in depression (Hashimoto et al. 1994) and an increased neopterin level is positively associated with a number of depressive episodes in depression patients (Celik et al. 2010).

Neuroinflammation also hampers neuronal growth and survival. Increased pro-inflammatory cytokines cause excitotoxicity via modulation of NMDA receptors, thereby reducing production of BDNF (Eyre and Baune 2012). Besides, oxidative stress caused by cytokines damages glial cells in the prefrontal cortex and amygdala, key structures for mood regulation (Leonard and Maes 2012). In addition to their effects on neural plasticity, cytokines dysregulate HPA axis functioning, a key characteristic of depression. In an inflammatory context, glucocorticoid resistance is acquired by inhibition of transcriptional activation of glucocorticoid response elements (GREs) by glucocorticoid receptors, attributed to several mechanisms (Shelton and Miller 2010); activation of IL-1 receptor activates mitogen-activated protein kinases (MKKs), leading to phosphorylation of MAPK and Jun N-terminal kinases (JNK) and activation of c-JUN, which in turn constitutes the activator protein-1 (AP-1) complex, which has been shown to interfere with GR–GRE interactions (Pace and Miller 2009). Activation of the TNF receptor triggers a signal transduction cascade that activates IκB kinase β (IKKβ), resulting in phosphorylation and dissociation of the IκB–NF-κB dimer. Released NF-κB translocates to the nucleus where it interferes with GR–GRE interaction (McKay and Cidlowski 1999). Finally, IFN receptor activation results in phosphorylation of Janus kinase-1 (Jak1) which activates STAT5, which, like NF-κB, inhibits GR–GRE interactions through protein–protein interactions in the nucleus (Hu et al. 2009). In these ways, cytokine signal transduction pathways through activation of inflammatory intermediaries, such as NF-κB, disrupt GR function and expression, leading to cytokine-dependent GR resistance that could further fuel depressive symptoms (Kiecolt-Glaser et al. 2015).

Inflammation may affect individuals differently; it may contribute to depression in a subset of individuals who have vulnerabilities in physiologic systems, in whom even low levels of inflammation is depressogenic. Raison and Miller (2011) call this phenomenon "immune response element amplification." This may include reduced parasympathetic signaling, reduced production of BDNF, insensitivity to glucocorticoid inhibitory feedback, increased activity to social threat in the anterior cingulate cortex or amygdala, and reduced hippocampal volume. Indeed, these are all correlates of major depression that would influence sensitivity to the depressogenic consequences of inflammatory stimuli (Kiecolt-Glaser et al. 2015).

### 15.4.5 Oxidative/Nitrosative Stress

During energy production in the mitochondria, free radicals such as reactive oxygen species (ROS) and reactive nitrogen species (RNS) are normally generated, and these perform numerous roles in regulation of cellular function. The ROS/RNS become excessive by the imbalance between their production and clearance by antioxidant defenses.

Excessive ROS/RNS can cause damage to cellular components, induce harmful autoimmune responses, and consequently facilitate failure of normal cellular processes (Moylan et al. 2014).

Several studies suggest that obesity can be associated with increased oxidative stress and a decreased defense system. Various factors associated with obesity such as a high-fat, high carbohydrate diet cause increased oxidative stress through activation of intracellular pathways such as NADH/NADPH oxidase and endoplasmic reticulum stress in adipocytes. Indeed, oxidative stress can cause obesity through adipogenesis regulated by ROS-mediated oxidative stress signals, and obesity may generate more ROS by various mechanisms including chronic adipocyte inflammation, fatty acid oxidation, overconsumption of oxygen, accumulation of cellular damage, diet, and mitochondrial activity. Thus, obesity and oxidative stress appear to be connected to each other through mutual sustenance mechanisms (Rani et al. 2016). Moreover, ROS modulate the activity of signaling cascades mediated by the redox-sensitive transcription factors, such as NF-κB and AP-1, which can stimulate several pro-inflammatory cytokines, which may further increase the overproduction of ROS (Rani et al. 2016; Moylan et al. 2014; Bryan et al. 2013).

Increased oxidative stress is accompanied by depression, as well (Berk et al. 2013). Depression is associated with decreased activity of enzymes involved in the respiratory chain, decreased ATP production, and other mitochondrial dysfunctions, which can be a source for the accumulation of free radicals (Vavakova et al. 2015). Mitochondrial dysfunction affects various cell-signaling molecules which may contribute in the pathophysiology of depression via increased production of ROS/RNS and a misbalance in $Ca^{2+}$ homeostasis. In many studies, biomarkers of oxidative and nitrosative stress, such as malondialdehyde (MDA), glutathione (GSH), NF-κB, and superoxide dismutase (SOD), are changed in depression. In addition to increased oxidative stress, depression is associated with lower plasma concentration of antioxidants and lowered total antioxidant status (Maurya et al. 2016). Taken together, it can be suggested that oxidative/nitrosative stress may underpin both depression and obesity, and it seems that integrated impairments in redox and inflammatory signaling pathways are the "common soil" from which obesity and depression develop, even though it is difficult to precisely trace which one precedes the other.

## 15.5 Conclusion and Clinical Implications

The bidirectional association between obesity and depression is complex and affected by several common pathways. As discussed, evidence shows that alterations in leptin, insulin, inflammatory signaling, and the HPA axis function, including glucocorticoid, may bridge obesity and depression. In addition, it was suggested that the moderating effects of behavioral and social actors should be considered when examining the relationship between obesity and depression. While this chapter has been limited to the discussion of a few key biological pathways, it is acknowledged that several other factors are important in the association between depression and obesity (Hryhorczuk et al. 2013).

The shared biological mechanisms underlying depression and obesity and their moderators bring to the forefront the necessity to identify the "obese subtype" or "metabolic subtype" of depression as discussed by Mansur et al. (2015). The validation of the concept of this subtype may have important clinical implications. Several studies have suggested that obesity worsens treatment response (Woo et al. 2016), and weight loss is often associated with improvements in depressive symptoms, and vice versa, by inducing improvements in several physiological pathways that are disturbed in depression and obesity (Jantaratnotai et al. 2017). Thus, patients with obesity should be evaluated for depression, and patients presenting depressive symptoms should be evaluated for obesity. The obese patient with depression should, in turn, be evaluated for eating behavior, distress, and impairment owing to both conditions. It is also important to prevent further weight gain in these patients.

Moreover, in recent years, several novel interventions which target metabolic or inflammatory mechanisms have been proposed for both obesity and depression (Mansur et al. 2015). Although they have been mostly inconsistent and the effect sizes have been small to modest, these clinical trials have been promising (Mansur et al. 2015). As discussed, depression and obesity have quite a heterogeneity, and the relationship between depression and obesity and its therapeutic implications would be better understood through well-designed, stratified, and prospective investigations. Further, integrated and personalized treatment to manage obesity and depression simultaneously should be developed and examined.

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# Part IV

# Therapeutic Issues of Depression

# 16 Ketamine: A Promising Rapid-Acting Antidepressant

Samuel T. Wilkinson, Robert B. Ostroff, Rachel B. Katz, and John H. Krystal

## 16.1 Significance of Major Depressive Disorder

### 16.1.1 Major Depressive Disorder (MDD) Represents a Substantial Public Health Burden

Depression is mankind's oldest known brain disorder and is now recognized as the leading cause of disability worldwide (2017). Formally termed major depressive disorder (MDD), it is the most common mental illness worldwide, with a lifetime prevalence of approximately 16% (Kessler et al. 2003) and a 12-month prevalence of approximately 7% (Wittchen et al. 2011). MDD is associated with significant morbidity and mortality (Kessler et al. 2003), substantially impairing work productivity (Stewart et al. 2003) and costing the USA over $80 billion per year (Greenberg et al. 2003). Furthermore, MDD is associated with a significantly elevated risk of suicide (Cavanagh et al. 2003).

All FDA-approved antidepressants used as monotherapies have shown only modest benefits, with response rates (e.g., 50% or greater reduction in symptoms) ranging between 45 and 55% and remission rates (e.g., minimal or no depressive symptoms) ranging between 30 and 35% (Anderson 2000, 2001; Entsuah et al. 2001; Steffens et al. 1997).

### 16.1.2 Burden of Treatment-Resistant Depression (TRD)

Treatment-resistant depression (TRD) is defined as MDD that does not respond or remit to one or more adequate antidepressant trials (Fava 2003). Although there are now more than 20 different antidepressant medications available in the USA, TRD remains an unfortunately common problem, with 29–46% of depressed patients failing to sufficiently respond to adequate trials of antidepressant medications (Fava and Davidson 1996). TRD contributes to the majority of the burden of disease of MDD: compared to patients with treatment-responsive depression, patients with TRD have been found to have a significantly higher chance of attempting suicide (Conway et al. 2015), are more frequently hospitalized for both medical and psychiatric reasons (Amital et al. 2008; Crown et al. 2002), spend longer time

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periods in depressed states (Amital et al. 2008), utilize 1.4–3 times more psychotropic medications (Crown et al. 2002), and are more likely to experience job loss (Amital et al. 2008). One recent estimate concludes that TRD may present added societal costs of $29–48 billion annually in the United States (Mrazek et al. 2014). Furthermore, therapies for TRD are limited. In the Sequenced Treatment Alternatives to Relieve Depression (STAR*D) study, remission rates for patients who did not remit after the first or second antidepressant trial were 13–14%, with response rates of approximately 16% (Rush et al. 2006). The overwhelming burden of TRD and the lack of effective treatments underscore the urgency and importance of developing and disseminating improved therapies in the area of mood disorders.

### 16.1.3 Burden of Bipolar Depression

The situation is also bleak for bipolar depression. Most drugs used to treat bipolar depression have been re-purposed after they were incidentally found to have modest benefit in BD. Today, the pharmacological treatment of BD involves a range of antipsychotics, anticonvulsants, and antidepressants. While controversy still exists as to whether antidepressants can cause a switch or flip to mania (Allain et al. 2017; Tundo et al. 2015), it is clear that they are not very effective in relieving depressive symptoms in individuals with bipolar disorder. Hence, while evidence exists of modest efficacy (Calabrese et al. 2004), they have been given lower priorities in treatment algorithms (Calabrese et al. 2004; Suppes et al. 2005).

## 16.2 History of the Development of Current Antidepressants

Despite the current need for continued development of improved antidepressant therapies, much progress has been made since the 1950s. Prior to this time, there were few effective "biological" treatments for depression. Electroconvulsive therapy (ECT) was the primary treatment employed for depression in the 1940s and 1950s. While ECT remains a mainstay of therapy in TRD today, several antidepressants were discovered and developed in the 1950s and 1960s that have allowed the treatment of depression in less invasive ways.

As a result of chlorpromazine's discovery as the first antipsychotic in 1950, there was a flurry of research activity searching for more potent agents. Imipramine, produced by the Geigy Chemical Corporation, was originally tested as a potential antipsychotic. Eventually, imipramine was shown to have no antipsychotic effect; however, its potent antidepressant actions were quickly discovered. Dr. Roland Kuhn, a Swiss psychiatrist, made the first clinical observations of imipramine's antidepressant effects in several hundred depressed patients. He noted that upon exposure to imipramine, patients' "facial expression[s] lose rigidity … modulation and expression abilities return. The patients become livelier … more communicative, and moaning and whining can no longer be heard. If the patient was discontented, querulous or irritated, he changes into a friendly, content and amenable person" (Brown and Rosdolsky 2015).

Now classified as a tricyclic antidepressant, imipramine was later found to have chemical effects via blocking of the reuptake of serotonin and norepinephrine, two neurotransmitters that play important roles in mood regulation. As a result, imipramine caused higher concentrations of both serotonin and norepinephrine in the synaptic cleft, which is thought to underlie its mechanism of action.

Around the same time, researchers noticed that iproniazid, a compound similar to isoniazid (used to treat tuberculosis), had significant effects on mood, sleep, and appetite. A systematic clinical investigation in depressed patients showed a 70% response (Loomer et al. 1957). While iproniazid was formally marketed as an antitubercular compound using the trade name Marsilid, it became the first off-label monoamine oxidase inhibitor (MAO-I) used to treat depression (Hillhouse and Porter 2015; Pletscher 1991). The pharmaceutical industry, searching for compounds that mimicked iproniazid's mechanism of action, developed a number of other MAO-Is that were commonly used from the 1960s through the 1980s to treat depression,

including tranylcypromine and phenelzine. Like imipramine, iproniazid was thought to cause an increased concentration of monoamines within the synaptic cleft, believed critical for its antidepressant effects.

From the serendipitous discoveries of these first antidepressants (and their purported mechanisms of actions), as well as the clinical observations of the depression-inducing effects of reserpine (which depletes monoamines) (Hirschfeld 2000; Muller et al. 1955), researchers converged upon the monoamine deficiency hypothesis as the prevailing theory of the neurobiological cause of depression. This hypothesis posits that depression is related to a deficiency of the monoamine neurotransmitters (serotonin, dopamine, and/or norepinephrine) in the synaptic cleft (Hirschfeld 2000). Today, virtually all available medications for MDD act on this monoamine neurotransmitter system.

## 16.3 Limitations of Monoamine Deficiency Hypothesis and Rise of Glutamatergic System

### 16.3.1 Limitation of Monoamine Deficiency Hypothesis of Depression

While the monoaminergic deficiency hypothesis has brought many advances, including the majority of FDA-approved antidepressants that form our current pharmacological armamentarium, it cannot fully explain the underlying neurobiology of mood disorders. This is most notably seen in the relatively high rates of TRD that exist, given that the overwhelming majority of antidepressants target the monoamine system. As discussed above, up to 46% of patients fail to response to monoaminergic-based antidepressants as first- or second-line therapies.

Another example of the failure of the monoamine deficiency hypothesis is reflected in the delay to onset of action of current antidepressant therapies. Although serotonin and norepinephrine reuptake inhibitors exert initial effects on intrasynaptic neurotransmitters within hours to days, the improvement in core depressive symptoms only emerges several weeks later (Sanacora et al. 2008).

The failure of the monoamine deficiency hypothesis has also become evident as researchers have been unable to replicate experiments similar to the ones where reserpine (which depletes monoamines) induces a depression-like state. For example, in the late 1990s, a group of researchers at Yale performed a series of experiments in which they tried to produce a depressive syndrome in healthy individuals through monoamine depletion. Rapid depletion of monoamine levels did not induce depressive symptoms in health subjects or remitted depressed patients (Delgado et al. 1993; Salomon et al. 1993). These were also attempted with tryptophan depletion alone (targeting serotonin), alpha-methyl-paratyrosine (AMPT, targeting norepinephrine and dopamine), and tryptophan depletion in combination with AMPT (serotonin, NE, and DA) (Salomon et al. 1993). The limitations of the monoaminergic approach provide a strong impetus for the development of novel antidepressant treatments with unique targets of action.

### 16.3.2 Glutamatergic System

The glutamatergic system has important functions throughout the brain and may provide more efficient therapeutic targets in the development of novel antidepressants. While an exhaustive review of the glutamatergic system is beyond our scope, we highlight some key points relevant to our discussion. The reader is referred to more thorough reviews on this topic for further information (Abdallah et al. 2015; Krystal et al. 1999, 2002).

Glutamate is abundant throughout the brain. Abnormal levels of glutamate/glutamine have been reported in CSF, plasma, serum, and brain tissue samples of individuals with mood disorders (Altamura et al. 1993; Francis et al. 1989; Frye et al. 2007; Levine et al. 2000; Mauri et al. 1998; Mitani et al. 2006). Magnetic resonance spectroscopy imaging studies have also detected

abnormalities in glutamate/GABA levels and their ratios in several key brain regions (Abdallah et al. 2014a, b; Sanacora et al. 2006), though the direction and magnitude of these abnormalities bear further inquiry. Several lines of research have also noted key differences between individuals with and without mood disorders in the *N*-methyl-D-aspartate (NMDA) receptor, one of the key glutamatergic receptors (Sanacora et al. 2008). An important line of research has also found that some NMDA receptor antagonists have antidepressant properties and that traditional antidepressants (monoamine based drugs, tricyclic antidepressants, and ECT) may converge upon NMDA receptor expression and function as a final common pathway for lasting effect (Sanacora et al. 2008).

### 16.3.3 The Development of Novel Therapeutics for MDD/TRD Has Stalled

Unfortunately, because of an incomplete understanding of the neurobiology of mood disorders, the development of novel therapeutics in mood disorders has stalled in the past decade. New therapeutics have failed to demonstrate appreciable benefits over older generation antidepressants. Because of this and other factors, many pharmaceutical companies have stopped investing in research and development of psychotropic medications. Furthermore, the efficacy of currently available antidepressants may be overstated due to reporting and publication bias (Turner et al. 2008).

## 16.4 History of Ketamine, Development as an Alternative to PCP

Upon this scene unfolds the continuing story of ketamine, the first compound that has shown rapid-acting antidepressant effects. Ketamine was initially developed as an anesthetic agent by employees and consultants of Parke Davis, a pharmaceutical company. Drs. Calvin Stevens and Edward Domino had pioneered work in the development of a compound later named phencyclidine (PCP). Phencyclidine indeed produced anesthetic effects, but often caused elevated blood pressure and left patients in an unmanageable and distressing behavioral state post-operatively due to varying degrees of hyperactive behavior. The compound CI-581, later coined ketamine, was created in an effort to discover a suitable alternative to PCP. Early studies in humans suggested that although the chemical structure of ketamine was similar to that of PCP, it had fewer and less potent adverse effects (Chang et al. 2016).

Dr. Domino and his colleagues had difficulty describing the subjective experiences of research participants who were first exposed to ketamine. Eventually, they agreed on the term "dissociative anesthetic" which is still used today and is based in part on subjects being "disconnected from their environment" (Domino 2010) and from studies of visual and somesthetic evoked potentials, indicating that sensory inputs reach cortical areas but are not always perceived in association areas (Domino et al. 1965). After further research, ketamine was first approved by the US FDA in 1970 as an anesthetic agent for use in children, adults, and the elderly (Chang et al. 2016) and was marketed under the brand name Ketalar. It quickly gained popularity as a field anesthetic due to its ability to maintain blood pressure in trauma victims, its fast period of onset and recovery, and its lack of respiratory suppression.

In the 1990s, ketamine began to be studied in schizophrenia research at Yale. Krystal et al. developed the ketamine infusion paradigm that has subsequently been employed in the majority of treatment studies (Krystal et al. 1994). The dose of 0.5 mg/kg infused over 40 min enabled the investigators to achieve a blood level (150–200 ng/ml) where cognitive and behavioral alterations relevant to schizophrenia emerged. Further, the slow rate of infusion meant that drug effects occurred slowly and were relatively well tolerated. Also, if these effects were distressing, the infusion could be stopped and effects would rapidly abate.

Ketamine is available in two enantiomers: the R(−) and the S(+) configurations. Most research to date suggests that ketamine's effects as an antagonist of the *N*-methyl-D-aspartate

(NMDA) receptor are responsible for both its anesthetic (Kohrs and Durieux 1998) and antidepressant effects (Li et al. 2010). Notably, the S(+)-ketamine enantiomer has approximately three-to-fourfold higher binding affinity for the NMDA site compared to the R(−)-ketamine enantiomer (Vollenweider et al. 1997).

## 16.5 Clinical Studies Showing an Antidepressant Effect of Ketamine

### 16.5.1 Placebo-Controlled Studies of Ketamine

While early pilot studies evaluated ketamine as a pharmacologic aid to psychedelic psychotherapy sessions (Fontana and Loschi 1974; Kolp et al. 2007), the first study that led to the current wave of excitement about ketamine as an antidepressant was published in 2000 by Berman et al. (2000). In this small ($N = 7$) crossover trial, subjects with depression experienced a rapid improvement in mood symptoms (within 4 h) in response to ketamine (0.5 mg/kg infused over 40 min) but not in response to placebo (saline). The infusions were performed a week apart and there were some minimal but non-significant carryover effects when ketamine was the first drug administered. Following ketamine, there was a 13-point mean decrease in depression severity using the Hamilton Depression Rating Scale (HAM-D). It is important to note that significant improvements in depression assessments (using the HAM-D and Beck Depression Inventory [BDI]) were noted within 4 h of treatment, even when baseline scores for neurovegetative symptoms (sleep, appetite) had to be carried forward because it was unreasonable to expect changes in these symptoms in a 4-h period. This point highlights the limitations of assessing rapid changes in depression with antiquated scales that were designed to measure changes over 1 week. Nevertheless, the observed rapid changes in mood following low dose ketamine were dramatic and potentially revolutionary. It is also interesting to note that the antidepressant effects of ketamine were temporally disconnected from and occurred much later than the "high" and schizophrenia-like symptoms that subsided by the 2-h time point (Fig. 16.1).

This positive finding was first replicated by researchers at the National Institutes of Health (NIH), utilizing a similar crossover trial ($N = 18$). After medication washout, subjects with MDD who had failed to respond to at least two antidepressant trials were given either ketamine or placebo, and then crossed over after 1 week. A rapid antidepressant effect (within 2 h) was observed in the group receiving ketamine compared to the group receiving placebo, with a very large effect (Cohen's $d = 1.46$) after 24 h and a moderate/large effect ($d = 0.68$) after 1 week (Zarate et al. 2006). This same group of investigators have also performed studies of the same design examining the antidepressant effects of ketamine in patients with treatment-resistant bipolar depression (type I and type II, with $n = 18$ and $n = 15$, respectively) (Diazgranados et al. 2010; Zarate et al. 2012). Notably, patients were maintained on either lithium or valproic acid prior to initiating study protocol. Utilizing a crossover design with a 1-week washout period, they found ketamine exerted a rapid-acting antidepressant effect in bipolar depression, with 7/16 patients responding at 24 h in the first study and 6/14 responding in the second study. The antidepressant effects began to fade within a week in most patients. As detailed above, patients with bipolar depression have very low rates of response to traditional treatments (Nierenberg et al. 2006). The efficacy of ketamine for bipolar depression is unique, as there are few treatments that show substantial efficacy for both unipolar and bipolar depression (among them are ECT and second generation antipsychotics).

Another study was carried out by Sos et al. (2013), where 30 hospitalized patients were randomized to ketamine or placebo, and then crossed over to the opposite group after 1 week. In this protocol, the ketamine dosing was slightly different: participants received a 0.27 mg/kg loading dose over 10 min, and then 0.27 mg/kg over an additional 20 min (total of 0.54 mg/kg given over 30 min). Again, ketamine strongly outperformed placebo, with 10/27 subjects responding after

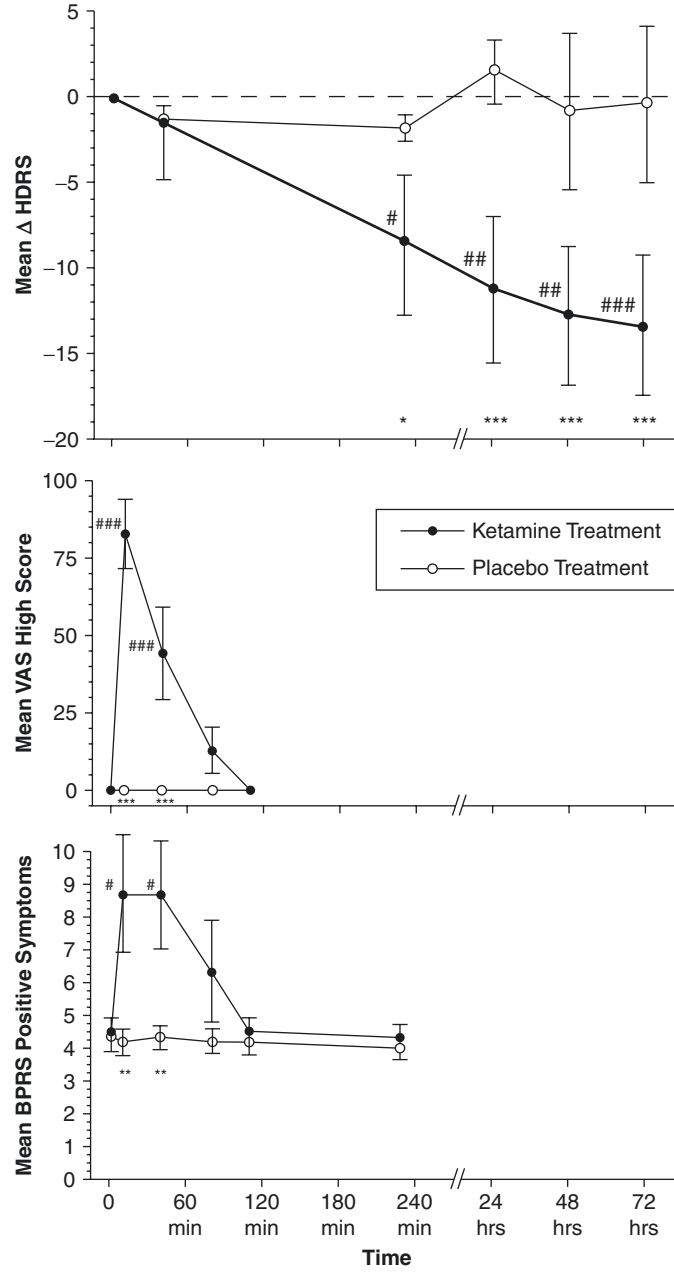


**Fig. 16.1** Improvement in depressive symptoms is seen in the top panel: mean changes (±SEM) from baseline in the 25-item Hamilton Depression Rating Scale scores (HDRS). The middle panel shows rapid increase and resolution of "high" symptoms of ketamine: the mean Visual Analog Scale "high" scores (VAS-high). The bottom panel shows the rapid increase and resolution of schizophrenia-like symptoms: mean positive symptom scores of the Brief Psychiatric Rating Scale (BPRS-positive). Ketamine infusion begins at time point 0 and ends at 40 min. Used with permission from Berman et al. (2000)

ketamine administration, and 1/19 subjects responding after placebo (Sos et al. 2013).

Hu et al. (2016) attempted to investigate the utility of a single-dose of ketamine in expediting the effects of standard antidepressants. In a parallel design, 30 patients with severe MDD were randomized to ketamine (0.5 mg/kg over 40 min intravenously) or placebo infusion. All patients initiated therapy with escitalopram open-label on the same day as the infusion. At 4 weeks, the ketamine group had greater response (92.3% v. 57.1%, $p = 0.04$) and remission (76.9% v. 14.3%, $p = 0.001$) rates compared to the placebo group. Furthermore, the ketamine group had a significantly shorter time to response (hazard ratio = 0.04, 95% CI 0.01–0.22, $p < 0.001$) and time to remission (hazard ratio = 0.11, 95% CI 0.02–0.63, $p = 0.01$).

Another study has investigated the effects of a longer infusion protocol. In an attempt to reproduce conditions under which chronic pain patients often receive prolonged ketamine infusions in the anesthesia literature (Goldberg et al. 2005), Lenze et al. conducted a randomized study in 20 participants (Lenze et al. 2016). One group received a prolonged ketamine infusion (0.6 mg/kg/h over 96 h) while the other received ketamine using the standard infusion (0.5 mg/kg over 40 min). This protocol used clonidine to minimize ketamine-induced increases in blood pressure as well as the dissociative and psychotomimetic effects of ketamine. Notably, positive symptoms of psychosis (hallucinations, bizarre or disorganized thoughts, as measured by the Brief Psychiatric Rating Scale) peaked at 3 days in the arm receiving the 95-h infusion, but were of similar magnitude to the standard protocol. The therapeutic benefit of both protocols was similar, with rapid and sustained improvement in symptoms in both groups.

There is also interest in examining whether ketamine can be administered via other routes of administration. In a crossover design, Lapidus et al. randomized 18 patients with TRD to 50 mg of racemic ketamine administered intranasally or placebo before crossing over after a 1-week washout period. After 24 h, 8/18 patients responded to the ketamine administration, while 1/18 responded 24 h following the placebo administration (Lapidus et al. 2014). Loo et al. assessed ketamine's antidepressant effects via different routes of administration: intravenous, intramuscular, and subcutaneous. In a randomized, dose-ascending study, 15 participants were randomized to one of the three routes of administration, with comparable results among groups. It should be noted that this study was not powered to detect differences between these routes of administration in terms of efficacy or tolerability.

### 16.5.2 Studies Using Midazolam as Active Comparator

It is important to note that the blinded nature of the placebo-controlled studies reviewed so far is difficult to maintain because, at the dose used, ketamine reliably produces clear dissociative effects which peak 15–30 min after the infusion starts. These effects generally subside within 30 min following the completion of the infusion. In an effort to improve blinding, some investigators have used midazolam (0.045 mg/kg given over 40 min) as an active control. Midazolam, a short-acting benzodiazepine, was chosen as a control because, like ketamine, it has noticeable effects on perception and cognition, a short half-life and rapid onset of action, and can be delivered intravenously.

It should be noted that early research suggests benzodiazepines may have some level of antidepressant effects (Gerz 1964). Other potential agents that might serve as active comparators to ketamine (psilocybin, lysergic acid diethylamide [LSD]) have also spurred interest for their potential antidepressant effects (Buchborn et al. 2014; Griffiths et al. 2016). Furthermore, despite the psychoactive effects of benzodiazepines, at least one study has showed a clear difference between ketamine and lorazepam in inducing mystical-type effects (Dakwar et al. 2014), including things such as having an experience that was both timeless and spaceless, an experience in which a new view of reality emerged, or an experience wherein the unity of all things was realized (Hood Jr 1975). An astute and educated research subject may be able to discern between ketamine and a benzodiazepine. Hence, no ideal active comparator agent has emerged in the ketamine literature, though midazolam clearly offers improved integrity of blinding compared to saline as a comparator in randomized trials.

Murrough et al. were the first to conduct a parallel, blinded, randomized trial of ketamine versus midazolam in TRD (Murrough et al. 2013a). In a two-site study, treatment-resistant but medication-free patients were randomized to ketamine or midazolam (2:1 ratio). Ketamine produced a response (50% or greater reduction in symptoms) at 24 h in 30/47, whereas midazolam produced a response in 7/25 patients. While ketamine was superior to midazolam in producing antidepressant effects, the magnitude of the difference was attenuated when compared with reports using saline as placebo.

One additional trial using midazolam as the control has been performed by Murrough et al.

This study examined the effects of ketamine in patients of various diagnoses who had clinically significant suicidal ideation (Murrough et al. 2015). Twenty-four patients of mood or anxiety spectrum disorders were randomized to a single-dose of ketamine (0.5 mg/kg infused over 40 min) or midazolam (0.045 mg/kg infused over 40 min). While the primary outcome (group difference in the Beck Suicidal Ideation [BSI] score at 24 h) was negative, there was a significant group difference in BSI at 48 h and in the suicidal ideation item of the MADRS at 24 h ($p = 0.05$). Further exploration of ketamine's effects on suicidal ideation is beyond the scope of this chapter, but the reader can find more in-depth reviews elsewhere (Ballard et al. 2014; Wilkinson and Sanacora 2016).

A multi-site, dose-finding study, randomizing patients to midazolam (0.045 mg/kg over 40 min) or one of four doses of ketamine (0.1 mg/kg, 0.2 mg/kg, 0.5 mg/kg, or 1.0 mg/kg, 1:1:1:1:1 ratio) was recently completed and results are forthcoming (Clinical Trial Identifier: NCT01920555).

### 16.5.3 Open-Label Studies of Ketamine

Since the original 2000 study showing ketamine's rapid and potent antidepressant effects, a number of open-label trials and case reports or series have been published, which generally show positive effects. It is beyond the scope of this chapter to exhaustively review these publications, however the reader is referred to other works for a more in-depth treatment of single-dose, open-label ketamine studies (Bobo et al. 2016).

### 16.5.4 Repeated Dosing

To date, relatively few studies have examined the effects of repeated doses of ketamine. Murrough et al. (2013b) were the first to test a standardized, repeated dosing protocol. In an open-label design, 24 medication-free subjects with treatment-resistant depression underwent 6 IV ketamine infusions, given thrice weekly for 2 weeks. Overall, 17/24 participants were responders by the end of the 2-week acute treatment phase. Notably, there was a clear separation between responders and non-responders in depression severity within 4 h following the initial dose, with 16/17 responders experiencing a 50% improvement within 4 h of the first infusion. Notably, most (13/17) responders relapsed within 1 month of the last exposure to ketamine, with a median time-to-relapse of 18 days.

In a similar protocol, Rasmussen et al. (2013) enrolled ten patients with treatment-resistant MDD. Participants underwent infusions thrice weekly for six total infusions. The infusion protocol was given over 100 min, unlike most protocols which utilized 40 min, though the total dose (0.5 mg/kg) was the same. At the end of the 2-week protocol, 8/10 had achieved response (50% reduction) at some point during the study and 5/10 had achieved remission.

Shiroma et al. utilized a similar protocol, wherein 14 participants with treatment-resistant depression underwent 2 weeks of thrice weekly infusions (0.5 mg/kg over 40 min intravenously) (Shiroma et al. 2014). These subjects were on a stable regimen of antidepressant medications for at least 2 months. Almost all (91.6%) of the 12 subjects who completed the protocol responded (per traditional criteria of 50% decrease in symptom severity) and 66.6% remitted. Notably, only three (25%) subjects responded following the first infusion. There was a growing cumulative effect of the antidepressant effects of ketamine with additional treatments.

In an effort to examine the optimal dosing protocol, Singh et al. performed a randomized controlled study looking at two different dosing protocols over a 2-week treatment period: twice weekly versus thrice weekly dosing. In this four-arm trial, 68 subjects were randomized (1:1:1:1 ratio) to ketamine 3×/week, ketamine 2×/week, placebo 3×/week, or placebo 2×/week. Ketamine (0.5 mg/kg) or placebo was given over 40 min intravenously. Both ketamine treatment groups had significant improvements in depression severity compared to both placebo groups. There was no difference in improvement between the twice weekly ketamine group versus the three times weekly ketamine group (Singh et al. 2016).

### 16.5.5 Relapse Prevention

Relapse following ketamine is a major clinical problem though is not wholly unexpected given the chronic and cyclical nature of mood disorders and relatively short exposure to the drug in protocols to date. Due to concern for potential adverse long-term clinical consequences of repeated exposure to ketamine (discussed below), there is great interest in developing protocols for maintaining response/remission without indefinite exposure to the drug.

The Murrough et al. (2013b) study described above was the first to look at repeated dosing in an effort to sustain ketamine's antidepressant effect. While this group found a slightly improved time-to-relapse duration compared to studies using a single-infusion protocol, the median time-to-relapse was only 18 days, with approximately 70% of subjects relapsing within 30 days of the last infusion.

Two small randomized trials have examined the potential effect of riluzole, a glutamatergic agent with a complex mechanism of action, in sustaining the antidepressant effects of a single-dose of ketamine (Ibrahim et al. 2012; Mathew et al. 2010). In both studies, following a single dose of intravenous ketamine (0.5 mg/kg infused over 40 min), patients were randomized to receive riluzole or placebo. However, both studies failed to show that riluzole could help sustain ketamine's antidepressant effects.

Vande Voort et al. (2016) have developed a protocol wherein patients are infused thrice weekly for up to six infusions or until remission is achieved. In a small, open-label trial of 12 enrollees, five achieved remission at some point during the acute six-infusion period. In an effort to prevent relapse, these five shifted into a continuation phase, where they received four infusions given over a 4-week period. In a month-long follow-up period following the end of continuation, all five lost remission but were still classified as responders (50% or great improvement compared to pre-treatment baseline).

Wilkinson et al. have explored cognitive behavioral therapy (CBT) as a relapse prevention strategy (Wilkinson et al. 2017b). This concept was based on the idea that ketamine may induce synaptic plasticity in the immediate (12–48 h) period following exposure, which may present an opportune time for cognitive and behavioral interventions. CBT, which has excellent evidence as a relapse prevention strategy in patients with MDD (Hollon et al. 2006), may sustain ketamine's antidepressant effects. In a recent protocol, 16 subjects received open-label ketamine (0.5 mg/kg infused over 40 min) given twice weekly for 2 weeks (based on the Singh et al. 2016 protocol). They concurrently began a course of CBT for 10 weeks, extending 8 weeks beyond the last ketamine infusion. Of eight responders, two (25%) relapsed at the end of the study period (8 weeks following last exposure to ketamine). On long-term follow-up, most (5/8) responders eventually relapsed, though the median time-to-relapse (12 weeks) in this study was much longer than that reported in other trials (17–24 days) (Ibrahim et al. 2012; Mathew et al. 2010). These promising results should be interpreted with caution given the small sample size and open-label design of the study. A subsequent study with a randomized design is underway (Clinical Trials Identifier: NCT03027362).

## 16.6 Ketamine for Other Disorders: Posttraumatic Stress Disorder, Obsessive-Compulsive Disorder

Ketamine is now being explored for the treatment of other psychiatric disorders, including posttraumatic stress disorder (PTSD) and obsessive-compulsive disorder (OCD). In a randomized controlled trial of 41 patients with PTSD, patients received a single-dose of ketamine (0.5 mg/kg infused over 40 min) or midazolam (0.045 mg/kg infused over 40 min) and then were crossed over to the other treatment after a 2-week washout. Compared to the midazolam control, ketamine resulted in a greater reduction in PTSD symptom severity at 24 h following infusion. One week following the infusion, there were no differences in PTSD symptom severity (Feder et al. 2014).

Rodriguez et al. (2013) performed a randomized controlled crossover trial of ketamine in OCD. Fifteen medication-free participants underwent a single ketamine infusion (standard

dose) or saline and then were crossed over to the opposite treatment after a 1-week washout period. Only first-period data was used for analyses due to significant carryover effects persisting beyond the washout period. Those receiving ketamine reported significant improvement in OCD symptoms and had a much higher response rate compared to those receiving placebo.

Notably, Bloch et al. (2012) conducted an open-label trial of ketamine (0.5 mg/kg infused over 40 min) in ten patients with treatment-refractory OCD. While there was a statistically significant decrease in OCD symptom severity, this improvement was minimal (<12%) and none of the subjects experienced a response (defined as a 35% or greater reduction in symptom severity) during the first 3 days following exposure. Potential explanations for the different findings in the Bloch and Rodriguez studies were a cohort of more severely ill in the open-label study as well as the functional unblinding that may have occurred in the randomized study against a saline placebo.

In a follow-up to their prior study, Rodriguez et al. (2013) conducted an open-label trial in which participants with OCD received a single-dose of ketamine (standard dose) followed by exposure and response prevention therapy (a specialized form of CBT for OCD). Similar to the rationale by Wilkinson et al. in treatment-resistant depression, the conceptual framework for this combination was that ketamine may enhance synaptic plasticity and thereby facilitate extinction learning, creating an opportune time for cognitive and behavioral interventions. In the eight patients who completed the infusion and reported a rapid reduction in OCD symptoms, 63% retained response 2 weeks later.

## 16.7 Biomarkers and Other Predictors of Ketamine Response

Considerable interest exists regarding potential biomarkers of response to ketamine. The most promising of these involves a single nucleotide polymorphism (SNP) in the coding region of brain derived neurotrophic factor (BDNF). In a sample of 61 patients with MDD, Laje et al. investigated the interaction of the Val66Met SNP and response to ketamine. Patients who were Met carriers experienced a 24% (SD 31) improvement in symptoms, while those who were Val carriers experienced a 41% (SD 24) improvement. In a general linear model, genotype was significantly associated with response ($F = 5.59$, df = 4, $p = 0.0007$), and genotype accounted for 28% of the variance in ketamine response (Laje et al. 2012). In a secondary analysis of a small sample ($N = 22$), ketamine responders had significantly higher plasma BDNF levels compared to non-responders 4 h post-infusion, with depression severity negatively correlated with plasma BDNF at this time point (Haile et al. 2014). While these results are intriguing, especially given that the purported antidepressant mechanism of ketamine involved enhancement of neurotrophic factor (i.e., BDNF), these studies await replication.

Clinical factors that may predict a better response to ketamine include a positive family history of alcohol use disorder (Pennybaker et al. 2017) and anxious symptoms at baseline (Ionescu et al. 2014). The latter finding is especially interesting given that depression with anxious features is typically less responsive to traditional antidepressant therapies and more prone to side effects (Fava et al. 2008).

Other potential biomarkers of ketamine response have included amino acid neurotransmitter changes (which have been shown to normalize following traditional antidepressant therapy) in the occipital cortex, though there is no conclusive direction or magnitude of abnormalities of GABA, glutamate, or glutamine that have been shown to consistently predict or correlate with ketamine response. Peripheral pro-inflammatory markers have also been associated with response to ketamine in an animal model of depression (Walker et al. 2015), though these relationships have not been examined in humans.

While some of these findings are promising, further work is needed to develop accurate biomarkers of clinical response to ketamine.

## 16.8 Mechanism of Action

Through studies using rodent models, it was originally believed that the antidepressant effects of ketamine are mediated through its antagonism of the NMDA receptor and subsequent downstream effects on the enhanced expression of process and proteins leading to synaptogenesis (Li et al. 2010). More recently, preliminary evidence disputes this and suggests that the behavioral effects are mediated through the AMPA receptor via hydroxynorketamine, a ketamine metabolite (Zanos et al. 2016). Further work is needed to definitively elucidate the mechanism of action of ketamine's antidepressant effects.

## 16.9 Adverse Clinical Consequences

The potential therapeutic effects of ketamine must be weighed carefully against possible adverse clinical consequences that might come from long-term exposure. These possible adverse consequences include abuse liability, cognitive changes, and interstitial cystitis. Generally, what is known thus far about adverse effects from long-term ketamine exposure in humans comes from longitudinal studies of ketamine abusers.

### 16.9.1 Abuse Liability

Ketamine abuse is a widely recognized social problem throughout the world, most prevalent in Southeast Asia. In Hong Kong, ketamine is now estimated to be the most common drug of abuse (Li et al. 2011). In Taiwan, ketamine is the third most common drug of abuse for individuals ages 12–64, with rates of abuse among high school students as high as 1.8%, and a rate of 1.1% among adult workers/laborers (Li et al. 2011).

In the United States, the prevalence of abuse seems comparatively lower, though still common. An estimated 0.8–1.7% of adolescents report recreational ketamine use any time within the past year (Sassano-Higgins et al. 2016). Approximately 0.4% of college students reported ketamine use in 2012 (Bokor and Anderson 2014). An estimated 2.3 million people have used ketamine recreationally at least once in their life (2008). Data for ketamine abuse within the United States is unfortunately sparse.

Much remains unknown about ketamine abuse, including risk factors that may predispose patients to abuse. In particular, it is not known whether careful pre-screening of depressed patients might reduce or minimize the risk of exposure leading to dependence/abuse.

There has been at least one case report of a patient with a strong history of substance abuse (alcohol and benzodiazepines) who was receiving ketamine off-label for the treatment of depression developing an abuse pattern, with a catastrophic outcome (Schak et al. 2016).

### 16.9.2 Cognitive Effects, Perceptual Disturbances, and Schizophrenia-Like Symptoms of Ketamine

During the acute infusion period of the standard protocol (0.5 mg/kg over 40 min intravenously), healthy volunteers have been shown to experience symptoms similar to those of schizophrenia, impairment of cognition, as well as dissociative experiences (Krystal et al. 1994; Morgan et al. 2004). Cognitive functioning is also impaired during this acute infusion period. These effects resolve approximately 40–80 min following completion of the infusion. Patients with mood disorders have been shown to develop some level of tolerance to the acute dissociative and psychotic symptoms induced by ketamine with multiple infusion protocols (Singh et al. 2016).

An important question is whether repeated use of ketamine can induce long-lasting cognitive or perceptual changes or psychotic symptoms. This is especially important given that there is no clearly demonstrated way of sustaining ketamine's antidepressant effects without repeated exposure to the drug. The best available evidence of ketamine's long-term effects

on these domains comes from studies of persons who abuse ketamine.

In a cross-sectional study of subjects who abuse drugs, Morgan et al. studied cognitive abilities and schizophrenia-like symptoms of five different groups ($N = 30$ per group): frequent ketamine users (defined as use greater than four times per week), infrequent users (defined as less than four times per week but at least once monthly), ex-ketamine users (abstinent at least 1 month), non-ketamine polydrug users, and non-drug users. Compared to other groups, frequent ketamine users showed impairments on spatial working memory and pattern recognition tasks (Morgan et al. 2009). Also, frequent ketamine users scored higher on measures of dissociative and delusional symptoms than other groups, and to a lesser extent, ex-ketamine/infrequent ketamine users had higher rates of these symptoms compared to non-drug users (Morgan et al. 2009). When these groups were followed over a 12-month period, increasing ketamine use was correlated with decreasing performance on spatial working memory and pattern recognition tasks (Morgan et al. 2010). Furthermore, frequent ketamine abusers were more likely to report delusional symptoms compared to other groups, and infrequent and ex-ketamine users were more likely to report delusional symptoms compared to non-drug users (Morgan et al. 2010).

While concerns of the effects on cognition and abuse from repeated ketamine exposure are relevant, there have been no systematic reports of iatrogenic addiction or persisting psychosis thus far from the literature examining the therapeutic effect of ketamine in MDD.

### 16.9.3 Off-Label, Clinical Use of Ketamine

The above referenced studies have led to considerable excitement about the use of ketamine as a treatment for severe and refractory mood disorders. Despite the comparatively limited evidence, there has been significant growth in providers within the United States using ketamine outside of research as a clinical, off-label treatment (Wilkinson et al. 2017a). Several professional organizations have provided consensus statements regarding the safety of ketamine in research and/or clinical settings (Table 16.1). The European Psychiatric Association (EPA) has stated that ketamine is an essential addition to safe and effective therapies for severe and refractory-depression (Gaebel et al. 2015). The Canadian Agency of Drugs and Technologies in Health recommends restricting the use of ketamine in psychiatric disease to research settings because of limited information on safety and duration of

**Table 16.1** Statements or recommendations from professional organizations regarding the off-label use of ketamine for psychiatric indications

| Professional organization | Statement(s) or recommendation(s) |
|---|---|
| European Psychiatric Association (EPA), 2015 | • EPA opposes classification of ketamine as schedule 1 drug ("no meaningful medical use")<br>• Ketamine represents an essential addition to the available safe and effective therapeutic options for severe and treatment-refractory depression<br>• Ketamine is a valid tool in research for the improvement of treatment of mental disorders |
| Canadian Agency for Drugs and Technologies in Health (CADTH), 2017 | • Recommends restricting the off-label use of ketamine to research settings among psychiatric disease, citing limited information on ketamine's safety and duration of effect |
| American Psychiatric Association (APA) Council of Research Task Force on Novel Biomarkers and Treatments, 2017 | • Important to consider limitations of the available data and the potential risks when considering off-label ketamine as treatment option<br>• Recommends a comprehensive pre-procedural evaluation for appropriateness of off-label ketamine treatment, including urine toxicology and documentation of failed standard antidepressant therapies<br>• Treatment facility should be equipped to rapidly assess and stabilize medical and behavioral emergencies should such arise, including established plan to address sustained alterations in cardiovascular function<br>• Strongly advises against at-home self-administration of ketamine |

effect (Kim and Mierzwinski-Urban 2017). The American Psychiatric Association does not formally endorse the clinical use of ketamine for psychiatric disorders but has provided a consensus statement with recommendations on how it should be used if providers consider that benefits outweigh the risks in individual cases (Sanacora et al. 2017). Notably, it recommends (1) a comprehensive pre-procedural evaluation should be done, including urine toxicology screen and documentation of failed antidepressant therapies; (2) treatment facilities should be equipped to handle medical and behavioral emergencies should such arise; and (3) at-home self-administration of ketamine is strongly advised against.

## 16.10 Summary

In summary, the monoamine deficiency hypothesis does not fully explain the neurobiology of mood disorders. A large evidence base supports the role of the glutamate/GABA neurotransmitter system in the pathophysiology of mood disorders. A growing body of evidence demonstrates that ketamine, which acts directly on the glutamate neurotransmitter system via NMDA receptor antagonism, exerts a rapid-acting antidepressant effect at sub-anesthetic doses; however, the short duration of sustained response following a single or even multiple (4–6) infusions warrants optimization of treatment protocols. The safety of long-term exposure to ketamine is not well known, and is currently extrapolated in the human population from small observational studies of ketamine abusers. Given that a growing number of providers have begun offering ketamine off-label for the treatment of psychiatric disorders (Wilkinson et al. 2017a), future research is urgently needed to better understand long-term risks as well as evidence-based treatment regimens.

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# Antidepressant Therapy for Depression: An Update

17

Deepali Gupta and Radhakrishnan Mahesh

## 17.1 Introduction

Depression is among the most severe mental disorders with a lifetime prevalence of 14.4% (Kessler et al. 2012). According to a survey by World Health Organization, depression was ranked as the third leading cause of the global burden of disease in 2004 and will move into first place by 2030 (World Health Organization 2012).

Despite a dramatic rise in treatment options (both pharmacological and nonpharmacological), the pharmacotherapy of depression remains inadequate (Hindmarch 2002; Ruhé et al. 2006; Xue et al. 2013). This could be attributed, at least in part, to the unclear pathophysiology of depression. During last several years, efforts have been made to understand the different aspects of multifaceted pathophysiology of depression. Previous studies have examined potential biological markers or predictors of depression and related disorders. Although work in this area has been inconclusive, impairment of brain neurotransmission, hypothalamic-pituitary-adrenal axis hyperactivity, alteration in neurogenesis signaling pathways, enhanced brain oxidative stress and inflammatory activity have been reported to be strongly associated with depressive behavior, both in patients and animal models of depression (Behr et al. 2012; Gupta et al. 2016; Hanson et al. 2011; Lanfumey et al. 2008; Leonard 2014; Tobe 2013). Thus, therapeutic approaches targeting overlapping set of multifaceted systems are critically needed for the effective pharmacological intervention. In this chapter, we will provide a brief history on the evolution of clinically available antidepressant drugs followed by an update on the relative efficacy and plausible mechanism of antidepressant activity of most current therapeutic approaches, targeting different systems implicated in the pathophysiology of depression.

### 17.1.1 Antidepressant Drugs: The Evolution

The observations made in the 1950s of the effects of reserpine and isoniazid, in altering monoamine neurotransmitter (serotonin, noradrenaline, and dopamine) levels and affecting depressive symptoms, have led to the adoption of the monoamine hypothesis of depression (Delgado 2000; Hirschfeld 2000; Schildkraut 1965). First put forward over 50 years ago, it states that depression is caused by the underactivity of monoamines in brain and that targeting this neuronal deficit would tend to restore normal function in depressed patients. Accordingly, at present, therapy for depression relies mainly on several approaches intended to improve the

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monoaminergic transmission: reuptake inhibitors, which increase synaptic concentration of monoamines by inhibiting their synaptic reuptake; monoamine oxidase inhibitors (MAOIs), which act to reduce metabolic degradation of monoamines; and monoamine receptor modulators, which facilitate monoamine neurotransmission (Fig. 17.1). However, these therapies have reported limited efficacy, limited tolerability and significant mechanism-based side effects. In example, despite the vast therapeutic potential of MAOIs, the cheese reaction (characterized by increased heart rate, hypertension, and sweating), due to concomitant use of food containing high amounts of tyramine, has reduced the popular usage of MAOIs (Alkhouli et al. 2014). Problems associated particular to the tricyclic antidepressants (TCAs) are dizziness, memory impairments, and drowsiness, due to antagonism of adrenergic, muscarinic, and histaminergic receptors, respectively (Gray et al. 2015; Hillhouse and Porter 2015). Later on, selective serotonin reuptake inhibitors (SSRIs) came into existence, which were reported to have better safety profile than TCAs, both in acute and long-term treatment of depression (Hillhouse and Porter 2015). Subsequently, SSRIs have become first line antidepressants in all depressive conditions. However, this class of medications is not without untoward effects, most notably that approximately one half of patients do not respond (Kaplan 2002) and, during longer-term therapy, a significant minority, if not a majority, of individuals report sexual dysfunction as a side effect (Cassano and Fava 2004). Delayed onset of therapeutic effects is

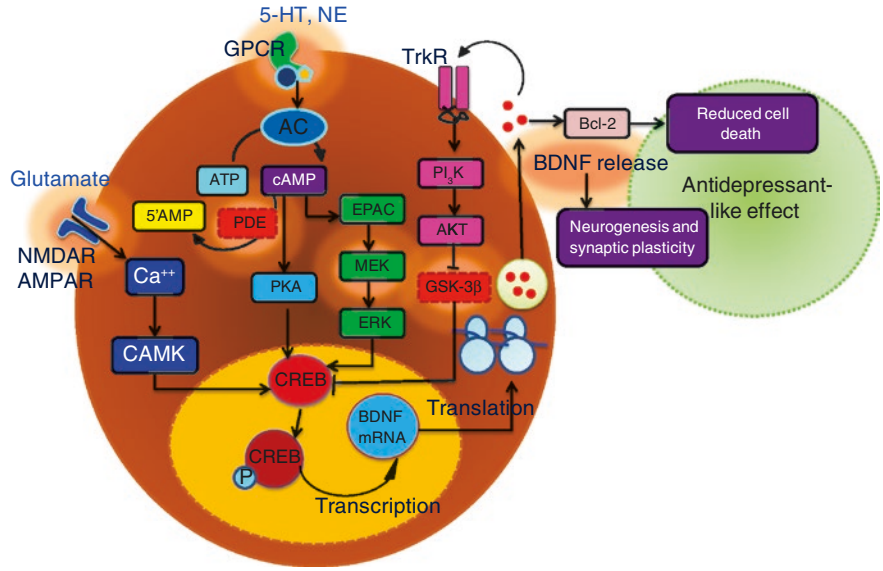


**Fig. 17.1** Signaling pathways regulating neurogenesis and synaptic plasticity. Stimulation of postsynaptic G protein-coupled receptors (GPCR) by neurotransmitters like serotonin (5-HT) and norepinephrine (NE) leads to activation of a variety of second messenger systems, including the cAMP (cyclic adenosine monophosphate)–protein kinase A (PKA)–cAMP response element-binding (CREB) pathway and cAMP-EPAC (exchange proteins activated by cAMP)–MEK (mitogen-activated protein/ERK kinase)–ERK (extracellular signal-regulated kinase) pathway (Duman and Voleti 2012; Quiroz and Manji 2002). Glutamate produces fast excitation of neurons via stimulation of ionotropic receptors, including AMPA and NMDA receptors, resulting in rapid depolarization and induction of Ca++-calmodulin-dependent protein kinase (CAMK). CREB activation triggers expression of brain-derived neurotrophic factor (BDNF) and other neurotrophic factors. BDNF downstream signaling via tropomyosin-related kinase receptor (TrkR) stimulate phosphatidyl inositol-3 kinase (PI3K)-AKT (A serine threonine kinase) pathway lead to neuroprotection, neuroplasticity and neurogenesis. Activated glycogen synthase kinase-3β (GSK-3β) inhibits CREB-BDNF signaling by CREB phosphorylation and gets inhibited by AKT mediated phosphorylation. Phosphodiesterase enzymes (PDE) metabolize cAMP to 5′AMP (5′ adenosine monophosphate) and hence reduce the level of cAMP (Duman et al. 2000; Krishnan and Nestler 2008; Quiroz and Manji 2002). Abbreviations: *Ca++* calcium ions, *ATP* adenosine triphosphate, *CREB-P* phosphorylated CREB, *AC* adenyl cyclase

another major concern with few SSRIs (Edwards and Anderson 1999).

Several new atypical antidepressants have been developed since then, which produce antidepressant activity by inhibiting reuptake of other monoamines as well, such as serotonin-norepinephrine reuptake inhibitors (SNRIs) and the norepinephrine-dopamine reuptake inhibitor (NDRI), bupropion. Although, some clinical trials suggests that SNRIs may be more effective for the treatment of depression as compared to SSRIs, these differences are relatively modest (Papakostas et al. 2007; Stahl et al. 2005). Bupropion, on the other hand, is reported to be equally effective drug with lowest risk of sexual dysfunction, compared to TCAs, MAOIs, SSRIs, and SNRIs (Papakostas et al. 2007; Thase et al. 2005). However, these classes of drugs tend to cause a broader array of side effects than the SSRIs, including signs of noradrenergic activity such as dry mouth, constipation, increased pulse, and blood pressure (Thase and Sloan 2006).

Till date there is no ideal intervention for the management of depression that is effective and free from untoward effects. This could be due to the fact that the current therapeutic approaches were largely developed in the absence of defined molecular targets or even a solid understanding of disease pathogenesis. Within the past few years, the understanding of biochemical pathways associated with the development of depression has expanded. There is an unprecedented range of molecular drug targets within these pathways. They have been identified on the basis of predicted roles in modulating one or more key aspects of the pathogenesis of depression. Several mechanistic categories for new therapeutic approaches can be considered, which are discussed in later sections.

## 17.2 New Targets and Treatments for Depression

### 17.2.1 Neurotransmitter Modulators

Monoamine hypothesis is still being a dominated theory of depression. Several new antidepressants acting on the monoaminergic system have been developed with improved efficacy and reduced side effects. Since major side effects of the current antidepressants are largely based on their activity on catecholamines, focus has been given on targeting serotonergic system.

#### 17.2.1.1 5-$HT_3$ Receptor Antagonists

In recent years, 5-$HT_3$ receptors (5-HT3Rs) have been recognized as a potential target for antidepressants. The only ligand-gated ion channel receptors of 5-HT receptor family, 5-HT3Rs, have been determined to a play key role in several brain signaling processes affecting learning, memory, cognition, depression, and anxiety. The functional role of 5-HT3Rs in depression was initially identified in late 1990s, when drugs in clinical use (such as ondansetron and zacopride), known to be potent 5-HT3R antagonists, reversed depressive-like state in rat learned helplessness test (Martin et al. 1992; Thiebot and Martin 1991). Since then, several investigators, including us, have demonstrated the antidepressant-like effects of different 5-HT3R antagonists in acute and chronic preclinical models of depression (Table 17.1). In support of the preclinical findings, few clinical trials have evidenced the effectiveness of 5-HT3R antagonists. Separate studies have shown that 5-HT3R antagonists ameliorated depressive behavior predisposed in hepatitis-infected patients (Piche et al. 2005), alcohol-dependent patients (Johnson et al. 2003), bulimic patients (Faris et al. 2000), and in patients with fibromyalgia (Haus et al. 2000). Although no information is available on the antidepressant effect of 5-HT3R antagonists in patients with depression alone, the reduction in depression scores associated with 5-HT3R antagonist treatment in patients with chronic illness clearly suggests the efficacy of these candidates and warrants further evaluation. Moreover, based on the outcome of the preclinical and clinical studies, it may be suggested that 5-HT3R antagonists possess faster onset of action, better efficacy, relatively good safety profile, and good therapeutic activity in drug-resistant cases (for review see Rajkumar and Mahesh 2010).

The plausible mechanism of their antidepressant action is still not clearly elucidated;

**Table 17.1** The effect of 5-HT3R antagonists in acute and chronic models of depression

| 5-HT3R antagonists | Behavioral model | Observation | Activity | References |
|---|---|---|---|---|
| *Effect of 5-HT3R antagonists in acute models of depression* | | | | |
| Ondansetron (GR 38032F) | Mouse forced swim test | Reduced duration of immobility | AD | Ramamoorthy et al. (2008) |
| | Mouse tail suspension test | Reduced duration of immobility | AD | |
| | Rat forced swim test | Potentiated reduction of immobility time by paroxetine | AD | Bétry et al. (2015) |
| Tropisetron (ICS205-930) | Rat forced swim test | Reduced immobility time | AD | Bravo and Maswood (2006) |
| Bemesetron (MDL72222) | Mouse tail suspension test | Produced anti-immobility effects | AD | Kos et al. (2006) |
| QCF-3 ((4-benzylpiperazin-1-yl) (quinoxalin-2-yl) methanone) | Mouse forced swim test | Reduced duration of immobility | AD | Devadoss et al. (2010) |
| | Mouse tail suspension test | Reduced duration of immobility | AD | |
| 4i (*N*-(3-Chloro-2-methylphenyl) quinoxalin-2-carboxamide) | Mouse forced swim test | Reduced duration of immobility | AD | Gupta et al. (2014a) |
| | Mouse tail suspension test | Reduced duration of immobility | AD | |
| Vortioxetine (Lu AA21004) | Mouse forced swim test | Increased mobility, swimming and climbing durations | AD | Guilloux et al. (2013) |
| Vortioxetine (Lu AA21004) | Rat forced swim test | Reduced immobility time<br>Produced no effect on swimming and climbing time | Partial AD | Mork et al. (2012) |
| A6CDQ, 4 (2-Amino-6-chloro-3,4-dihydroquinazoline hydrochloride) | Mouse tail suspension test | Reduced immobility time | AD | Dukat et al. (2013) |
| 6z (*N*-(Benzo[d]thiazol-2-yl)-3-methoxy quinoxalin-2-carboxamide) | Mouse tail suspension test | Reduced immobility duration | AD | Gupta et al. (2014b) |
| 7a (2-(4-phenylpiperazin-1-yl)-1, 8-naphthyridine-3-carboxylic acid) | Mouse forced swim test | Reduced duration of immobility | AD | Gautam et al. (2013) |
| | Mouse tail suspension test | Reduced duration of immobility | AD | |
| Ondansetron (GR 38032F) | Mouse forced swim test | Reduced duration of immobility | AD | Kordjazy et al. (2016) |
| | Mouse tail suspension test | Reduced duration of immobility | AD | |
| Tropisetron (ICS205-930) | Mouse forced swim test | Reduced duration of immobility | AD | Kordjazy et al. (2016) |
| | Mouse tail suspension test | Reduced duration of immobility | AD | |
| *Effect of 5-HT3R antagonists in chronic models of depression* | | | | |
| 6o (*N*-n-butyl-3-methoxy quinoxaline-2-carboxamide) | Mouse chronic unpredictable mild stress | Reversed stress induced increase in duration of immobility and decrease in sucrose consumption | AD | Bhatt et al. (2014) |

**Table 17.1** (continued)

| | | | | |
|---|---|---|---|---|
| QCM-4 (3-methoxy-*N*-*p*-tolylquinoxalin-2-carboxamide) | Mouse chronic unpredictable mild stress | Reversed stress induced increase in duration of immobility and decrease in sucrose consumption | AD | Kurhe et al. (2014) |
| Vortioxetine (Lu AA21004) | Mouse forced swim test | Increased mobility, swimming and climbing durations | AD | Guilloux et al. (2013) |
| 6z(*N*-(Benzo[d]thiazol-2-yl)-3-methoxyquinoxalin-2-carboxamide) | Mouse chronic unpredictable stress | Reversed stress induced increase in duration of immobility and decrease in sucrose consumption | AD | Gupta et al. (2014b) |
| Ondansetron (GR 38032F) | Mouse chronic unpredictable stress | Reversed despair effects in FST and reward-related deficits in sucrose preference test | AD | Gupta et al. (2014c) |
| 4i (*N*-(3-Chloro-2-methylphenyl) quinoxalin-2-carboxamide) | Olfactory bulbectomized rat | Reversed reward-related deficits in sucrose preference test | AD | Gupta et al. (2014a) |
| 4i (*N*-(3-Chloro-2-methylphenyl) quinoxalin-2-carboxamide) | Corticosterone-induced depression in mice | Reversed despair effects in FST and reward-related deficits in sucrose preference test | AD | Gupta et al. (2015) |

however, studies have reported that they do so by facilitation of 5-HT neurotransmission. Blockade of 5-HT3Rs has been shown to facilitate 5-HT neurotransmission, indirectly, by inhibiting GABA-mediated negative feedback mechanism of 5-HT release (Artigas 2013). 5-HT3Rs are highly distributed in cortical GABAergic interneurons, where their activation triggers the release of GABA (Puig et al. 2004), which in turn mediate tonic inhibition of 5-HT in dorsal raphe nucleus (Puig and Gulledge 2011; Zhang et al. 2011). The other plausible modes of action have also been investigated. These include modulation of other brain neurotransmitter (NE and DA) systems, normalization of HPA-axis hyperactivity, enhanced brain oxidative stress, and altered synaptic plasticity (for review see, Gupta et al. 2016).

All these findings suggest the prominent participation of 5-HT3Rs in an overlapping set of molecular and cellular signaling pathways involved in the pathogenesis of depression and that 5-HT3Rs antagonists may offer an effective approach for the management of multicausal depression.

#### 17.2.1.2 5-HT$_4$ Receptor Agonists

Recent research supports a role for 5-HT$_4$ receptors (5-HT4Rs) in the pathogenesis of depression as well as in the mechanism of action of antidepressant drugs. Indeed, it has been found that 5-HT4R agonists induce similar molecular and behavioral changes, as common antidepressants, in rodents. A 2-week treatment of RS67333, a 5-HT4R agonist, completely abolished depression-like behavior in the olfactory bulbectomy or chronic mild stress rat models (Lucas et al. 2007). In line, short-term treatment of RS67333 reversed novelty-suppressed feeding (NSF), anhedonic-like state (sucrose consumption), and despair behavior in defeated mice (Gómez-Lázaro et al. 2012; Pascual-Brazo et al. 2012). It has been suggested that these effects could be associated with increased 5-HT levels in hippocampus. If fact, after only 3 days of administration, RS67333 increased basal hippocampal 5-HT levels (Licht et al. 2010), suggesting a more rapid response in comparison with classical antidepressants. Although evidence lacks clinical significance, changes

in 5-HT4Rs binding sites in discrete brain regions of the depressed suicide victims (Rosel et al. 2004) strongly suggest further research in 5-HT4R agonists as innovative and rapid onset therapeutic approach to treat depression.

#### 17.2.1.3 5-HT$_6$ Receptor Modulators

Preclinical studies have brought new insights into the possible role of recently discovered serotonin 5-HT$_6$ receptors (5-HT6Rs) in depression. EMDT, WAY-181187, and WAY-208466, the 5-HT6R agonists, reduced immobility in the mouse TST and rat-modified FST, a behavior produced by several antidepressant drugs (Carr et al. 2011; Svenningsson et al. 2007). In contrast, antagonists have also been reported to produce similar effects in animal models for depression (Wesolowska and Nikiforuk 2007). SB-399885, a 5-HT6R antagonist, reduced immobility time and augmented the anti-immobility effects of antidepressants in rat during FST (Wesolowska 2007; Wesolowska and Nikiforuk 2008).

It is well established that the reduction in immobility time depends on the enhancement of central 5-HT and catecholamine neurotransmission (Borsini 1995; Cryan et al. 2005). Although the effect of EMDT on the levels of serotonin and catecholamines is not reported yet, a recent study has shown that the partial 5-HT6R agonist, EMD386088, produced anti-immobility effects in rat FST by activation of dopaminergic system, while noradrenergic and serotonergic systems remained unaltered (Jastrzębska-Więsek et al. 2016). Furthermore, a microdialysis study has only shown that selective 5-HT6R agonist WAY-181187 decreased the basal release of 5-HT, DA, and NE in frontal cortex, striatum, and amygdala of freely moving rats (Schechter et al. 2008). In contrast, studies have shown that 5-HT6R antagonists (such as SB-271046 and SB-399885) produced a significant increase in extracellular levels of DA and NE without altering 5-HT neurotransmission (Lacroix et al. 2004; Li et al. 2007). Altogether, it suggests the role of 5-HT6Rs in the pathogenesis of depression. However, extensive research investigating the exact receptor signaling pathways is required to develop effective ligands of this receptor subtype for antidepressant strategy.

#### 17.2.1.4 5-HT$_7$ Receptor Antagonists

The 5-HT$_7$ receptor (5-HT7R) is the most recently identified member of the 5-HT receptor family (Hedlund and Sutcliffe 2004). Soon after the discovery, the role of 5-HT7Rs have been identified in diverse processes of the central nervous system, modulated by 5-HT (Thomas et al. 2003; Faure et al. 2006). Moreover, the antidepressant activity of an atypical antipsychotic, known to be a potent 5-HT7R antagonist, proposed the idea that blockade of 5-HT7Rs might represent a key determinant for antidepressant therapy. More direct evidence, such as antidepressant-like behavioral activity exhibited by 5-HT7R knockout mice (Hedlund et al. 2005; Guscott et al. 2005), downregulation of 5-HT7Rs in hypothalamus after chronic treatment with antidepressants (Sleight et al. 1995), and antidepressant-like effects produced by selective 5-HT7R antagonists (such as SB-269970) (Hedlund et al. 2005) strengthen this hypothesis.

Furthermore, the potent antidepressant profile of amisulpride (Montgomery 2002), aripiprazole (Berman et al. 2009), or lurasidone (Loebel et al. 2014), most likely mediated by the blockade of 5-HT7Rs, provides clinical relevance of this target. However, a recent clinical trial showed that JNJ-18038683, a selective antagonist of 5-HT7Rs, had no statistically significant improvement over a placebo on the Montgomery-Åsberg Depression Rating Scale (MADRS). Besides, in this study, the ineffective response of escitalopram administration (as that of JNJ-18038683) indicates the lack of assay sensitivity, and hence the interpretation of these results is inconclusive.

#### 17.2.1.5 Other Neurotransmitter Modulators

Emerging evidence has proved that depression is not only associated with the monoaminergic but also with other non-monoaminergic neurotransmitter (such as GABA and glutamate) alterations (Krystal et al. 2002). Accordingly, researchers have investigated the antidepressant potential of several new candidates with GABA and/or glutamate modulatory effects.

In view of the findings that depression and anxiety disorders are often overlapping and may share a common pathophysiology, the neurophysiologi-

cal deficits of GABA is speculated to be related to depression. Subsequently, the importance of both GABA receptors ($GABA_A$ and $GABA_B$) has been established in pathogenesis of depression. Initially identified antidepressant-like effects of selective $GABA_B$ receptor agonists in preclinical studies was later confirmed to be weak and inconsistent, relative to the effects observed by the $GABA_B$ receptor antagonists. Notably, it was found that the antidepressant effect of selective $GABA_B$ receptor antagonists was blocked by 5-HT depletion using tryptophan hydroxylase inhibitor (para-chlorophenylalanine) pretreatment (Slattery et al. 2005) and that antidepressants caused an upregulation of $GABA_B$ receptor number and function (Sands et al. 2004). Based on these results, it may be speculated that decrease in $GABA_B$ receptor tone secondary to a decrease in GABAergic activity may result in prolonged activation of 5-HT system, which may account the antidepressant-like activity of $GABA_B$ receptor antagonists.

The significance of $GABA_A$ receptor modulators in depression came into existence from a study which reported that eszopiclone, a positive allosteric modulator of $GABA_A$ receptor, potentiated the antidepressant response of fluoxetine in patients with depressive symptomology (Fava et al. 2006; Snedecor et al. 2010). These initial results warrant efforts to profile GABAergic modulators as novel antidepressants.

Moreover, compelling evidence from clinical studies indicate that glutamate transmission is abnormally regulated in discrete brain areas of depressed individuals. Indeed, several postpartum studies reported elevated tissue glutamate levels in patients with major depressive and bipolar disorders (Frye et al. 2007; Hashimoto et al. 2007; Lan et al. 2009). In line, chronic treatment with antidepressants from different classes reduced presynaptic and stress-induced increase in glutamate release (Michael-Titus et al. 2000; Musazzi et al. 2010; Reznikov et al. 2007). Accumulated evidence from previous findings indicates that *N*-methyl-D-aspartate (NMDA) receptor antagonists, group 1 metabotropic glutamate receptor antagonists (mGlu), and α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) agonists have antidepressant properties. Consistently, based on glutamatergic signaling, a number of existing drugs and novel compounds have been investigated for their antidepressant potential. Some of these include ketamine, memantine, amantadine, tianeptine, pioglitazone, riluzole, lamotrigine, AZD6765, magnesium, zinc, guanosine, adenosine aniracetam, traxoprodil (CP-101,606), MK-0657, GLYX-13, NRX-1047, Ro25-6981, LY392098, LY341495, D-cycloserine, D-serine, dextromethorphan, scopolamine, pomaglumetad methionil, LY2140023, LY404039, MGS0039, MPEP, and 1-aminocyclopropanecarboxylic acid. It is interesting to quote here that glutamate receptor modulators have shown to induce rapid and long-lasting antidepressant effects in several clinical trials (Berman et al. 2000; Brennan et al. 2010; Diazgranados et al. 2010; Teng and Demetrio 2006; Valentine et al. 2011; Zarate et al. 2006), suggesting that glutamate system-based therapy may represent an effective alternative to biogenic-amine-based agents for depression.

Other studies have shown acetylcholine receptor modulators also influence neural processes that mediate antidepressant effects of several drugs. The clinical efficacy of mecamylamine (Shytle et al. 2002) and varenicline (Philip et al. 2009) (the antagonist and partial agonist of nicotinic acetylcholine receptor (nAChR), respectively) constitutes a compelling argument for further evaluation of the nAChR as a target for novel antidepressant drug development.

## 17.3 HPA-Axis-Targeted Therapy and CRF Antagonists

It is now well established that persistent HPA-axis hyperactivity, characterized by elevated circulating glucocorticoid levels and impaired negative feedback mechanism, plays a key role in the development of depression (Holsboer 2001; Pariante and Lightman 2008). Physiologically activated corticotropin-releasing hormone (CRF) from the hypothalamus triggers the release of adrenocorticotrophic hormone (ACTH) from the anterior pituitary. ACTH traverses down the circulation and increases release of glucocorticoids (GCs, corticosterone (CORT) in rodents and cortisol in

humans) from the adrenal medulla. The chain of events then subside by the negative feedback signals from GC to the CRF and ACTH releasing centers. However, persistent triggering stimuli, as in depression, impair the negative feedback inhibition that leads to consistent release of GCs into the circulation (Pariante and Lightman 2008). Depressed patients often exhibit high cortisol levels and abnormal HPA-axis control (Holsboer 2001), whereas several antidepressants have been reported to alleviate depression with concomitant reduction in HPA-axis overactivity (Nikisch et al. 2005). Interestingly, a number of non-peptide molecules with CRF1 receptor antagonistic action, which suppress HPA-axis hyperactivity (such as antalarmin, CP-154, CRA1000, 526, DMP904, DMP696, R121919/NBI-30775, R278995/CRA0450, LWH234, and SSR125543A), have shown to possess potential antidepressant effects in preclinical animal models (Valdez 2009). However, the efficacy of CRF1 receptor antagonists in controlled clinical trials with depressed patients was mostly negative (Binneman et al. 2008; Zobel et al. 2000). Moreover, the test drug candidates were associated with several untoward effects and worsening of depressive symptomology after drug discontinuation. As a result, no CRF1 receptor antagonist has yet been approved for clinical use in patients with depression (Griebel and Holsboer 2012). It could be due to the fact that not all depressed patients exhibit hyperactivity of CRF and/or impaired stress response regulation and that all clinical trials with CRF1 receptor antagonists have so far been conducted in unselected patient samples. Accordingly, specific CRF1 antagonistic treatments are likely to be effective only in patients with depression associated with CRF-related abnormalities. Development of specific biomarkers for identifying such patients and CRF1 receptor antagonists with high efficacy and safety profiles may eventually lead to a more successful treatment of depression.

## 17.4 Inflammatory System-Targeted Therapy

Another major pathological concern in depressed patients is increase in inflammatory biomarkers such as C-reactive protein (CRP), cytokines like interleukin-6 (IL-6), and tumor necrosis factor-α (TNF-α) (Penninx et al. 2003). Accordingly, anti-inflammatory strategies may be a promising approach for the treatment of depression in patients who do not respond to the current medication. In support of this notion, separate studies have reported that central administration of TNF-α produced depressive-like behavior (Moretti et al. 2015), whereas blocking of TNF-α signaling using etanercept or infliximab produced antidepressant-like effects in mice (Karson et al. 2013; Krügel et al. 2013). In line, several clinical trials consistently demonstrated the potential antidepressant effects of a number of TNF-α inhibitors, although reductions in depressive symptomology was observed only in subjects with higher baseline levels of inflammation (Maas et al. 2010; Raison et al. 2013; Weinberger et al. 2015). Other clinical studies have reported cyclooxygenase (such as celecoxib and acetylsalicylic acid) and cytokine inhibitors (etanercept, infliximab, ustekinumab, and adalimumab) as effective strategies with rapid onset of action (either alone or in combination with existing medications) in patients who fail to respond to the current therapies (Köhler et al. 2014; Mendlewicz et al. 2006; Na et al. 2014). While the reduced depressive symptoms without increased risks of adverse effects, with these agents, support the use of anti-inflammatory treatment in depression, identification of specific subgroups that could benefit from such treatment might be warranted.

## 17.5 Neurogenesis-Targeted Therapy

Although most antidepressants exert their initial effects by interacting with one or more neurotransmitter system in the brain, their clinical antidepressant effects occur only after chronic administration (days to weeks). Therefore, it is speculated that a cascade of downstream pathways are ultimately responsible for their therapeutic effects. These signaling pathways undoubtedly involved neurogenesis and neuroplastic events that regulate complex psychological and emotional processes. Consequently, considerable attention has been given to the alter-

ations in neuroplasticity and cellular resilience that might underlie the pathophysiology of depression (Quiroz and Manji 2002). Extensive series of studies have demonstrated that an important pathway involved in neurogenesis and plasticity, the cyclic adenosine monophosphate (cAMP)–cyclic response element binding protein (CREB) cascade, is upregulated by chronic antidepressant treatment (Blendy 2006; Duman et al. 2000). Antidepressant drugs increase the CREB phosphorylation and the expression of brain-derived neurotrophic factor (BDNF), a major protein involved in plasticity and neurogenesis. Consistent with these findings, a variety of antidepressants have been reported to increase hippocampal neurogenesis and prevent stress-induced atrophy of hippocampal neurons, coupled with increased performance in behavioral models of depression (Blendy 2006; Duman et al. 2000). Therefore, a more direct approach targeting critical molecules to enhance neurotrophic factor signaling may hold considerable promise for the development of improved and effective treatments. Some of these molecules are currently under development, which include phosphodiesterase (PDE) inhibitors, glycogen synthase kinase (GSK)-3β inhibitors, and molecules targeting MAP kinase cascades (Blendy 2006; Duman et al. 2000; Krishnan and Nestler 2008; Quiroz and Manji 2002), given that increasing cAMP levels (by inhibiting negative regulators, PDE and GSK-3β) exert neurotrophic effects via CREB-mediated upregulation of BDNF, anti-apoptotic protein bcl-2 (Fig. 17.1).

## 17.6 Oxidative Stress and Antioxidants

Past studies have shown that oxidative stress plays a role in depression and that antidepressant activity may be mediated via improving oxidative stress/antioxidant function. The link between depression and oxidative stress may arise from the fact that brain is particularly vulnerable to oxidative damage, due to large consumption of oxygen resulting in the production of free radicals, high amount of lipids as a substrate for oxidation, and diminished antioxidant enzymatic activity (Scapagnini et al. 2012). Several clinical reports have shown that depressed patients were associated with elevated prooxidant markers in both central and peripheral systems (Bilici et al. 2001; Michel et al. 2007) and reduced antioxidant enzyme activity (Stefanescu and Ciobica 2012). In contrast, several antidepressants have shown additional antioxidant effects associated with amelioration of depressive symptoms in animals as well as in humans (Bilici et al. 2001; Herken et al. 2007). Alternatively, several antioxidants have reported antidepressant-like effects by themselves or to improve effectiveness of current antidepressants. For example, a number of dietary antioxidants (such as ascorbic acid, vitamin E, lipoic acid, rutin, caffeic acid, polyunsaturated fatty acids (PUFA), and rosmarinic acid) exhibited antidepressant-like effects in animal models of depression (de Sousa et al. 2015; Manosso et al. 2013; Venna et al. 2009; reviewed by Bouayed (2010)). Combination therapy with omega-3 fatty acid and vitamin C augmented the antidepressant activity of SSRIs (Amr et al. 2013; Gertsik et al. 2012). Moreover, the antidepressant activity of the antioxidants was observed at relatively lower doses (0.2–1 mg/kg) as compared to the antidepressants such as imipramine or fluoxetine, which were active at higher doses (≥10 mg/kg) in animals (reviewed by Bouayed 2010). On the other hand, the combined therapy of currently prescribed antidepressants with some of these antioxidants indicated to be more effective than only antidepressant treatment in depressed patients (Amr et al. 2013; Gertsik et al. 2012).

**Conclusion**

Depression is a complex disorder, which is likely to have multiple pathogenic pathways. Although, a large array of antidepressants has been prescribed based on correction of monoamine deficit, a significant portion of population do not show therapeutic recovery and experience several untoward effects. Over time, several biological systems have been found to be involved in development of depression. Indeed, impairment of neurotransmitter system, HPA-axis hyperactivity, stimulated inflammatory activity, reduced neurogenesis, and enhanced oxidative stress has been implicated in the pathogenesis of depression. Accordingly, several monoaminergic and non-monoaminergic

neurotransmitter modulators such as 5-HT3/4/6/7R agonists/antagonists, $GABA_A$ agonists and $GABA_B$ antagonists, NMDA, AMPA, mGlu, and nACh receptor antagonists; CRF1 receptor antagonists effective in reducing HPA-axis hyperactivity; TNF-α cytokines and cyclooxygenase inhibitors that repress inflammatory signaling; several modulators effective in enhancing brain neurogenesis and plasticity like PDE and GSK-3β inhibitors; and a number of antioxidants have shown efficacy against depressive condition in preclinical and clinical settings. Some of these therapeutic strategies have reported better in terms of efficacy and side effect profile than the existing treatments. Besides, the search for better antidepressant drugs continued, particularly the search for a drug with faster onset of action and an assured effectiveness.

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# Atypical Antipsychotics in Major Depressive Disorder

18

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## 18.1 Introduction

Major depressive disorder (MDD) is a widespread disease, with a lifetime prevalence of 15% and an annual incidence of approximately 7%, which has been predicted to be the leading cause of disability among the Western countries by 2013, being associated with one of the highest risk of mortality (odds ratio [OR] = 1.81), compared to general population (Gruenberg et al. 2008). Despite antidepressants (ADs) representing the first-line treatment for MDD, approximately 10–15% of patients do not adequately respond to a pharmacological therapy, while around 30–40% of patients show only a partial remission of symptomatology (Bromet et al. 2011). Treatment-resistant depression (TRD) is a condition characterized by a poor or an unsatisfactory response to at least two adequate (optimal dosage and duration) trials of two different classes of ADs (Souery et al. 1999; Ward and Irazoqui 2010). Furthermore, it has been estimated that around 10–30% of patients with MDD do not respond to typical AD medications, and this group of patients needs trials of a variety of treatment strategies (Joffe et al. 1996). Overall, literature data seems to support the beneficial effects of atypical antipsychotics (APs), as adjunctive treatment to the ongoing antidepressants, particularly to the selective serotonin reuptake inhibitors (SSRIs), in ameliorating drug-resistant forms of unipolar depression (Papakostas 2005; Shelton and Papakostas 2008; Rogóż 2013). Furthermore, as recently, the latest edition of the *Diagnostic and Statistical Manual* (DSM-5) codified a new nosological entity characterized by subthreshold hypomanic or manic symptoms occurring during depressive episodes of either MDD or bipolar I or bipolar II disorder (APA 2013). Hence, atypical APs have been as well suggested to be prescribed in the treatment of mixed characteristics in a MDD (Stahl et al. 2017).

Preclinical studies demonstrated how the augmentation of atypical APs (e.g., olanzapine, risperidone, clozapine, and quetiapine) to ADs (e.g., citalopram, fluoxetine, and fluvoxamine) would increase the extracellular level of dopamine in the prefrontal cortex, rather than the intake of a single antidepressant agent. At low doses, atypical APs enhanced the antidepressant effect of ADs, mainly due to the activity at 5-$HT_{1A}$, 5-$HT_{2A}$, and adrenergic α2-receptors, by hence showing a good efficacy and effectiveness as adjunctive therapy in TRD. The major concern regards their side effects profile (especially, metabolic profile), being clozapine and olanzapine at higher risk for weight gain and glucose balance and aripiprazole, asenapine, lurasidone, and ziprasidone at lower risk (Hasnain et al. 2012; Orsolini et al. 2016).

Nowadays, the Food and Drug Administration (FDA) released the approval of aripiprazole as augmentative drug in MDD and for autism spectrum disorder; asenapine, clozapine, iloperidone, and olanzapine have been approved in combination with fluoxetine for MDD and bipolar depression, while paliperidone and quetiapine (both as extended-release and immediate-release formulation) have been described as effective in monotherapy in bipolar depression; extended-release quetiapine has been approved as augmentation strategy in MDD, whereas risperidone and ziprasidone have been approved in autism spectrum disorders (Gigante et al. 2012; Maher and Theodore 2012).

Hence, it should be mandatory to furtherly improve novel efficacious and effective agents or, at least, combos for acute and residual depressive exacerbations, particularly in TRD (Muneer 2016). Among these potential strategies, atypical APs have been properly investigated as adjunctive drugs able to improve depressive symptomatology (Lin et al. 2014) or as first-line strategy in major depressive episode with mixed characteristics (Fornaro et al. 2016; Stahl et al. 2017). The present chapter aims at reviewing the literature regarding the treatment of MDD with APs.

### 18.1.1 Aripiprazole

Currently, aripiprazole has been approved for the treatment of bipolar disorder (mania and mixed episodes and as maintenance treatment) and

represents the first atypical AP to be approved in the USA as adjunctive treatment in adult patients with MDD by the FDA in 2007 (Weber et al. 2008). Despite its antidepressant mechanism of action remains still unclear, however, it has been supposed a role as a partial agonist at $D_2$, $D_3$, and 5-$HT_{1A}$ receptors and its antagonism at 5-$HT_{2A}$ receptors (Khan 2008; Pae et al. 2011).

A multicenter, randomized, double-blind, placebo-controlled trial evaluated the efficacy and safety of aripiprazole vs placebo as adjunctive treatment to standard AD in patients with MDD who showed an incomplete response to ADs, by showing promising results (Berman et al. 2007). A further multicenter, randomized, double-blind, placebo-controlled study, carried out on a sample of MDD patients who showed an inadequate response to at least one and up to three historical and one additional prospective AD treatment, reported a significantly greater mean change in MADRS total score with adjunctive aripiprazole vs placebo ($p = 0.001$) and a greater significantly improvement in remission rates ($p = 0.016$) and response rates ($p < 0.001$) (Marcus et al. 2008). In addition, a double-blind, placebo-controlled study evaluating MDD patients with inadequate response to ADs reported a clinically significant improvement in MADRS total score from baseline to endpoint (week 14) in aripiprazole vs placebo group ($p < 0.001$). Remission rates were greater for adjunctive aripiprazole vs placebo ($p < 0.001$) (Berman et al. 2009).

A review and meta-analysis carried out on a pool of randomized placebo-controlled trials evaluating the efficacy of aripiprazole in treating both depression and manic phase of bipolar disorder, both as monotherapy and adjunctive therapy, with a placebo, included 9 RCTs ($n = 3046$ patients). Aripiprazole was associated with a significant increase of response rate in depressive patients (7.7%) and manic patients (15.7%), compared to placebo. While there was no significant improvement of remission rate in depressive patients between aripiprazole and placebo group (Arbaizar et al. 2009). A systematic review reported in three studies statistically significant greater mean change in MADRS total score from baseline to endpoint with 2–20 mg aripiprazole as adjunctive drug to SSRI/SNRI compared with placebo combined with SSRI/SNRI ($p < 0.01$) (Chen et al. 2011). A meta-analysis evaluated the efficacy of adjunctive aripiprazole in patients with minimal response to prior ADs, by pooling data from three randomized, double-blind, placebo-controlled studies assessing the efficacy of adjunctive aripiprazole to ADs in patients with MDD who had a minimal response (i.e., <25% reduction on the Montgomery-Åsberg Depression Rating Scale [MADRS]) to an 8-week prospective AD treatment (Nelson et al. 2012). The post hoc analysis reported that aripiprazole adjunctive to standard ADs is a clinically meaningful treatment option for patients who own a prior minimal response to antidepressant therapy. Patients statistically improved in their symptom scores and response rates after the combination with aripiprazole (Nelson et al. 2012).

A dosage ranging 2–5 mg daily (starting dose), titrated until 5–10 mg/day or 15 mg/day, has been recommended as adjunct to ADs for the treatment of MDD, while the treatment of manic/mixed episodes in bipolar disorder has been recommended with a starting dose of 15 mg/day then titrated until 30 mg/day (Weber et al. 2008).

### 18.1.2 Asenapine

Asenapine belongs to the same class of clozapine, olanzapine and quetiapine, sharing with them a rather complex pharmacological binding profile. It has been approved for the acute treatment of schizophrenia and manic/mixed episodes in 2009. Asenapine exhibits high affinity for 5-$HT_{1A}$ (partial agonism), 5-$HT_{1B}$, 5-$HT_{2A}$, 5-$HT_{2B}$, 5-$HT_{2C}$, 5-$HT_5$, 5-$HT_6$, and 5-$HT_7$ receptors (antagonism); dopamine receptors $D_2$, $D_3$, $D_4$, and $D_1$; $\alpha_1$ (antagonism)- and $\alpha_2$-adrenergic receptors; and $H_1$ histamine receptors (antagonism) and a moderate affinity for $H_2$ receptors.

Asenapine has been approved in the treatment of manic/mixed episodes in bipolar disorder (Azorin et al. 2013; Marazziti et al. 2016).

In vivo microdialysis in freely moving rats and in vitro intracellular recording of pyramidal cells of the medial prefrontal cortex (mPFC) of rats evaluated how asenapine as adjunctive drug to escitalopram may enhance catecholamine output in the prefrontal cortex and, hence, ameliorate treatment-resistant depression (Björkholm et al. 2014). In vivo electrophysiological and behavioral assays in rats reported that asenapine failed to alter immobility time in the forced swim test, in the ACTH-treated rats, a model of antidepressant-resistance (Delcourte et al. 2017).

A post hoc analysis carried out on two 3-week randomized, placebo- and olanzapine-controlled clinical trials demonstrated that asenapine may significantly reduce depressive symptoms in bipolar I disorder patients experiencing acute manic or mixed episodes with clinically relevant depressive symptoms at baseline; despite further studies should be properly integrated to confirm the generalizability of the current findings (Szegedi et al. 2011). A post hoc analysis evaluating the effects of asenapine in bipolar I patients with current moderate-to-severe mixed major depressive episodes reported that asenapine was associated to a significantly greater reduction in depressive symptoms ($p = 0.0195$) (Berk et al. 2015).

### 18.1.3 Amisulpride

Amisulpride is an alkylsulphone derivative of the substituted benzamide, with a high affinity at pre/postsynaptic dopamine $D_2$ and presynaptic $D_3$ receptors. At low dosages (100–300 mg daily), it preferentially binds to presynaptic autoreceptors $D_2/D_3$, raising the levels of dopamine in the prefrontal cortex and showing a "disinhibiting and psychostimulant" profile. While, at higher doses (400–800 mg daily), it displays its antagonistic activity at postsynaptic $D_2$ in the limbic areas, by exerting antipsychotic effects. Its antagonism at 5-$HT_7$ receptors may explain its antidepressant efficacy at low doses (Orsolini et al. 2016). It has been supposed its antidepressant activity due to 5-$HT_{7A}$ antagonism, independent of the dopamine receptor (Abbas et al. 2009). At low doses (50 mg daily), amisulpride preferentially blocks presynaptic autoreceptors, producing an increase in dopamine release, hence, by acting as a dopaminergic compound able to resolve the dopaminergic hypoactivity that characterizes MDD; while at higher doses (400–1200 mg daily), it exerts its activity on postsynaptic $D_3/D_2$ receptors located in the limbic region and prefrontal areas, by producing selective dopaminergic inhibition, eliciting antipsychotic effects (Orsolini et al. 2016).

Recent reports support the role of amisulpride in the treatment of mood disorders, such as dysthymia with or without MDD, or as add-on drug in the treatment of bipolar disorder (Montgomery 2002; Carta et al. 2006; Jarema 2007). A preclinical study evaluating the antidepressant-like property of amisulpride per se and its comparison with fluoxetine and olanzapine using forced swimming test in albino mice reported contrasting findings as there was no statistically significant difference between amisulpride and olanzapine in terms of immobility and swimming phases in mice ($p > 0.05$) even though it was reported a greater superiority of fluoxetine vs amisulpride and olanzapine ($p < 0.01$) (Pawar et al. 2009).

A trial carried out by Cassano and Jori (2002) reported a similar efficacy of low-dose amisulpride (50 mg/day) and low-dose antidepressant treatment with paroxetine (20 mg/day) in subjects affected with TRD. A case report of a woman at her first depressive episode reported a significant clinical improvement of depressive symptomatology after the combination of low-dose amisulpride with citalopram after a failure in remission (Carvalho et al. 2007). A prospective, intention to treat, 4-week study evaluated the efficacy of administration of amisulpride in the short-term treatment of depressive and physical symptomatology in cancer patients during chemotherapy, by showing a significant clinically improvement ($p < 0.002$) (Torta et al. 2007). A study showed

promising findings in the treatment of elderly patients with psychotic depression by using amisulpride (75–100 mg daily) in combination with an antidepressant therapy (Politis et al. 2008). A clinical trial carried out on 20 MDD women who were given fluvoxamine (100 mg daily) and amisulpride (50 mg daily) throughout a 6-week period reported a clear improvement of depressive symptomatology in 19 out of 20 patients recruited ($p < 0.0001$) (Hardoy and Carta 2010). A systematic review reported in only one study a statistically significant greater mean change in the MADRS with 50 mg amisulpride compared to placebo ($p < 0.01$) (Chen et al. 2011). A recent successful case report reported the efficacy of 100 mg/day of amisulpride in a patient with atypical depression, who failed previous trials with fluvoxamine, bupropion, fluoxetine, and valproate (Agarwal et al. 2012).

More evidence coming from studies carried out on subjects affected by dysthymia show that amisulpride significantly improves depressive symptomatology, compared to placebo antidepressant treatment (Lecrubier et al. 1997; Smeraldi 1998; Amore and Jori 2001). Amisulpride was generally given in doses of 50 mg/day (Komossa et al. 2010).

### 18.1.4 Brexpiprazole

Brexpiprazole is a serotonin-dopamine activity modulator, acting as partial agonist at $D_2$, as antagonist with a higher potency compared to aripiprazole regarding 5-$HT_{2A}$, as agonist at 5-$HT_{1A}$, and antagonist at $\alpha_{1B}$ (Maeda et al. 2014; Rexulti 2015; Stahl 2016; Parikh et al. 2017).

Overall, data so far published (Citrome 2015; Thase et al. 2015a, b; McIntyre et al. 2016; Davis et al. 2015; Menard et al. 2015; Krystal et al. 2015; Parikh et al. 2017) support the efficacy of brexpiprazole over placebo in MDD with NNT of 12 or response and 17–31 for remission. No studies comparing brexpiprazole with aripiprazole or other antipsychotic augmenting agents in MDD exist although one trial comparing brexpiprazole with extended-release quetiapine in MDD is currently in the recruiting phase.

### 18.1.5 Cariprazine

Cariprazine is a novel antipsychotic drug that exerts partial agonism of dopamine $D_2/D_3$ receptors with preferential binding to $D_3$ receptor, antagonism of $5HT_{2B}$ receptors, and partial agonism of $5HT_{1A}$. Currently, cariprazine is in late-stage clinical development (phase III clinical trials) in patients with schizophrenia and in patients with bipolar disorder, as well as an adjunctive treatment in patients with MDD and TRD. Cariprazine has completed phase III trials for the acute treatment of schizophrenia and bipolar mania and phase II trials for the bipolar depression and MDD, while it is undergoing phase III trials as an adjunct to antidepressants. Preliminary animal models showed that low-dose cariprazine exhibits antidepressant-like effects (De Berardis et al. 2016). However, preliminary findings coming from studies evaluating the efficacy of cariprazine as add-on therapy in MDD patients with current depressive episode without psychotic symptoms but who previously failed to respond to adequate trials of ADs do not seem to completely confirm previous antidepressant-like efficacy observed at low doses in animal models (Dimitrakopoulos and Konstantakopoulos 2015; De Berardis et al. 2016). Therefore, further studies are needed in order to draw up definitive and clear conclusions regarding its clinical and efficacy profile as add-on treatment in TRD.

### 18.1.6 Clozapine

Adverse drug reactions of clozapine are commonly a factor discouraging clinicians from prescribing it (Li et al. 2015). By the way literature data reports that clozapine could have a role in psychotic mood disorders (Banov et al. 1994). Available case reports and retrospective studies suggest that clozapine may be particularly effective in the treatment of TRD and treatment-resistant depressive phases of bipolar disorder (BD) (McElroy et al. 1991; Frakenburg 1993; Li et al. 2015.) Randomized clinical trials showed that clozapine is an effective add-on treatment to

antidepressants for TRD (Yan 2001). Clozapine could be used as monotherapy or in combination with other treatments for treatment-resistant bipolar depression. It is associated with improvement of mania, depression, rapid cycling, and psychotic symptoms (Li et al. 2015).

### 18.1.7 Iloperidone

Iloperidone exerts a high affinity at serotonin 5-$HT_{2A}$ and dopamine $D_2$ and $D_3$ receptors and a moderate affinity at $D_4$, 5-$HT_6$, 5-$HT_7$, and norepinephrine $NE_{\alpha1}$ receptors (McDonagh et al. 2010). It has been approved only in the treatment of schizophrenia. No clinical trials have been documented for the off-label use of iloperidone in MDD or TRD (Maher and Theodore 2012). Therefore, further studies should be carried out in order to better improve the knowledge and potentialities of iloperidone in the treatment of MDD and/or TRD (Tarazi and Stahl 2012).

### 18.1.8 Lurasidone

Lurasidone hydrochloride, a benzisothiazol derivative, is a second-generation (atypical) antipsychotic agent that is approved for the treatment of schizophrenia in the USA, Canada, Europe, Switzerland, and Australia and also for bipolar depression in the USA and Canada. In addition to its principal antagonist activity at dopamine $D_2$ and serotonin 5-$HT_{2A}$ receptors, lurasidone exerts a distinctive 5-$HT_7$ antagonistic activity and displays a partial agonism at 5-$HT_{1A}$ receptors, as well as modest antagonism at noradrenergic $\alpha_{2A}$- and $\alpha_{2C}$-receptors (Orsolini et al. 2016). Lurasidone is devoid of antihistaminic and anticholinergic activities. Its pharmacokinetic profile requires administration with food, and it is flexibly dosed 20–120 mg/day for bipolar depression (Greenberg and Citrome 2017). Lurasidone has been approved for the treatment of depressive episodes associated with bipolar disorder type I (20 mg daily to 120 mg daily). The efficacy of lurasidone as monotherapy was established in a 6-week, multicenter, randomized, double-blind, placebo-controlled study of adults with major depressive episodes associated with bipolar I disorder, with or without rapid cycling, and without psychotic symptoms. Lurasidone (20–60 mg/day or 80–120 mg/day) has been demonstrated to be superior to placebo in reduction of MADRS and CGI-S scores at week 6. The high dosages did not provide additional efficacy on average, compared to the low-dose range (20–60 mg/day). It has been as well demonstrated to be efficacious as an adjunctive therapy with lithium or valproate (Loebel et al. 2014; Muneer 2016).

### 18.1.9 Quetiapine

Quetiapine is a dibenzothiazepine derivative which shows a greater in vitro binding affinity for 5-$HT_2$ receptors than for dopamine $D_2$ receptors and a high $\alpha_{1A}$-adrenoceptor and $H_1$ receptor antagonist activity. It shows a lower $D_2$ and 5-$HT_2$ receptor antagonism and a minimal antagonist activity at $D_1$, $D_4$, 5-$HT_{2C}$, and $\alpha_{2A}$-adrenoceptors. At therapeutic doses, it has been shown to occupy approximately 30% of $D_2$ receptors, as it has a more rapid "runoff" or rapid dissociation (the so-called kiss and run hypothesis). Its partial agonistic activity at 5-$HT_{1A}$ may explain its antidepressant effect (Orsolini et al. 2016).

Currently, quetiapine is available as an immediate-release (IR) and extended-released (ER) quetiapine. It has been approved for the treatment of manic (quetiapine IR in 2003 at the dosage ranging 400–800 mg/day; quetiapine XR in 2008 at the dosage 400–800 mg/day, once a day) and depressive (quetiapine IR in 2006 at dosages ranging 300–600 mg/day as monotherapy, quetiapine ER in 2008 at dosages ranging 300 mg/day as monotherapy) phases of bipolar disorder. Furthermore, it has been approved in the maintenance therapy of bipolar disorder (quetiapine IR and ER at dosages of 400–800 mg/day, as add-on drug to lithium or divalproex, in 2008). In addition, quetiapine ER (150–300 mg/day) was approved in 2009 in the treatment of MDD as adjunct to ADs, while the FDA did not approve quetiapine IR (FDA 2009).

Results from pivotal registration trails evaluating the acute and maintenance efficacy and tolerability of quetiapine XR (as monotherapy and as adjunctive treatment) in MDD demonstrated that quetiapine at dosages ranging 50–300 mg/day provided rapid and sustained symptomatic improvement in the acute and maintenance treatment of MDD (McIntyre et al. 2009). A systematic review reported two 8-week placebo-controlled studies with a statistically significant greater mean change in MADRS total score from baseline to endpoint with 50 mg quetiapine in monotherapy ($p < 0.05$) and 150 mg ($p < 0.01$) and 300 mg ($p < 0.01$) of quetiapine extended release compared with placebo (Chen et al. 2011), while one study in TRD patients found a statistically significant greater mean change in MADRS total score with 150 and 300 mg extended-release quetiapine combined with ADs compared with placebo combined with ADs ($p < 0.01$). Another study found a statistically significant greater mean change in MADRS total score with 300 mg extended-release quetiapine combined with ADs compared with placebo combined with ADs ($p < 0.01$), even though they did not found difference between 150 mg extended-release quetiapine combined with ADs and placebo combined with ADs (Chen et al. 2011). Quetiapine XR has been demonstrated to be effective at the dosage of 150–300 mg/day as adjunctive to ADs in MDD, with MDD response rates significantly higher with adjunctive quetiapine XR 300 mg/day (but not 150 mg/day) than with ADs plus placebo. The NNT to achieve an additional response over ADs vs placebo was 11–18 and 8–9 in the quetiapine XR 150 and 300 mg/day dosage groups, respectively (Sanford 2011). A recent meta-analysis reported the efficacy of quetiapine as monotherapy, even though the authors described a high dropout rate due to side effects and recommended considering the risk vs benefit for an individual patient with MDD (Maneeton et al. 2012). A pooled analysis performed from two studies evaluating the efficacy of once-daily quetiapine XR monotherapy for patients with MDD reported a statistically significant difference versus placebo in MADRS total score both in anxious depressive and non-anxious depressive patients, after the administration of quetiapine XR 150 mg/day ($p < 0.01$) and 300 mg/day ($p < 0.05$) at week 6 (Thase et al. 2012). Another pooled analysis evaluating the efficacy of quetiapine XR monotherapy in MDD from two 6-week, double-blind, placebo-controlled studies reported a significant improvement at week 6 at 150 mg/day ($p < 0.001$) and 300 mg/day ($p < 0.001$) vs placebo. The response rates (at week 6) were 52.7% ($p < 0.001$) quetiapine XR 150 mg/day and 49.5% ($p < 0.001$) quetiapine XR 300 mg/day vs placebo (33%). MADRS remission was significant only with quetiapine XR 300 mg/day (28.8%) vs placebo (19.4%), at week 6 ($p < 0.01$) (Weisler et al. 2012).

### 18.1.10 Olanzapine

Olanzapine is a thienobenzodiazepine derivative which displays a significantly high in vitro inhibitory activity at $D_1$, $D_2$, $D_4$, 5-$HT_{2A}$, 5-$HT_6$, 5-$HT_{2C}$, $H_1$, and $\alpha_1$-adrenergic receptors. In addition, it shows a moderate affinity at 5-$HT_3$ and $M_4$, $M_5$, $M_1$, $M_2$, and $M_3$ muscarinic receptors (Orsolini et al. 2016). Currently, olanzapine has been approved for the treatment of manic/mixed episode (10–15 mg/day) of bipolar disorder I in monotherapy or as add-on therapy to lithium or valproate. A combination of the antidepressant fluoxetine and olanzapine (OFC, olanzapine/fluoxetine combination) is also available in USA under the trade name *Symbyax*, and it has been approved for the treatment of depressive episodes associated with bipolar I disorder and TRD (5 mg of oral olanzapine and 20 mg/day of fluoxetine once daily).

A systematic review described one study evaluating olanzapine in combination with fluoxetine which showed a statistically significant greater mean change in MADRS total score from baseline to endpoint compared with olanzapine alone or fluoxetine alone ($p < 0.01$). Furthermore, the systematic review reports as well one RCT comparing olanzapine in combination with fluoxetine vs venlafaxine and one study evaluating olanzapine in

combination with fluoxetine vs nortriptyline showing a greater mean change in MADRS total score during the trials but no difference by the endpoints (Chen et al. 2011). A recently published meta-analysis of RCT evaluating whether OFC is superior to olanzapine or fluoxetine monotherapy in TRD patients reported a greater change from baseline in MADRS ($p < 0.001$), HAM-A ($p < 0.001$), CGI-S ($p < 0.001$), and BPRS ($p < 0.001$); a significant higher response rate with OFC (RR = 1.25; $p = 0.001$); and remission rate (RR = 1.71; $p < 0.001$) (Luan et al. 2017).

### 18.1.11 Paliperidone

Paliperidone represents the major active metabolite of risperidone. The actions of paliperidone are pharmacological like its precursor risperidone, displaying a high binding affinity at $D_2$ and 5-$HT_{2A}$ as antagonist. However, it differs from risperidone on its ability to block $D_2$ receptors, as it owns a $D_2$ receptor affinity approximately three times lower than risperidone. The estimated occupancy of $D_2$ receptors at a dose of 6 mg/day is around 72%. It also binds to $\alpha_1$- and $\alpha_2$-adrenoceptors but less than risperidone. In addition, it binds less at $H_1$ receptor than risperidone and does not block 5-$HT_{2C}$ receptors (Orsolini et al. 2016). It has been approved for the treatment of schizophrenia and schizoaffective disorder. Recent findings demonstrated its efficacy as well in preventing depressive or manic episodes in schizoaffective and bipolar disorder patients (Dimitrakopoulos and Konstantakopoulos 2015). However, a significant improvement has been observed in the prevention of manic (but not depressive) episodes (Keller and Nesse 2006).

### 18.1.12 Risperidone

Risperidone has high affinity to 5-$HT_{2A}$, $D_2$, $\alpha_{1A}$-, and $D_4$ receptors. It also binds with a moderate affinity to $\alpha_{2A}$-, $H_1$ and 5-$HT_{2C}$ receptors. Risperidone displays a lower affinity to $D_1$and 5-$HT_{1A}$ (Orsolini et al. 2016). A multicenter, double-blind, placebo-controlled, randomized trial carried out on 274 subjects affected with MDD who were suboptimally responsive to ADs and were randomly assigned to receive risperidone (1–2 mg/day) or placebo demonstrated a statistically significant mean reduction in depressive symptoms, a substantially increased remission and response, and a general improvement of other patient- and clinician-rated measures (Mahmoud et al. 2007). A randomized, placebo-controlled trial of risperidone augmentation for patients with difficult-to-treat unipolar, nonpsychotic MDD randomized subjects to risperidone (0.5–3 mg/day) or placebo augmentation, demonstrating a significant more improvement in quality of life than patients in the placebo group (Keitner et al. 2009). A systematic review reported one study that described a statistically significant greater mean change in the 17-item Hamilton Depression Rating Scale with risperidone 1–2 mg combined with antidepressants compared with placebo combined with antidepressants ($p < 0.01$) (Chen et al. 2011).

### 18.1.13 Ziprasidone

Ziprasidone possesses the highest 5-$HT_{2A}$/$D_2$ receptor binding affinity ratio among all FDA-approved APs. It acts as a 5-$HT_{1A}$ receptor partial agonist (Papakostas et al. 2015; Richelson and Souder 2000; Tatsumi et al. 1999), and it has been shown (in vitro) to be able to inhibit the neuronal uptake of serotonin and norepinephrine, with a potency similar to ADs such as imipramine and desipramine (Schmidt et al. 2001). In an open-label ziprasidone augmentation study for TRD, a positive antidepressant response after 6 weeks of treatment with ziprasidone as add-on therapy to SSRI has been reported (Papakostas et al. 2004). Ziprasidone as an adjunct to escitalopram demonstrated an antidepressant efficacy in adult patients with MDD experiencing persistent symptoms after 8 weeks of open-label treatment with escitalopram alone (Papakostas et al. 2015). Ziprasidone augmentation is equally efficacious in treating depression in patients with or without anxious

depression (Ionescu et al. 2016; Heo et al. 2015). Furthermore, it has been documented to improve sleep continuity and sleep architecture among MDD patients, after administering ziprasidone as add-on or in monotherapy (Monti 2016).

**Conclusion**

Although each possible AP agent may be useful in the treatment of MDD, particularly TRD and mixed states associated with depressive episodes, available evidence recommends prescribing aripiprazole (at low doses) as adjunctive treatment; amisulpride (at low doses), especially if associated with dysthymia; cariprazine (at low doses), particularly if associated with psychotic features; ziprasidone, both in non-anxious and anxious depression; lurasidone; quetiapine; and olanzapine. Further studies are needed for asenapine, brexpiprazole, clozapine, risperidone, paliperidone, and iloperidone. Despite this preliminary evidence, it should be better investigated the therapeutic potentialities of newer atypical APs in the treatment of MDD, both as monotherapy and as adjunctive therapy.

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# 19 Neurobiology and Evidence-Based Review on Novel Therapeutic Strategy for Treatment-Resistant Depression (TRD)

Salih Selek and Jair C. Soares

## 19.1 Introduction

Although the antidepressant era brought new hopes for treating depression with fewer side effects and better tolerability, at least one fifth of the patients do not respond very well and about half of the patients experience a chronic or recurrent course of illness (Lepine et al. 2012; Sackeim 2001), and numerous definitions have been used to describe resistance/refractoriness in depression, and six different criteria were employed to define the categorical presence of TRD ranging from non-response to one antidepressant to non-response to two or more antidepressants from different pharmacological classes so far (Berlim and Turecki 2007). A research on US commercial insurers database showed 6.6% of the treated depression episodes met the criteria for TRD, and a median time for an episode to evolve to TRD was estimated about 1 year, resulting in increase of average health costs about 3.72 times higher for TRD than non-TRD episodes (Kubitz et al. 2013). Potential risk factors contributing to treatment resistance that have been reported as comorbid are other psychiatric disorders such as social anxiety, panic disorder, personality disorder, number of hospitalizations, number of previous episodes, onset of age before 18, melancholic features, obstructive sleep apnea, and suicidality (Best et al. 2013; Gorwood et al. 2010; Souery et al. 2007). Patients that have residual symptoms of depression including poor concentration, sleeping difficulties, low energy level, and minor persistent anxiety symptoms, concomitant substance abuse, comorbid medical illnesses such as diabetes mellitus, malignancies, or cardiovascular disease are shown to be at higher risk of recurrence and TRD (Hirschfeld 1994; Iosifescu et al. 2004; Nierenberg et al. 2003; Pollack 2005). A study in the adolescent TRD group showed physical abuse had significantly lower rate of response to combination antidepressant therapy (Shamseddeen et al. 2011). On the other hand, pseudo-resistance that is defined as inadequate treatment, misdiagnosis, or having unrecognized comorbid psychiatric or general medical conditions that contribute to treatment resistance is also common; thus, a comprehensive assessment including assessment of medical and psychiatric comorbidities as well as personality features and psychosocial evaluation including evaluation of social support system is essential to rule out pseudo-resistance (Keitner and Mansfield 2012; Kornstein and Schneider 2001). A recent study showed that many patients still are not prescribed an adequate antidepressant trial before switching to a second-line treatment that is an indicator of pseudo-resistance problem (Hassan et al. 2016).

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In addition to common known criteria of TRD described as failure to respond two adequate trials, several authors also suggested "prophylaxis" resistance in bipolar disorder that is defined as experiencing five or more mood episodes, and two of these episodes should occur in the past 3 years despite two adequate medication trials (Bauer and Ströhle 1999).

In this current paper, we will review the current treatment approaches based upon neurobiology and evidence-based view. Regarding pharmacological treatments, there are three options: optimization, augmentation, and substitution (Bauer et al. 2016). Substitution to another class of antidepressant, such as switching from SSRIs to SNRIs, which has been a common practice before has shown not to improve response or remission in TRD, and there is little data about how to switch to another class of antidepressant. (Souery et al. 2011). Pharmacogenetic testing for rapid or poor metabolizers may be considered for pharmacotherapy-resistant patients, but there is currently no reliable basis for such testing (Keitner and Mansfield 2012).

### 19.1.1 Novel Treatments Based Upon New Neurobiological Findings

As an introduction to neurobiology, the classical hypothesis of antidepressant efficacies has been addressed through monoamine hypothesis for years. In summary, deficiencies in monoaminergic neurotransmitters have been strongly correlated with depression, and antidepressants have been believed to be exerting their effect through monoaminergic pathways (Delgado 2000). Although the link between inflammation and affective disorders has been suggested at the end of the nineteenth century, the phenomenon has been revisited extensively based upon observations that comorbidities of inflammatory disorders in depression. Moreover, shown alterations in inflammatory cytokines in depression such as TNF-alpha, IL-1B, and IL-6 brought the hope of another target for treating depression (Liu et al. 2014). Therefore, potential molecules targeting inflammatory pathway have been considered as potential antidepressants, but among the suggested molecules, only TNF-alpha antagonist has been tried for TRD: 60 patients were given IV infusion of infliximab or place for 12 weeks, and there was no difference between groups according the depression scale scores. On the other hand, when the patients are grouped according to their severity of inflammation based upon CRP levels, those patients that had higher inflammatory markers had better response to TNF-alpha antagonist (Raison et al. 2013).

Abnormal dexamethasone suppression test findings in depressed patients that have been shown for decades suggested a deficit in HPA axis; thus, several hormones including oxytocin were tried for depression but not for TRD (Coppen et al. 1983). Major depression trials had different outcomes making an interpretation difficult at this time regarding oxytocin (Sasaki et al. 2016).

#### 19.1.1.1 Ketamine

Ketamine is an old NMDA receptor antagonist anesthetic agent that has also been used in chronic pain as a low-dose infusion for at least two decades (Maher et al. 2017). Since NMDA receptor antagonists have shown to be effective for depression in animal models, glutamate pathway gained interest of researchers in terms of enhancing dopamine neurotransmission. Although it has been used as an anesthetic agent in ECT and in psychotherapy, using it in treatment-resistant depression is relatively new (Bryson and Kellner 2014; Krupitsky et al. 2007). In a placebo-controlled, double-blind, crossover study, rapid improvement of depressive symptoms after infusion and up to 3-day remittance were noted (Machado-Vieira et al. 2009). Several studies used ketamine in unipolar depression either with single infusion or with repeated infusions and most of them yielded more than half response rates (DeWilde et al. 2015). A recent study indicated similar outcomes in twice weekly infusion and thrice weekly infusion with 0.5 mg/kg dose and in both arms antidepressant activity extending to 15 days (Singh et al. 2016). Growing off-label use of ketamine also brought some concerns that lack of long-term studies and deal with risk

of dependency (Schatzberg 2014). A recent Cochrane database review found limited evidence for ketamine's efficacy over placebo at time points up to 1 week in terms of the primary outcome and response rate, and the effects were less certain at 2 week posttreatment (Caddy et al. 2015). In order to balance the pros and cons creation of a joint statement, formation of a registry of ketamine receiving patients and support of continued research is recommended by a group of ketamine researchers (Sanacora et al. 2017). In addition, there are some uncertainties about how any acute benefit from ketamine, which is often clinically evident, can best be sustained (Goodwin et al. 2016). There have been efforts of combination of ketamine infusion (0.5 mg/kg) with ECT, but outcomes did not show substantial benefit (Anderson et al. 2017).

Ketamine may have positive outcomes on several symptom clusters such as memory improvement, anhedonia, or suicidality (Lally et al. 2015; Price et al. 2009; Shiroma et al. 2014). Despite the concerns of ketamine abuse, it is addressed as "currently not appear to pose a sufficient public-health risk of global scale to warrant scheduling" in the 36th meeting of World Health Organization Expert Committee on Drug Dependence (World Health and Dependence 2015). A new study conducted in mice pointed out the antidepressant effects of ketamine may be by one of its metabolites, (2R,6R)-hydroxynorketamine (HNK) that has low affinity to NMDA receptors. In addition, this metabolite exerted its antidepressant effect without dissociation, ataxia, and abuse liability of ketamine in animal tests (Gould et al. 2017).

### 19.1.2 Evidence-Based Treatments

Initially, we will review bipolar depression. Mainly depressive episodes predominate in the course of bipolar disorder causing more functional impairment than other states (Birmaher et al. 2012). Although there are several treatment guidelines available for bipolar disorder, little attention is given to the management of treatment resistance. Recently, the authors reviewed several guidelines and summarized their suggestions: The guidelines, those without mention of treatment resistance, were formularized according to their stepwise approach, and 3rd-line treatments were accepted as interventions for treatment resistance in bipolar depression (Selek et al. 2017): American Psychiatric Association (APA), World Federation of Societies of Biological Psychiatry (WFSBP) guidelines, and British Association for Psychopharmacology (BAP) guidelines recommend ECT with substantial clinical confidence for treatment-resistant cases (Goodwin et al. 2016; Grunze et al. 2010; Hirschfeld et al. 2002). Although a revision of the APA guideline cited positive outcomes of the preliminary study with Pramipexole, in one of latest trials, neither the response rates nor the remission rates were significantly different than placebo (Cusin et al. 2013; Hirschfeld 2005). Canadian Network for Mood and Anxiety Disorders (CANMAT) guidelines offer the following combinations if the third step is taken into account as treatment resistance: lithium with carbamazepine, pramipexole, MAOI, TCA, venlafaxine or SSRI (except paroxetine) and lamotrigine; divalproex with venlafaxine, TCA, or SSRI (except paroxetine); and lamotrigine and quetiapine with lamotrigine (Yatham et al. 2013).

Pacchiarotti et al. (2009) has described a stratified model of treatment resistance in bipolar disorder: According to his definition, treatment-resistant bipolar depression is defined as failure to reach remission with adequate trials of lithium, combination of lamotrigine with an ongoing mood stabilizer, or quetiapine monotherapy (over 600 mg per day) (Pacchiarotti et al. 2009). The author recommends olanzapine and fluoxetine combination or quetiapine or lamotrigine combination for the first step of treatment-resistant bipolar depression, and failure to respond to this step is called as "refractory" bipolar I depression. The following suggestions are recommended for refractory depression: adjusting the olanzapine-fluoxetine dose or starting of lithium and SSRI or bupropion with therapeutic doses or quetiapine antidepressant combination including SSRI and bupropion or novel agent trials. According to this approach, ECT is reserved for last treatment if the patients

fail to respond what is called "involutional" depression. Pacchiarotti et al. (2009) also differentiate treatments for bipolar I and II. Although a similar stepwise approach to bipolar II depression is recommended, MAO inhibitors were suggested as combination instead of combination SSRI or bupropion in the second step of the treatment.

#### 19.1.2.1 Electroconvulsive Therapy (ECT) and Other Interventions

Electroconvulsive therapy is recommended by most of the guidelines for treatment-resistant bipolar depression (Goodwin et al. 2016; Yatham et al. 2013) including Canadian Network for Mood and Anxiety Disorders (CANMAT) guideline that recommends ECT as a first-line treatment for TRD (Milev et al. 2016).

However, a randomized controlled trial compared the efficacy of ECT to an algorithm-based pharmacological treatment. Although the response rate was significantly higher in the ECT (73.9% versus 35.0%), the remission rates were similar (34.8% versus 30.0%) (Schoeyen et al. 2015). On the other hand, ECT has been consistently found effective short-term treatment for depression and is probably more effective than drug therapy (The UK ECT Review Group 2003). Even though the patients reach to remission with ECT, they need to be on maintenance treatment such as maintenance medications or maintenance ECT. Despite the little difference between maintenance and continuance ECT, they have been interchangeably used and maintenance ECT has been accepted as a more wide term. Data for maintenance ECT (mECT) are few. Several studies showed mECT's efficacy in reducing the hospitalization for TRB patients both in unipolar and bipolar depression (Vaidya et al. 2003). A recent German retrospective study including unipolar depression cases also showed reduced hospitalizations after mECT (Post et al. 2015; Vaidya et al. 2003). Numerous hypotheses have been proposed on how ECT works in depression including anti-inflammatory effects, cortical inhibition, and pigment epithelium-derived factor (Jarventausta et al. 2017; Ryan et al. 2017; Voineskos et al. 2016). Although Dr. Cerletti's, who is the inventor of ECT, dream was also finding the substance, as defined by him acroagonine that was supposed to be ECT's effective "molecule," the exact mechanism is still remains elusive (Passione 2004).

Transcranial Magnetic Stimulation (TMS): TMS basically applies electromagnetic waves to generate an electric current in the brain without direct contact. Since this treatment is more reimbursed by insurance companies, its use has recently increased in the United States. An add-on low-frequency TMS of the right dorsolateral prefrontal cortex in treatment-resistant bipolar depression patients was found to be effective. However, in addition to small sample size, this study excluded ECT non-responsive patients that may interfere with the findings. A recent comparative study of TMS to ECT showed significantly lower depression scale scores and better effect size compared to those undergoing rTMS (Micallef-Trigona 2014).

Vagus Nerve Stimulation (VNS): Few data exist in TRB depression as discussed before (Selek et al. 2017). Also, the limitations of this treatment including slow onset of antidepressant action and moderate response rates make conventional use difficult at this time.

### 19.1.3 Other Novel Treatment Approaches

Deep Brain Stimulation (DBS): DBS has been used for Parkinson's disease more than 3 decades, but it is a new technique in treatment of TRD. In the first clinical trial, the electrodes were placed in the subcallosal cingulate region (SCC), leading to a notable sustained antidepressant response (Mayberg et al. 2005). Despite promising outcomes in open-label studies, a randomized sham controlled trial of DBS failed to show significant improvement (Dougherty et al. 2015). Different outcomes raised the discussion of place of electrode targeting thus, subcallosal region, DR nucleus, subgenual cingulate region have been tried with different outcomes (Torres-Sanchez et al. 2017). Based upon electrophysiological

studies in animal models and preliminary studies, we suggest superolateral medial forebrain bundle (sl-MFB) as the primary site for DBS because sl-MFB has more projections to the frontal cortex (Fenoy et al. 2016).

Despite being safe, TMS has been known for inducing seizures (Conca et al. 2000). Magnetic seizure therapy is a new treatment that induces convulsions by strong transcranial magnetic stimulation, in order to achieve the safety of the latter. Although initial studies were promising, few researches included TRB cases into their study. A recent meta-analysis showed up to 30 or 40% remission rates overall in depression (Cretaz et al. 2015). Up till now, there were no head-to-head comparison between ECT and MST.

**Conclusion**

Although numerous antidepressants are available, there are still very few armaments for TRD. Among those ECT emerges as an evidence-based approach. Ketamine, anti-inflammatory treatments, and DBS might be promising, but further researches are needed for a final outcome.

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# Clinical Application of Neurostimulation in Depression

20

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## 20.1 Introduction

There is a growing interest in biological non-pharmacological treatments for depressive disorders, and this is probably due to the limitations of psychotherapies and psychopharmacological treatments. Many patients do not adhere to psychotherapies, and even for those who adhere, it frequently takes a long time for the improvements to occur. A significant portion of patients does not respond or has a weak response to antidepressants and other pharmacological agents. The side effects of these drugs are very common; some patients do not tolerate them and abandon the treatment. Psychopharmacological agents are also contraindicated for special populations, such as pregnant women, patients with liver failure, and other clinical conditions.

The terms neuromodulation and neurostimulation have been used to describe procedures that use magnetic or electrical stimulation on the brain to treat psychiatric or neurological disorders through cortical activity modulation. The term neurostimulation is more adequate for those treatments, since neuromodulation is also applied to neurobiological changes from chemicals and drugs. Neurostimulation methods may be noninvasive, like transcranial direct current stimulation (tDCS), repetitive transcranial magnetic stimulation (TMS), electroconvulsive therapy (ECT), and magnetic seizure therapy (MST), or invasive, such as vagus nerve stimulation (VNS) and deep brain stimulation (DBS) (Table 1.1).

As discussed in Chap. 15, the use of electrical charges in the brain has been studied since the classical antiquity, but the major turning point was the invention of ECT in the 1930s. For many decades, ECT was the most important treatment for depressive disorders, but the discovery and development of psychopharmacological agents, along with cultural and political influences, produced a decrease in the use of ECT. However, ECT is still considered an invaluable treatment option for depressive disorders, especially for severe or treatment-resistant major depressive disorder (MDD). On the one hand, there is abundant evidence demonstrating the efficacy of ECT, both as short-term and long-term treatment for MDD. On the other hand, studies also show that the risks, side effects, and costs of ECT may become a problem in some cases.

The TMS has been extensively studied since its discovery in the 1980s. Clinical trials indicate that magnetic stimulation is effective in the treatment of depressive disorders, even in treatment-resistant disorders. Most of the studies with TMS are short-term studies, but there are also a few long-term studies. TMS is associated with less

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**Table 1.1** Neurostimulation methods

| Modality | Pretreatment | Target region | Mode of action | Recommendation |
|---|---|---|---|---|
| ECT | Anesthesia and muscle relaxant | Cerebral cortex | Electrical current produces seizure | +++ |
| MST | Anesthesia and muscle relaxant | Cerebral cortex | High-intensity magnetic pulses produce seizure | + |
| TMS | – | Cerebral cortex | Low-intensity magnetic pulses produce low electrical currents in the brain | +++ |
| tDCS | – | Cerebral cortex | Low-intensity continuous electrical current | ++ |
| VNS | Implantation of pulse generator and electrode | Vagus nerve | Electrical pulses are transmitted to the brain through the vagus nerve | ++ |
| DBS | Implantation of pulse generator and electrode | Nucleus accumbens, ventral striatum, inferior thalamic nucleus, peduncle, lateral habenula, subgenual cingulate | Electrical pulses are delivered to deep brain structures by electrodes | + |

*ECT* electroconvulsive therapy, *TMS* repeated transcranial magnetic stimulation, *MST* magnetic seizure therapy, *tDCS* transcranial direct current stimulation, *VNS* vagus nerve stimulation, *DBS* deep brain stimulation (Milev et al. 2016; Akhtar et al. 2016)

risks and side effects than ECT. Nevertheless, magnetic stimulation seems to be less effective than electroconvulsive stimulation, especially in the treatment of severe depressive disorders. Both ECT and TMS are approved by the US Food and Drug Agency (FDA) and are widely used throughout the globe.

MST, tDCS, DBS, and VNS are mainly experimental treatments for depressive disorders, and the clinical trials with these techniques are scarce. The FDA approved VNS vagus nerve stimulation (VNS) only for adult patients with severe or recurrent treatment-resistant depression; the other treatment modalities are not FDA approved.

## 20.2 Electroconvulsive Therapy

ECT is the oldest somatic treatment among those currently used in psychiatric practice, and it is also the most controversial. ECT was a popular treatment for mental disorders between the 1940s and 1960s. After the 1960s, the use of ECT met resistance, and it was no longer a treatment option for many psychiatrists and psychiatry services. It was seen as a psychiatric asylum practice, and there was an erroneous association with punishment and torture. The prejudice against this technique was probably due to ECT applications without the patient's consent and its indiscriminate use. Rudimentary ECT devices, lack of anesthesia, and lack of muscle relaxants were associated with higher risks and side effects, reinforcing the negative public perception of ECT. In the 1990s, a new interest on ECT emerged with a great increase of clinical trials and publications. The efficacy of ECT has been confirmed by several studies in the last two decades. In addition, modern devices and advanced anesthesia methods made ECT an extremely safe method that does not produce any discomfort for the patients. Despite all that, ECT is frequently considered as the last therapeutic resource, reserved for very severe and refractory cases, demonstrating that the stigma about this method still exists (Mochcovitch et al. 2016).

Recent studies indicate that methods used in ECT applications, such as the position of the electrodes, current intensity, wavelength, frequency, session duration, time between applications, and number of sessions, may influence both positive

and negative outcomes of this therapy. In order to produce effective seizures, unilateral ECT requires higher electrical current doses, bifrontal ECT requires lower doses, and the lowest doses are those applied in bitemporal ECT. This electrode placement is associated with more cognitive side effects, especially memory deficits, compared to unilateral and bifrontal positions. However, it is still under debate if bifrontal and right unilateral ECT are as effective as bitemporal ECT. In right unilateral ECT, the application of brief pulses (1.5 ms) was demonstrated to be more effective than ultrabrief pulses (0.3 ms), although the former is associated with more cognitive side effects than the latter. Ultrabrief pulses are not effective in bitemporal ECT. Prolonged convulsions and poor ventilation were also correlated to cognitive deficits (Mochcovitch et al. 2016; Sackeim et al. 2008; Tor et al. 2015). The Canadian Network for Mood and Anxiety Treatments (CANMAT) classified right unilateral ECT and bifrontal ECT as a first-line treatment and bitemporal ECT as a second-line treatment, due to its cognitive side effects (Milev et al. 2016).

### 20.2.1 Short-Term Treatment

The American Psychiatric Association (APA) and the CANMAT consider ECT the most recommended treatment when there is a need for rapid improvement, severe depression symptoms, high risks related to drugs, lack of response to pharmacological agents, patient preference, pregnancy, or lactation. APA also points out that ECT should also be considered when the psychopharmacological treatment is only partially effective or produces intolerable side effects. The World Psychiatric Association (WPA) also recommends ECT as an early acute treatment for severe MDD, especially in depression with psychotic symptoms or at high risk of suicide. ECT is highly effective in unipolar and bipolar depression, with remission rates of 55, 61, and 64% for right unilateral, bifrontal, and bitemporal ECT, respectively. It is also effective in the treatment of antidepressant-resistant depression, rapid improvement of catatonia symptoms, or prolonged severe manic disorder. Both unipolar and bipolar depressive disorders are the main indications for ECT, accounting for 80–90% of them. This is probably due to the superior efficacy of ECT in relation to pharmacotherapy. ECT is effective for patients with or without psychotic symptoms, but the latter respond more rapidly to this treatment. It may be administered to pregnant or lactating women, children, elderly people, or patients with severe clinical comorbidities, neuroleptic malignant syndrome, or Parkinson's disease. Recent studies indicate that maintenance ECT is also effective, and its efficacy is equivalent to the efficacy of continuation pharmacological treatment (Kellner et al. 2006; Milev et al. 2016; Mochcovitch et al. 2016; Pastore et al. 2008).

Patients should receive ECT until there is remission of symptoms or the response reaches a plateau. The clinical response should dictate how many sessions a patient should receive, usually ranging from 6 to 15 sessions. Cognitive side effects are cumulative, and if they are too severe, the treatment should be abbreviated. On the one hand, low charges are not effective; on the other hand, high charges produce more cognitive side effects. For this reason it is important to determine the adequate dose for each patient. The best method to find the correct dose is to administer repeated stimuli with increasing loads until there is a generalized seizure, consequently establishing the seizure threshold. Typically, for bitemporal or bifrontal ECT, the charge should be about 1.5 to 2 times the seizure threshold, whereas for unilateral ECT, the load should equal 6 times the seizure threshold (Milev et al. 2016; Mochcovitch et al. 2016).

In the past, the occurrence of generalized seizures was considered necessary and sufficient to produce the therapeutic effect of ECT. However, it is now clear that seizures can be ineffective, and this depends on the anatomical position of the electrodes, the dose of the electrical stimulus, and the patient's seizure threshold. The minimum duration of the observed seizure should be 20 s or 25 s if measured with the electroencephalogram. Studies have shown that the efficacy of ECT is correlated with a high ictal amplitude, especially in slow waves, and with great postictal suppres-

sion. Modern ECT devices allow quantitative analysis of the ictal and postictal EEG, so that mathematical parameters (such as ictal power and coherence) can be calculated, helping to determine if a seizure was effective or not. If the ictal power is low or there is no postictal suppression, the stimulus dose should be augmented. Increased blood pressure and heart rate just after the seizure are also associated with a greater efficacy of ECT (Mochcovitch et al. 2016).

### 20.2.2 Long-Term Treatment

Maintenance ECT may be administered after the remission of depressive symptoms for an indefinite period of time. The applications of maintenance ECT usually occur two to four times per month (Mochcovitch et al. 2016).

A study with MDD patients (Kellner et al. 2006) compared maintenance ECT with the combination of nortriptyline and lithium for 6 months. Differences regarding efficacy and tolerability between the two treatments were not observed. In a clinical trial with elderly patients with psychotic depression (Navarro et al. 2008), nortriptyline was compared to nortriptyline plus ECT for 2 years. In patients who received the combined treatment (nortriptyline + ECT), the relapse rate was significantly lower than in the nortriptyline group.

### 20.2.3 Adverse Events

The most frequent immediate side effects of ECT are headache, muscle soreness, nausea, and emesis, which vary depending on the anesthetic used. More than 45% of patients report headache, which can be treated symptomatically with the use of analgesics. Patients suffering from migraine attacks are more predisposed to headache after ECT. Mild and transient cardiac arrhythmias may occur during ECT application, especially in patients with prior heart disease. Arrhythmias result from brief postictal bradycardia and therefore can often be prevented by increasing the dosage of anticholinergic medication. Other arrhythmias are secondary to the tachycardia observed during the seizure and may occur while the patient returns to consciousness. The short-term neurological side effects normally associated with ECT are mental confusion and delirium, shortly after the seizure and anesthesia recovery. Significant confusion may occur in up to 10% of patients within the first hour after the seizure. Delirium is usually more prominent after the first applications and in patients who received bilateral ECT or who have coexisting neurological disorders. Delirium typically disappears within days or a few weeks at most. The severity, type, and duration of cognitive dysfunctions seem to be associated with the methodology of ECT administration, including electrode positioning, wave type, and frequency of procedure. Impairment of anterograde memory is one of the most commonly observed short-term side effects, but it lasts only for a few days. These side effects can be attenuated with the use of ultrabrief pulses, unilateral electrode position, and a larger interval between sessions (Milev et al. 2016; Mochcovitch et al. 2016).

Cognitive effects may be persistent, and its intensity and duration are closely related to the ECT parameters. Anterograde amnesia remits faster than retrograde amnesia, which may be persistent in some patients. Apparently, cognitive impairments before ECT and postictal disorientation predict amnesia. Usually cognitive side effects improve after the end of the treatment, and 6 months after the last treatment, there are no memory deficits anymore (Cohen et al. 2000; Ghaziuddin et al. 2000; Mochcovitch et al. 2016).

The mortality rate related to ECT is 2 in 10 per 100,000 patients, which is comparable to the risk of death from anesthesia in general procedures. There is an increased risk of complications in patients with arrhythmias, severe arterial hypertension, congestive heart failure, large aneurysms, insulin-dependent diabetes, brain tumors, traumatic brain injury, cerebrovascular accident, epilepsy, cerebrovascular malformations, and narrow-angle glaucoma, but these are not absolute contraindications for ECT (Milev et al. 2016; Mochcovitch et al. 2016).

## 20.3 Repetitive Transcranial Magnetic Stimulation

In TMS, repetitive magnetic pulses are delivered over cortical areas through a coil positioned on the scalp. The magnetic field produces electrical currents in the brain, stimulating or inhibiting brain structures. There are two types of TMS, one is more superficial and the other is deeper. In conventional TMS treatment, the electromagnetic waves have a reach of 3 cm from que coil surface to the cortex, while in deep TMS the reach is approximately 5 cm. Several types of coils are used in TMS, and they vary in size, format, focality, and reach. Theta burst (TBS) is a new form of TMS, which consists of three bursts of pulses at 50 Hz every 200 ms. This form of TMS is as effective as TMS with 10 Hz, but the duration of the session decreases about 5 times, which allows services to treat a larger number of patients (Milev et al. 2016).

All kinds of TMS can be inhibitory or excitatory. These treatments can be an add-on treatment or monotherapy for depression. Commonly, psychotropic medications are maintained while performing neurostimulation treatment. The patient sits in an upright position and is conscious during the whole procedure, and there is no need for anesthesia.

Usually the sites of stimulation are the left and right dorsolateral prefrontal cortex (DLPFC) and dorsomedial prefrontal cortex. Regarding DLPFC, excitatory stimuli are applied on the left hemisphere, while inhibitory stimuli are applied on the right hemisphere. Some researchers had attempted to combine both excitatory stimulation on the left DLPFC and inhibitory stimulation on the right DLPFC, but it did not show additional benefits, compared to unilateral stimulation (Janicak and Dokucu 2015).

Stimulus intensity ranges from 1.5 to 3.0 tesla, but intensity is based on resting motor threshold (RMT), which is the minimum intensity to contract a patient's thumb. Patients have their own RMT, and the stimulus intensity is calculated as a percentage of this RMT. The stimulus intensity applied to patients is predetermined, generally 110–120% of RMT in TMS and 70–80% for TBS. Less intense stimuli are not effective (Janicak and Dokucu 2015).

Standard protocols for MDD consist of 20–30 daily sessions, over a course of 4–6 weeks. Clinical observations have shown that patients must demonstrate some improvement within 20 sessions. If not, they will probably not benefit from additional sessions. On the other hand, improvement before 20 sessions predicts response and remission in a 30-session treatment (Loo and Mitchell 2005; Milev et al. 2016). TMS treatments with three sessions per week (in different days) have been reported, but the total number of sessions remains the same. In accelerated protocols, the number of sessions is about the same as in conventional protocols too. Multiple TMS sessions (2–10) are administered in 1 day, producing quick results and decreasing the duration of the treatment (Loo and Mitchell 2005; Milev et al. 2016).

Frequencies of 1 Hz or less are considered inhibitory and are applied to right DLPFC. Excitatory frequencies, which are applied to the left DLPFC, range from 1 to 20 Hz. A 50 Hz excitatory frequency is used in TBS. The number of stimuli per session ranges from 120 to 3000, and better results were obtained with more than 1000 stimuli per session (Lefaucheur et al. 2014).

TMS is already considered a first-line treatment for patients with treatment-resistant depressive disorder, who have not had a significant improvement to at least one antidepressant (Milev et al. 2016). Several regulatory agencies approved TMS for the treatment of MDD in patients that have not responded to one antidepressant. Young patients, patients without psychiatric comorbidities, and those with few failures in previous treatment attempts tend to respond better to TMS, compared to those who do not have these features (Lee et al. 2012).

Due to its safety and efficacy in short-term treatment, especially in patients with treatment-resistant depression, TMS was considered by the CANMAT a first-line treatment for MDD patients who failed to respond to at least one trial with an antidepressant (Milev et al. 2016).

### 20.3.1 Short-Term Treatment

Several studies and meta-analyses showed similar efficacy of the right and left DLPFC TMS for MDD. Based on these evidences, it was hypothesized that bilateral stimulation, which is the combination of inhibitory and excitatory TMS over the right and left DLPFC, respectively, could have a better outcome, compared to unilateral stimulation. However, the results did not show a significant statistical difference (Milev et al. 2016). In a meta-analyses with 34 TMS studies, patients who received TMS ($n$ = 751) had more significant improvements compared to those who received sham stimulation ($n$ = 632), and the mean effect size weighted to sample sizes was 0.55. The effect size of unilateral TMS in the left DLPFC was similar to the one of bilateral TMS. Unilateral TMS at the right DLPFC yielded a somewhat higher effect size (0.82) (Slotema et al. 2010).

The most widely used and studied magnetic stimulation technique is conventional TMS, but experience with TBS is increasing rapidly. TBS protocols over DLPFC have demonstrated positive results for the left intermittent TBS, which is excitatory, but not for the right continuous TBS, which is inhibitory. Bilateral TBS stimulation studies have shown mixed results (Milev et al. 2016). One study demonstrated that TBS in dorsomedial prefrontal cortex was as effective as TMS in the left DLPFC. The advantage of TBS was the reduced session duration (6 min) compared to TMS (30 min). Some health-care systems are interested in treating larger numbers of patients, which is easier with TBS, compared to conventional TMS (Bakker et al. 2015). When a fast symptom improvement is needed, accelerated protocols using TBS could also be a good alternative to conventional TMS, in which the sessions are much longer (Loo and Mitchell 2005; Milev et al. 2016).

Other TMS optimization strategies are accelerated protocols and extended number of pulses per session. Indeed, additional studies are necessary to evaluate the efficacy of these methods and to observe the occurrence of adverse events, especially seizure (Lee et al. 2012).

The meta-analyses of 81 randomized controlled trials ($n$ = 4233) concluded that the efficacy and tolerability of low-frequency unilateral TMS and bilateral TMS had better results than other TMS modalities, especially new TMS methods for treatment-resistant depression, such as accelerated protocols and deep TMS (Brunoni et al. 2017).

ECT is the gold standard treatment for treatment-resistant MDD but requires anesthesia and frequently causes cognitive side effects, while in the treatment with TMS, there is no need of anesthesia, and cognitive side effects are not common. Six randomized trials compared ECT ($n$ = 102) and TMS ($n$ = 113) and demonstrated the superiority of ECT over TMS, with a mean weighted effect size of −0.47 (Slotema et al. 2010).

### 20.3.2 Long-Term Treatment

It is well established that depression relapse and recurrence are common after short-term pharmacological treatment. There is also a high risk of relapse from 2 to 12 months after acute treatment with TMS. However, evidence also indicates that, in patients with treatment-resistant MDD who achieved remission after acute treatment with TMS, maintenance treatment with the same neurostimulation method could prevent recurrence. Nevertheless, there is no consensus on the maintenance treatment protocols, and some maintenance studies had positive results, but further clinical trials are needed (Loo and Mitchell 2005; Milev et al. 2016).

In some studies, patients were followed after acute treatment with TMS, and in those who presented a new depressive episode, TMS was resumed. These studies showed that 50–85% of patients had benefited from additional TMS sessions (Demirtas-Tatlidede et al. 2008; Fitzgerald et al. 2013). However, it is still important to ascertain if a maintenance treatment could reduce relapse rates.

### 20.3.3 Adverse Events

The most common adverse events are mild, and the patient can take symptomatic medications

to relieve them. Those adverse events usually decrease in intensity or disappear during the treatment. Common adverse events are scalp discomfort or pain, headache, facial twitching, and local erythema. Drowsiness and tearfulness have also been reported (Slotema et al. 2010).

The most severe adverse events that can occur are vasovagal syncope and seizure, but both are rare. Until now, fewer than 30 cases of seizure have been reported worldwide despite the large number of treatments that have been performed. In the current available literature, no cognitive impairment has been reported (Loo and Mitchell 2005; Milev et al. 2016). In order to avoid or minimize risks and adverse events related to TMS, safety guidelines must be followed (Rossi et al. 2009).

## 20.4 Other Neurostimulation Methods

### 20.4.1 Magnetic Seizure Therapy

MST is a noninvasive convulsive technique that generates tonic-clonic seizures through a strong electromagnetic field. A coil positioned on the skull produces this electromagnetic field in the same way as in other magnetic neurostimulation techniques (Milev et al. 2016). As in ECT, anesthesia and muscle relaxants are needed in MST. Due to the loud clicking of the device, earplugs are also recommended (Engel and Kayser 2016). MST stimulates the superficial cortex producing seizures, but there is no direct electrical stimulation of the temporal cortex, which explains the absence of cognitive side effects in this treatment. Recent studies demonstrated that MST is effective for treatment-resistant MDD, but it is not as effective as ECT (Cretaz et al. 2015).

Still there is no consensus on the optimal delivery parameters for MST, but most studies have used a coil placement at the vertex with a frequency of stimulation of 100 Hz, pulse width of 0.2–0.4 ms, and stimulation duration of 10 s. The schedule for MST is similar to the one for ECT, with a total of 12 sessions spread over a period of 4–6 weeks (Milev et al. 2016). The "figure of 8" coil is not considered effective to produce seizures, but the nonfocal round coil and the double-cone coil are considered reliable to induce seizures. In MST, the stimulus intensity is always above the seizure threshold (Cretaz et al. 2015).

Currently, there are a few studies with small samples sizes evaluating the effectiveness of MST in treatment-resistant depression. In one of the MST studies with a large sample ($n$ = 13), three patients responded and two achieved remission (Fitzgerald et al. 2013). In the largest MST study (Kayser et al. 2015), 26 patients with treatment-resistant depression were enrolled in an open-label clinical trial. The response rate was 69%, and the remission rate was 46%. This study showed that MST was effective in the treatment of treatment-resistant depression and anxiety (Kayser et al. 2015). Both studies found that MST is a safe and well-tolerated treatment. Overall, studies show response and remission rates similar to ECT (Milev et al. 2016). A systematic review of eight studies of MST treatment in patients with treatment-resistant MDD showed remission rates from 30 to 40% and less cognitive impairment, compared to ECT (Cretaz et al. 2015). There are no maintenance treatment studies following MDD patients after MST short-term treatment.

One randomized within-patient study (Lisanby et al. 2003) compared MST to ECT in what regards adverse events and seizure characteristics. Ten inpatients in a major depressive episode were directed to ECT. Then, they were randomized to receive two MST sessions in the first four ECT sessions. Side effects and cognition were evaluated before and after sessions. MST seizures were shorter, with smaller ictal amplitude, and patients showed faster poststimulus reorientation.

The adverse events associated with MST are headache, muscle aches, disorientation after the procedure, and anterograde and retrograde amnesia (Milev et al. 2016). Cognitive side effects are usually mild or absent (Cretaz et al. 2015).

Due to the low level of evidence on MST, especially on maintenance treatment, the

CANMAT rated this neurostimulation technique as investigational (Milev et al. 2016).

### 20.4.2 Transcranial Direct Current Stimulation

tDCS is an electrical neurostimulation method with constant low-amplitude current focalized in specific cortical areas through electrodes placed on the scalp. This neurostimulation method increases cortical excitability in cortical areas under the anodal electrode, while it decreases cortical excitability where the cathodal electrode is placed. This effect is produced by the neuronal depolarization and hyperpolarization, respectively. There are basically two options of electrode placing: (1) anodal electrode over the left DLPFC and cathodal electrode grounded in a noncortical area or (2) anodal electrode over the left DLPFC and the cathodal over the right DLPFC. The stimulus intensity ranges from 1 to 2 mA, and the sessions last for 30 min or more. Daily sessions for at least 2 weeks are needed to obtain an antidepressant effect. Six-week treatments were more effective than shorter treatments, and tDCS combined with antidepressants was more effective than tDCS alone (Milev et al. 2016).

Studies using tDCS to treat treatment-resistant MDD have shown mixed outcomes, with small to moderate effect sizes of active treatment, when compared to sham (placebo). Two meta-analyses (Kalu et al. 2012; Shiozawa et al. 2014), which included, respectively, six and seven randomized controlled trials ($n$ = 259), concluded that active tDCS was more effective than sham (Kalu et al. 2012; Shiozawa et al. 2014). On the other hand, the meta-analysis from Berlim et al. (Berlim et al. 2013), which also included six randomized controlled trials, did not find any significant difference between both groups, even when analyzing only studies with at least 10 sessions and 2 mA.

In some studies, patients were followed for 1 month after the end of treatment to evaluate the sustained improvement of depression. In three of four studies, it was confirmed that patients who received active tDCS maintained their levels of improvement (Kalu et al. 2012). tDCS has also been evaluated as a cognitive improvement tool. In a double-blind, randomized, controlled study (Fregni et al. 2006) with 18 outpatients with unipolar depression, patients showed working memory improvement after five tDCS sessions, even without depression enhancement. In the CANMAT guidelines, tDCS is considered a third-line treatment for MDD, although it is not recommended for relapse prevention because there are no controlled studies on maintenance treatment (Milev et al. 2016).

The most common adverse events of tDCS are discomfort, itching, tingling, burning sensation, and headache. Hypomania has also been reported (Kalu et al. 2012).

### 20.4.3 Deep Brain Stimulation

DBS consists of neurosurgical implantation of electrodes under magnetic resonance imaging (MRI) guidance in selected brain areas connected by a wire to a neurostimulator (NS) or an implantable pulse generator (IPG). The NS/IPG, usually placed into the right chest below the clavicle, sends electrical pulses to brain electrodes in order to modulate an adjacent neural network. DBS parameters can be monitored and programmed remotely with a handheld device in a similar way to pacemakers and VNS. There is also a patient controller to turn it on and off, check battery status, and self-adjust parameters provided by the DBS programmer (Milev et al. 2016).

DBS is mainly used to improve motor symptoms of Parkinson's disease, but it is also been studied in treatment-resistant depression, dystonia, essential tremor, epilepsy, Alzheimer's disease, and obsessive-compulsive disorder (OCD). Studies using DBS to treat treatment-resistant depression are increasing; but this technique still needs to find more appropriate brain areas related to this disorder for the implantation of electrodes to have more consistent results. The psychopharmacological and psychotherapeutic treatments are usually performed in tandem with each other (Milev et al. 2016).

The main anatomical target for DBS in most studies is the subcallosal cingulate (SCC) white

matter, but also the ventral capsule/ventral striatum (VC/VS), nucleus accumbens and medial forebrain bundle (MFB), inferior thalamic peduncle, lateral habenular complex, and rostral cingulate gyrus (Delaloye and Holtzheimer 2014; Milev et al. 2016).

Currently there is no consensus on what the optimal stimulation parameters are. However, trials in animals concluded that some parameters are more effective for the ventromedial prefrontal cortex/SCC such as high frequency (130 Hz) and current intensity (100–300 mA). These studies also identified that prelimbic stimulation was more effective than infralimbic stimulation and that left unilateral and bilateral stimulation had similar results (Milev et al. 2016).

DBS is indicated only when it is determined that other pharmacological and neurostimulation treatments, like ECT, do not produce a clinical response. Therefore, the patients submitted to DBS have ultra-resistant depression. Additionally, it is difficult to evaluate DBS effectiveness since the published literature is limited, and most studies are noncontrolled, nonrandomized, and consist of small sample sizes. Research shows that response rates range from 30 to 60% and the remission rates range from 20 to 40% after 3–6 months of treatment with DBS. Only a small open-label study with DBS over MFB, with 7 patients, showed higher response (85.7%) and remission (57.1%) rates (Milev et al. 2016).

Most studies followed up patients for 6–12 months, but one study (Malone et al. 2009) was able to follow up patients up to 51 months. In this study, response and remission rates were, respectively, 40% and 20% at 6 months and 53% and 40% in the last follow-up. In addition, DBS showed good tolerability.

In another study (Kennedy et al. 2011), MDD patients were followed for 3–6 years after DBS implantation to the subcallosal cingulate gyrus. This study had the following response rates over the years: 62.5% after 1 year, 46.2% after 2 years, 75.0% after 3 years, and 64.3% at last follow-up visit. It started with 20 patients, and at the end of the first year, 16 patients were still in the study and at the end of 3 years 14 patients, and at the end of the fourth year, nine patients completed the follow-up. Eight of the eleven patients that responded were already responders at the first year. Remission rates were 18.8% after 1 year, 15.4% after 2 years, 50% after 3 years, and 42.9% at the last follow-up visit. DBS was also well tolerated in this study; however, two patients committed suicide because of depressive relapse.

It is possible that some adverse events, such as intracranial hemorrhaging or infection, could result from the neurosurgery itself. Regarding adverse psychiatric events, psychosis and hypomania were reported after changes in stimulation parameters. Blurred vision and strabismus were also reported in patients after having increased the amplitude of the parameters. However, these events were reversible after an adjustment to the stimulation parameters (Milev et al. 2016). No cognitive side effects were reported. Approximately 11% of the patients abandoned the treatment before the end. Patients had no cognitive impairment in long-term treatment (Delaloye and Holtzheimer 2014).

The CANMAT considers DBS as an experimental treatment because there are too few studies documenting its safety and efficacy (Milev et al. 2016).

### 20.4.4 Vagal Nerve Stimulation

In VNS, an IPG is implanted subcutaneously in the left chest, and the electrodes from the IPG deliver low-frequency, intermittent pulses to the left vagus nerve (Daban et al. 2008). VNS vagus nerve stimulation (VNS)demonstrated to be safe in pregnant women. VNS can be used concomitantly with psychotropic drugs and electroconvulsive therapy (ECT) (Howland 2014).

The electrical stimulation through the vagus nerve provides stimulation to the nucleus tractus solitarius that modulates several subcortical and cortical regions of the brain through the neural networks (Milev et al. 2016). Treatment parameters are similar to other devices which include the intensity of the electrical stimulus (mA), pulse width (microseconds), frequency (Hz), duration of the stimulus, and interval between them (seconds or minutes) (Howland 2014). There is still no consensus on what the optimal stimulation

parameters for MDD would be. Most studies used the output current beginning at 0.25 mA, 500-μs pulse width, and 20- or 30-Hz frequency for 30 s of stimulation and a non-stimulation interval of 5 min. In one long-term study, the electric current was increased to 1 mA (Daban et al. 2008). There seems to be better response rates and decreased suicide attempts in VNS with higher electrical charges, compared to low charges (Milev et al. 2016).

Currently, there is only one randomized, controlled study with VNS to treat TRD (Rush et al. 2005). This 10-week study evaluated 235 patients, of whom 210 are with nonpsychotic treatment-resistant depression and 25 with bipolar depression. There were no statistically significant difference between VNS and sham in short term. A meta-analysis of uncontrolled studies of VNS in the treatment of TRD (Martin and Martin-Sanchez 2012) showed a significant improvement based on scale scores and response rates (31.8%, $p < 0.0001$).

Studies have shown that MDD patients improve with VNS over a long time. The average time necessary to show improvement was approximately 3 months, but patients may need to wait for another 6 months to have a significant improvement. The response and remission rates vary significantly across studies. A meta-analysis of six multicenter studies (Berry et al. 2013), with a total sample size of 1035 patients with treatment-resistant depression treated with VNS and 425 patients treated as usual, indicated a response rate of 32% for VNS and 14% for treatment as usual after 96 weeks of treatment. The response rates for VNS and treatment as usual after 48 weeks of treatment were similar.

The stronger predictor of bad response to VNS in patients with treatment-resistant depression (failure in at least two trials with antidepressants of different classes) is probably ultra-treatment-resistant depression. In the study from Sackeim et al. (Sackeim et al. 2001), patients who failed to respond to more than seven antidepressant trials or who have already been treated with ECT were unlikely to benefit from VNS.

Voice changes, hoarseness, coughing, and dyspnea with physical exertion are adverse events usually associated with the current intensity and usually improve with the reduction of current intensity. Other possible adverse events are headache, dysphagia, paresthesia, and pain (Howland 2014; Sackeim et al. 2001). Complications are expected in about 1% of surgeries and may include wound infection and hoarseness. Hoarseness may be the result of limited or long-lasting vocal cord paralysis (Howland 2014).

Considering these factors, only ultra-treatment-resistant depression patients are eligible for this treatment. VNS is considered a third-line treatment for MDD in CANMAT and merits further study (Milev et al. 2016).

## Conclusion

All neurostimulation techniques discussed in this chapter were beneficial to patients with MDD. In these treatments, the stimulation is targeted to brain areas related to MDD, avoiding stimulation of peripheral areas, due to its potential side effects. Depending on the method, neurostimulation can have a very fast antidepressant effect, or it could take many months for it to take effect. These non-pharmacological treatments may provide improvement for a group of patients that have already tried several psychopharmacological treatments and psychotherapy and did not achieve remission.

Above all, benefits and risks should be weighed before indicating a neurostimulation treatment. Patients should receive information about the treatment and consent to it. Patients and family members should know beforehand that these treatments have risks of adverse events and their efficacy is limited.

Neurostimulation is a field of psychiatry that is in continuous development. Currently, ECT and TMS are the most extensively studied neurostimulation methods, while MST, tDCS, VNS, and DBS have to be studied thoroughly so that their efficacy and safety are evaluated. There is a substantial amount of evidence supporting ECT and TMS as routine treatments for MDD; still technical refinements are needed to improve the efficacy and reduce adverse events.

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# 21 Is a Combination of Pharmacotherapy and Psychotherapy Superior to Each Alone?

Kwang-Yeon Choi and Yong-Ku Kim

## 21.1 Introduction

Both pharmacotherapy and psychotherapy are proven to be effective treatments for depression (Barth et al. 2013; Cuijpers et al. 2011). The question of whether combined therapy will show better efficacy than each therapy alone is the logical treatment progression. Since the tricyclic antidepressant era, this idea has been repeatedly explored by researchers. Innate difficulties exist to substantiate this idea. First, double-blinded placebo-controlled studies are lacking. Study design is forced to be open labeled or single blinded; thus estimated effects were often exaggerated. Second, it is difficult to attain the sample sizes necessary to detect a small effect size in a single placebo-controlled study. Third, in spite of a wave of efforts to standardize procedures in psychotherapy, intertherapist and interdisciplinary variations exist.

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In spite of these inherent limitations, a series of meta-analyses consistently support the superiority of a combination of psychotherapy and pharmacotherapy compared to each therapy alone for the treatment of adult depression (Cuijpers et al. 2009; de Maat et al. 2007; Khan et al. 2012). In detail, not only robust acute symptom relief but also relapse prevention effects were observed (Oestergaard and Møldrup 2011; Schramm et al. 2007). Furthermore, the effects of combined therapy were prominent in severe, but non-chronic, depression (Hollon et al. 2014). Combined therapy also has small benefits in cases of chronic depression (Keller et al. 2000; Wolff et al. 2012). Regarding specific age groups, additional benefits of combined therapy seem to be questionable in geriatric populations (Reynolds et al. 2010). Combined therapy has not been shown to be more effective than each therapy alone in cases of child and adolescent depression (Cox et al. 2014). Various psychotherapies, including cognitive behavioral therapy (CBT) and interpersonal therapy (IPT), similarly showed synergistic efficacy when combined with antidepressants (Palpacuer et al. 2017; Schramm et al. 2007).

Here, we provide a current overview of combined therapy from the perspective of learning theory and neuroplasticity. Memory reconsolidation and its derivative, reconsolidation-updating, have clinical implications for improving the effectiveness of psychotherapy. We review the mechanisms of antidepressant action regarding how non-pharmacological



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interventions, including psychotherapeutic interventions, can influence the effect of antidepressants. Then we discuss the addition of another drug (e.g., an HDAC inhibitor) to augment the effectiveness of combined therapy. Finally, we describe the future perspectives of combined therapy.

## 21.2 The Effects of Combined Therapy

### 21.2.1 Placebo Response of Combined Therapy

Therapy-specific effects were estimated to be surprisingly small (~10%) with the majority of the effect attributed to nonspecific factors, such as the therapeutic relationship and common factors (Ahn and Wampold 2001; Palpacuer et al. 2017; Wampold 2015). Among these nonspecific effects, patients' expectations of improvement and therapists' expectations for a good therapeutic alliance constitute a large portion of the effects of psychotherapy. Leuchter et al. showed that these nonspecific effects also contribute to the effects of combined therapy (Leuchter et al. 2014). Patients with depression were randomly assigned to three groups. All groups received supportive care during weekly visits. Additionally, antidepressants, a placebo, and no medication (control) were provided to each group during the 8-week study period. The placebo plus supportive care group showed a greater response than the supportive care only group. However, the antidepressant plus supportive care group showed a better response than the supportive care only group, but not the supportive care plus placebo group. A priori anticipation of the effectiveness of antidepressants predicted these therapeutic responses. Due to the small effect and sample size, the effectiveness of combined therapy over placebo plus supportive care was not demonstrated. A substantial portion of the beneficial effect of combined therapy comes from the placebo response, like the case of antidepressant treatment and other non-pharmacological treatment (Brunoni et al. 2009). Placebo effects of antidepressants are estimated to include up to 75% of the treatment response (Mora et al. 2011). The placebo effects of antidepressant trials have increased over the past 30 years (Rutherford and Roose 2013). The widespread belief in antidepressant efficacy strengthened participant expectations of obtaining positive effects. Positive public anticipation reinforces the placebo effect in clinical trials of antidepressants. This ironically contributes to the difficulties in demonstrating the efficacy of a new antidepressant in clinical trials.

Placebo effects were previously regarded as nonspecific effects. However, physiological and neural responses accompanying positive expectations identified these as placebo responses (Brunoni et al. 2009; Oken 2009; Peciña et al. 2015). If prior experience of benefits from a specific treatment exists, a placebo response elicits more prominent conditioned physiological responses (Porro 2009). The placebo response is explained from the perspective of classical conditioning and social learning (Colloca and Miller 2011). Some may argue that it is better to combine a placebo with psychotherapy in debates of placebo as a first-line treatment for depression (Brown 1994; Kelley et al. 2012; Kirsch 2014). However, this approach is not sustainable, because it will eventually weaken patients' and therapists' expectations of recovery (Kelley et al. 2012).

### 21.2.2 Synergistic Effects of Combined Therapy

Because psychotherapy cannot be blinded to clinicians and patients, the beneficial effect of combined therapy can only be demonstrated by placebo-controlled randomized studies to exclude the placebo response. The effectiveness of combined therapy is inclined to be exaggerated by studies designed without the placebo plus psychotherapy comparison mentioned above.

There are several studies that include a placebo-controlled psychotherapy group as a

control. A meta-analysis of 12 studies revealed that the effect of active medication is small but significant (effect size = 0.25) over placebo psychotherapy (Cuijpers et al. 2010).

Despite these small effects, we may wonder if we should pursue combined therapy for depressed patients. Is it better to recommend moderate exercise as an adjuvant therapy, for its cost-effectiveness? Exercise shows moderate efficacy as an adjunct to antidepressant medications, as well as to monotherapy for mild to moderate depression (Kvam et al. 2016; Schuch et al. 2016). Otherwise, we will need to find the clinical characteristics or biomarkers that predict better response to combined therapy to maximize their cost-effectiveness (Dunlop et al. 2017). Currently, one meta-analysis the project is examining clinical elements that predict better improvement with combined therapy (Weitz et al. 2017).

### 21.2.3 Mechanisms of Antidepressant Drugs

In the 1950s, a serendipitous discovery from an antituberculosis drug, iproniazid (MAO-A inhibitor), opened the era of pharmacotherapy in the treatment of depression. Since then, antidepressants such as tricyclic antidepressants (TCAs) and selective serotonin uptake inhibitors (SSRIs) have been developed. These drugs stem from the monoamine hypothesis of depression. However, it is doubtful whether this explains the etiology of depression. A 2–3 week gap occurs between neurotransmitter elevation and clinical response. Moreover, while tryptophan depletion, a precursor of serotonin, can cause depression (Young 2013), patients with depression do not necessarily have a serotonin deficiency in their brains (Gryglewski et al. 2014).

Newer hypotheses arrived with the discovery of adult neurogenesis. Depressed patients show diminished neurogenesis in the hippocampus, and chronic antidepressant treatment reverses this decreased neurogenesis, which correlates with clinical response (Perera et al. 2011). However, there also are limitations to this hypothesis. Impairing or blocking adult neurogenesis does not necessarily cause depression or alleviate the effect of antidepressants (Hanson et al. 2011).

Neuroplasticity is implicated in depression and the therapeutic action of antidepressants (Duman et al. 2016). Antidepressants, electroconvulsive therapy (ECT), and exercise enhance synaptic plasticity (Alme et al. 2007; Nordgren et al. 2013; Patten et al. 2013). Moreover, direct targeting of synaptic plasticity sufficiently showed rapid antidepressant effects (Kanzari et al. 2017). Brain-derived neurotrophic factor (BDNF) plays a critical role in antidepressant-induced enhancement of synaptic plasticity, but not all (Alme et al. 2007). Serotonin activates the transcription factor, cAMP response element (CREB), via intracellular signaling pathways (PKA-cAMP-CREB). CREB turns on various plasticity-related genes, including BDNF. BDNF is involved in not only adult neurogenesis but also new dendritic spine formation. It is well known that BDNF plays a key role in neural plasticity, such as functional and structural plasticity (Alme et al. 2007; Leal et al. 2014; Tanaka et al. 2008). Downstream of BDNF, the TrkB-p11-SMARCA3 signaling pathway is necessary for antidepressant effects (Oh et al. 2013; Seo et al. 2016; Svenningsson et al. 2013).

The rapid antidepressant effect of ketamine gives us new insight into the pathophysiology of depression and antidepressant effects. The neuroplasticity hypothesis of depression also explains the mechanism of the rapid-onset antidepressant effect of low-dose ketamine infusion (Browne and Lucki 2013). NMDA antagonism showed a rapid increase in the density of dendritic spines. NMDA antagonism inhibits tonic GABAergic interneurons that disinhibit glutamatergic transmission (Kavalali and Monteggia 2012). Increased AMPA transmission results in the activation of the BDNF-TrkB-Akt-mTORC1 pathway to increase local protein synthesis supporting synaptic plasticity (Yoshii and Constantine-Paton 2010). The fact that TrkB blockade abolishes the antidepressant effect of ketamine indicates that BDNF is a common convergent pathway of antidepressant action (Autry et al. 2011; Lepack et al. 2014).

### 21.2.4 Antidepressant-Environment Interaction

Antidepressants do not merely elevate mood in patients with depression. This is supported by the fact that antidepressants don't affect mood in healthy non-depressed individuals (Gelfin et al. 1998). The neuroplasticity hypothesis posits new expectations about the effect of antidepressants. Like a double-edged sword, enhanced neural plasticity by antidepressant treatment makes patients more susceptible to influences in their environment. The effect of antidepressants can make depression worse, as well as recovering mood symptoms, depending on the context in which treatment occurs. This issue was comprehensively reviewed in recent articles (Choi and Kim 2016; Rief et al. 2016).

Epidemiological studies indicate that depressed patients with low socioeconomic status show a diminished treatment response to antidepressants relative to patients with high socioeconomic status (SES) (Cohen et al. 2006; Trivedi et al. 2006). In a rodent model of depression, antidepressants reversed depression-like symptoms in an enriched environment. In contrast, antidepressants worsened depression-like symptoms in a stressful situation (Alboni et al. 2015; Branchi et al. 2013). Reevaluation of Sequenced Treatment Alternatives to Relieve Depression (STAR*D) also revealed that, when treated with a high dose (citalopram 40 mg), depressed patients with high SES showed a significantly higher response rate than did low SES patients (Chiarotti et al. 2017). This evidence supports the new expectation posed by the neuroplasticity hypothesis.

There is evidence that the anxiolytic effect of antidepressants, as well as the antidepressant effect, is strongly influenced by the therapeutic environment. A combination of antidepressants and extinction training (comparable to cognitive behavioral therapy) successfully attenuated a learned fear response, without relapse, in a rodent model of fear conditioning (model of anxiety disorders) (Karpova et al. 2011). However, neither antidepressants nor extinction training alone showed the robust and sustainable effects shown in their combination.

Taken together, the interaction between antidepressants and environment explains the effectiveness of combined therapy over nonspecific effects, such as the placebo response. To induce optimal recovery from depression, enhanced neuroplasticity by antidepressant treatment is necessary, but not sufficient. With non-pharmacologic intervention, the effectiveness of antidepressants can be improved.

## 21.3 The Mechanism of Psychotherapy

### 21.3.1 Mechanism of Psychotherapy from the Perspective of Learning Theory

There have been efforts to explain the effect of psychotherapy from the perspective of learning and memory. More specifically, memory reconsolidation theory has received considerable attention from psychotherapists. Memory types have been divided into implicit and explicit memory. Explicit memory encompasses episodic memory (autobiographical memory) and semantic memory. Implicit memory is divided into associative memory (emotional memory), procedural memory, and priming memory. During early life, social reciprocal interactions between infants and parents form long-lasting procedural memories, which function as a framework which determines how a person interacts with others over the course of his or her life. This is called attachment or self-schema depending on psychotherapy disciplines. Once negative automatic thoughts (which derived from negative self-schema), which cognitive therapy targets, are formed, patients habitually repeat the way they think in ambiguous situations. Mindfulness-based cognitive therapy (MBCT) also aims to reduce these negative automatic thoughts (Frewen et al. 2007). Many patients with depression use maladaptive coping strategies, such as avoidance, to alleviate emotional suffering. Because avoidance helps to alleviate symptoms in the short term, avoidance coping continues to be negatively reinforced. However, in the long term, avoidance leads to

detrimental consequences. Both an individual's mood and the situation get worse. Acceptance-commitment therapy (ACT) and behavioral activation therapy (BA) target this avoidance coping strategies in the treatment of depression (Chawla and Ostafin 2007; Jacobson et al. 2001).

Psychodynamic psychotherapy addresses the recollection of remote memory as an important therapeutic process. Not addressing simple episodic memory, therapists try to remind patients of implicit memories, such as emotional memory and transference (procedural memory), and then respond to patients in a different way than the patients experienced with their parents. This therapeutic concept was called *working through* by Freud and *corrective emotional experience* by Alexander. This concept also is regarded as reconsolidation-updating, as described below. Exposure therapy for a specific phobia and exposure and response prevention (ERP) therapy for obsessive-compulsive disorder modify habitual responses after the initial recollection of memory. Reconsolidation and extinction are based on these behavioral therapies.

### 21.3.2 Memory Reconsolidation

The concept of memory reconsolidation plays a pivotal role in explaining the therapeutic effect of psychotherapy (Lane et al. 2015). Before mentioning memory reconsolidation, it is necessary to understand memory consolidation. The most important discovery of memory research is that, once formed, a memory is not stable through the acquisition, maintenance, and recall processes. Rather, it is a dynamic process. Memory consolidation is the process of transforming short-term memory into long-term memory. During consolidation, memories get destabilized and are susceptible to external stimuli. Three to six hours after memory acquisition is called the consolidation window (Nader and Einarsson 2010). During this period, new protein synthesis occurs. After the consolidation window, memory again becomes stable. Memory reconsolidation mimics memory consolidation. After memory recall, stable memory again becomes destabilized, malleable, and vulnerable to the external environment (Nader and Einarsson 2010). Memory can be strengthened and weakened, according to the environment. After the reconsolidation process, memory restabilizes. Ten minutes to 6 h after memory recall is the reconsolidation window. During this period, disrupting the reconsolidation process with drugs (e.g., a protein synthesis inhibitor) or interfering with learning can dramatically attenuate the physical response to memory (Nader and Einarsson 2010). This method works well with procedural memory (Walker et al. 2003), operant conditioning (Goltseker et al. 2017; Tedesco et al. 2014), and classical conditioning (Björkstrand et al. 2017). There have been efforts to translate reconsolidation into the clinical setting. This concept has been applicable to behavioral therapy for anxiety disorders and substance use disorders (Chiamulera et al. 2014).

### 21.3.3 Reconsolidation-Updating

The memory reconsolidation process is distinct from the extinction process in that it directly modifies memory *per se*. In contrast, extinction is regarded as new learning that suppress the original memory. What happens if these two processes are combined? It has been shown that fear memory is successfully suppressed to the erasure level if extinction learning happens during the reconsolidation window in which plasticity is enhanced (Monfils et al. 2009). This paradigm is called reconsolidation-updating or reconsolidation-extinction. In general, after extinction, a fear memory can reappear spontaneously (spontaneous recovery) in different contexts than where the extinction training occurred (renewal) and with a foot shock alone (reinstatement). However, reconsolidation-updating successfully suppressed a fear response in the condition of rejuvenating a concealed fear memory. This phenomenon has been demonstrated to be effective in humans (Agren et al. 2012; Björkstrand et al. 2015; Schiller et al. 2010). Recently, not only fear memory but also craving related to nicotine addiction memory could be successfully attenuated by using this approach (Germeroth et al. 2017; Xue et al. 2017).

The reconsolidation phenomenon is observed in other forms of memory. Procedural memory

can be diminished by interfering with learning during reconsolidation (Walker et al. 2003). Episodic memory can be also distorted by cues presented after memory reactivation (Scully et al. 2016). Negative automatic thoughts, attachment, and transference can be categorized into implicit memory, such as procedural memory and emotional memory. If so, this reconsolidation-updating explains the effect of psychotherapy. As psychodynamic psychotherapists expected, reconsolidation-updating might be central to the effect of psychotherapy. We can optimize the current procedures of psychotherapy.

## 21.4 How to Improve Combined Therapy

Depression is a chronic and relapsing disease with a great socioeconomic burden. More major depressive episodes make the disease more intractable. Early identification and a complete recovery with no remaining symptoms are essential to prevent illness progression (Hetrick et al. 2008). Combined therapy shows efficacy in cases of mild-to-severe depression and in both chronic and non-chronic depression. In particular, combined therapy demonstrated better efficacy in preventing relapse than pharmacotherapy or psychotherapy alone. Thus, combined therapy deserves to be recommended as a first-line treatment for depression, although it remains a second-line treatment because of its cost-effectiveness, practicality, and the limited availability of psychotherapy (Parikh et al. 2009). Eventually, more patients will benefit from combined therapy if we improve its effectiveness and the availability of psychotherapy.

### 21.4.1 How to Improve Combined Therapy in Pharmacotherapy

#### 21.4.1.1 Pharmacological Augmentation of Reconsolidation-Updating

Although reconsolidation-updating can attenuate recent memory, remote memory (>1 month) is not modified by this paradigm (Costanzi et al. 2011). This limits the usefulness of reconsolidation-updating as a therapeutic target, because maladaptive memories, which psychotherapy targets, are usually formed a long time before the first psychotherapy visit. Fortunately, it was revealed that an epigenetic drug (HDAC2 inhibitor; CI-994) enables remote memory to be modified by the reconsolidation-updating paradigm (Gräff et al. 2014). Compared to recent memory recall, after retrieval of remote memory, the hippocampus is less activated and less acetylated. HDAC2 inhibition restored acetylation and activation levels in the hippocampus during remote memory retrieval.

Combined therapy in depression has been primarily restricted to the combination of antidepressants and psychotherapy. In the treatment of anxiety disorders, combining D-cycloserine (a dopamine partial agonist) with exposure-based therapy has been well studied during the last decade. A recent meta-analysis reported that D-cycloserine augmentation has a small but significant benefit (Mataix-Cols et al. 2017). Moreover, D-cycloserine showed a significant augmentation effect on virtual reality (VR)-based exposure therapy over an active placebo (Rothbaum et al. 2014).

#### 21.4.1.2 Beyond Antidepressants: HDAC Inhibitors as a New Augmentation Strategy

HDAC detaches an acetyl marker located on histone tails. HDAC1-11 isoforms are classified into classes I, IIA, IIB, III, and IV. Valproate and CI-994 are designated as class I HDAC inhibitors. Class I HDAC consists of HDAC1, HDAC2, and HDAC3. Isoforms perform diverse functions in cell-type-specific manners. Regarding learning, HDAC2 functions as a molecular brake, preventing aberrant expression of plasticity-related genes at baseline. Upon learning (neural activation), HDAC2 detaches from the histone tails wrapping target genes. The histone tail is now allowed to be acetylated by histone acetyltransferase (HAT). Closed chromatin (heterochromatin) turns into loose chromatin (euchromatin), which allows RNA polymerase and transcription factors to approach promoters of target genes. HDAC2 inhibition or genetic knockout of HDAC2 showed a cognitive enhancing effect via facilitating expression of neuroplasticity-related genes (Guan et al. 2009).

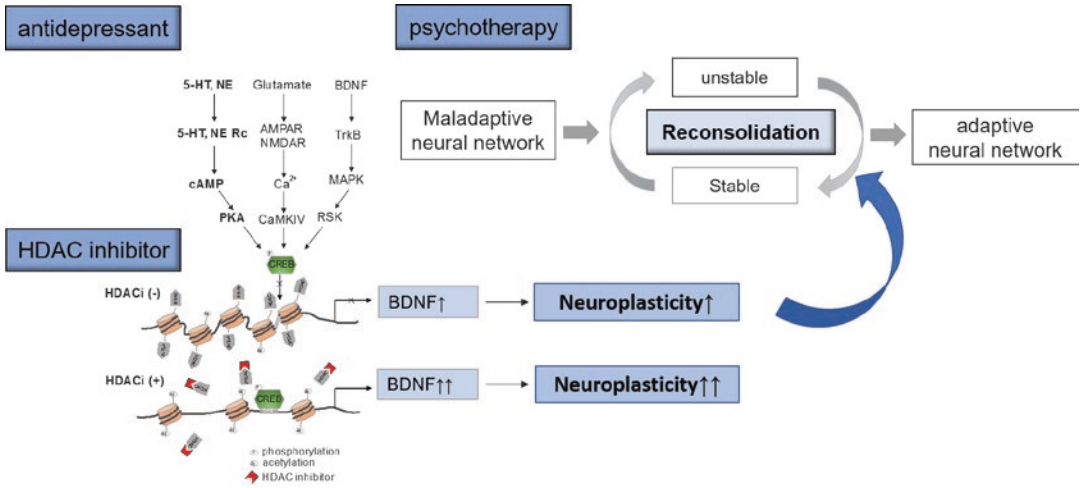


**Fig. 21.1** Synergistic effect of combined therapy. An antidepressant enhances BDNF expression. An HDAC inhibitor further augments this expression. Enhanced neuroplasticity facilitates the effect of psychotherapy. During psychotherapy, memory retrieval-induced reconsolidation can be modified by the interactions between patient and therapist

The beneficial effect of an HDAC inhibitor on the combination of psychotherapy and antidepressants will be the next big question to be answered (Fig. 21.1) (Choi and Kim 2016). HDAC inhibitors showed promising results in a rodent model of depression. HDAC inhibitors showed an antidepressant effect with local infusion (Covington et al. 2015, 2009, 2011) in the nucleus accumbens, medial prefrontal cortex, hippocampus and amygdala, as well as systemic infusion (Schroeder et al. 2007; Tsankova et al. 2006) in a rodent model of depression. In addition, HDAC inhibitors augmented the effect of antidepressants in rodents (Schmauss 2015). The underlying mechanism is that HDAC inhibitors facilitate BDNF gene expression by increasing H4 acetylation at promoter III of the BDNF gene (Schmauss 2015).

In particular, HDAC inhibitors and antidepressants can restore immature neuron-like plasticity. Antidepressant-induced juvenile-like, critical period-like plasticity is mediated by reducing perineuronal nets (PNNs). PNNs, extracellular matrix surrounding preferentially GABAergic interneurons, are lacking during critical periods. It appears that when a critical period is closed, synaptic connections prevent robust activity-dependent changes (Berardi et al. 2004). Antidepressants reduce PNN-like juvenile states (Ohira et al. 2013). Targeting PNNs with antidepressants or directly with HDACs showed promising results in boosting the effects of behavioral interventions, such as fear extinction (Karpova et al. 2011; Yang et al. 2016). HDAC inhibitors, as well as antidepressants (Vetencourt et al. 2008), can restore critical period plasticity, which has been translated into the treatment of amblyopia (Lennartsson et al. 2015; Silingardi et al. 2010). Antidepressants show hope in facilitating rehabilitation after strokes via elongating the critical period of recovery (Ng et al. 2015).

#### 21.4.1.3 Avoid Benzodiazepine Use

Benzodiazepines are widely prescribed with antidepressants to manage anxiety symptoms in depressed patients (Furukawa et al. 2001). However, there is concern that concurrent benzodiazepine use might ameliorate the beneficial effects of combined therapy.

Benzodiazepine has been shown to downregulate enhanced neurogenesis by antidepressants in rodents and humans (Boldrini et al. 2014; Sun et al. 2013). Furthermore, benzodiazepine decreased the behavioral effects of antidepressants in an animal model of depression (Sun et al. 2013). Benzodiazepine impedes functional recovery during rehabilitation after a cerebral infarct (Schwitzguébel et al. 2016). Currently,

benzodiazepine is no longer recommended for use in patients with PTSD (post-traumatic stress disorder) or recent trauma (Jeffreys et al. 2012), because it increases the risk of developing PTSD and worsens psychotherapy outcomes (Guina et al. 2015). Direct clinical evidence addressing this issue in the combined therapy of depression is lacking. However, it is prudent to avoid benzodiazepine use in combined therapy. Concurrent use of benzodiazepines should be regarded as a major confounding factor in future research on combination therapy.

## 21.4.2 How to Improve Combined Therapy in Psychotherapy

### 21.4.2.1 Education System vs. Psychotherapy Practice

No one contradicts the evidence that education changes people's brains and their life. Good nurturing during early life helps people engage in good psychosocial relationships and maintain physical and mental health throughout their lifetime. Mental health-care professionals are also expected to reshape one's life. However, relative to parents and teachers, mental health practitioners are placed in disadvantageous situations while public expectation is high.

During school age, individuals spend 3~8 h per day at school for many years until graduation. In addition, students participate in 45–50-min tutoring sessions into a subject during each semester at least once per week. Only after entering graduate school can interactions with a supervising professor be reduced to approximately 1 h per week. Only this small amount of interaction is the time allowed for psychotherapists to positively influence patients' lives. Postdoc fellows who are preparing their independent research need far less time than once a week interactions with their advisors to achieve their purpose of achieving independence. By analogue, psychotherapists treat all students as graduate students, regardless of middle school, high school, and university achievement. A more flexible health-care system is needed to meet the wide spectrum of patients' and clinicians' needs.

### 21.4.2.2 How to Innovate a Psychotherapy-Providing Platform

A barrier to the widespread use of combined therapy is the accessibility of psychotherapy. Patients have the right to access various non-pharmacological treatment options, from exercise and nondirective supportive psychotherapy to more specialized therapies, such as interpersonal psychotherapy and cognitive behavioral therapy. Many patients prefer to attend psychotherapy rather than taking medication (McHugh et al. 2013; van Schaik et al. 2004). However, complex factors, including financial and time costs, lack of information about the nearby validated therapists, and the health-care system, hinder patients/clinicians from choosing psychotherapy alone or combined therapy.

There is a move to improve the mismatch problem between clients and providers, just as Uber and AirBnB connect consumers and potential providers. In the near future, it may be popular to use a new platform service connecting clients with nearby therapists (Baumel 2015). This has the potential to innovate current psychotherapeutic practice. Patients save on effort to find a nearby therapist providing a particular form of psychotherapy. The platform should have an apparatus to validate providers' proficiency and certificates before enrollment, and then therapists will be further evaluated on their reputation. This information will help clients to choose therapists. From the therapists' perspective, they save the time they would have spent rescheduling a client's request. The missed session fee will be automatically paid. And this system will provide clients with a more flexible reservation schedule while minimizing default/empty reservations.

Computerized CBT reduces the need for face-to-face sessions and extends coverage to people who need CBT but can not actually apply it. If therapists combine internet-based apps with cognitive behavioral therapy, more intensive monitoring or feedback will be provided. Behavioral therapy using a mobile application showed initial promising effectiveness in the management of obesity (Chin et al. 2016; Kim et al. 2017). Recently, a computerized CBT-insomnia (CBT-i) program showed efficacy compared to a conven-

tional CBT-i program (Cheng and Dizon 2012). At a minimum, guided self-help intervention is also effective for subthreshold and mild-to-moderate depression (Fledderus et al. 2012) (Buntrock et al. 2016; Gellatly et al. 2007).

These approaches will be helpful for patients who have subthreshold depression, who are seeking something more than self-help, and who want interactive experiences while they are not in the therapist's office. In particular, early intervention for subthreshold depression is important to prevent the development of depression (Buntrock et al. 2016; Beardslee et al. 2013; Brent et al. 2015). Primary prevention for an individual at risk for depression might be an effective strategy to reduce the socioeconomic burden of depression, considering that experiencing a single major depressive episode is associated with a 60% recurrence and that pharmacologic treatment only reduces recurrence by 10–30% (Hirschfeld 2001).

In the future, face-to-face sessions would be partially replaced with video calls (Corruble et al. 2016; van der Vaart et al. 2014). This will increase the accessibility of psychotherapy and combined therapy. Preferences of the clinician and patient, validation of effectiveness, and legal and institutional issues remain to be resolved. More studies validating their effectiveness compared to face-to-face treatment are needed (Bee et al. 2008; Dagöö et al. 2014; Thorp et al. 2012; Watkins et al. 2016).

#### 21.4.2.3 How to Maximize the Effect of Reconsolidation-Updating

Accessing the process of recall requires waiting until it appears naturally, although there are direct interventions, such as psychodrama or exposure during cognitive-behavioral therapy. Before the formation of the therapeutic alliance, it is better to wait until patients autonomously engage in memory recollection. We wonder whether this strategy is still the best if months or years have elapsed. Assuming that reconsolidation-updating is an active ingredient to achieve psychotherapeutic effectiveness, maximizing therapeutic components during each session will shorten treatment duration and improve outcomes. Facilitating the recollection of a maladaptive memory in the early half of a session will be helpful to utilize the reconsolidation window (10 min to 6 h) as much as possible.

Active engagement of memory retrieval is already applied to the treatment of anxiety disorders (exposure-based therapy for PTSD and acrophobia). Facilitating recollection of emotional memory engaged with unresolved interpersonal conflict is used in the psychodrama technique. For a more immersive experience, a virtual reality device is being developed (Coelho et al. 2009; Shapiro et al. 2005). If we can simulate the interpersonal relationship in virtual reality, the direct experimental approach used in psychodrama based on individual therapy will be possible. This will help the depressed patient who will benefit from interpersonal therapy.

Simple recall of a memory is not enough to cause reconsolidation-updating. Prediction error is an indispensable component. Reconsolidation-updating occurs only when patients experience a different outcome than expected (Ecker et al. 2012). Psychoanalytic psychotherapy and cognitive-behavioral therapy utilize this factor. Empiricism is based on a patient's subjective experience. Clinicians encourage patients to willingly experience repeated failures of their expectations about the self, others, and the environment. Without these elements, psychotherapy would not differ from self-help books or psychoeducation.

## 21.5 Maintenance Strategies for Combined Therapy

If patients respond well to combined therapy, it is recommended they maintain the combined therapy during the continuation phase. Combined therapy showed a superior relapse-free ratio to antidepressants alone and psychotherapy alone (Oestergaard and Møldrup 2011; Reynolds et al. 1999). However, for patients who need maintenance treatment to prevent recurrence, it remains unclear which strategy is the best (Huijbers et al. 2012). There are three maintenance options: antidepressant maintenance, maintenance psychotherapy, and slowly tapering antidepressants with psychotherapy maintenance. In the case of panic disorder, CBT therapy combined with antidepressants showed a worse relapse prevention

effect than did CBT alone 6 months after discontinuation of therapy, while combined therapy outperformed CBT before discontinuation (Barlow et al. 2000).

This drawback might arise from state-dependent learning (Overton 1966), or the tendency to easily recall a memory in the setting where the memory was formed. The learning that occurs while taking antidepressants is not generalized to states without antidepressants. Overlapping antidepressant tapering and maintenance psychotherapy will mitigate this concern. Reconsolidation-updating aided by HDAC inhibitors showed promise for preventing relapse of learned fear memory in rodents. Time-limited use of HDAC inhibitors (e.g., valproate, CI-994) combined with conventional combination therapy might produce a better relapse rate after discontinuation, comparable to psychotherapy alone (Choi and Kim 2016). This research question is of clinical significance.

### Conclusion

Combined therapy has additional benefits in the treatment of depression. As in the case of antidepressants, a substantial portion of these benefits arise from a placebo response. However, a true synergistic effect of combined therapy exists. According to the neuroplasticity hypothesis, various non-pharmacological interventions, including psychotherapy, help patients to better recover from depression. Beyond antidepressants, HDAC inhibitors will be of interest in research on combination therapy. The accessibility and practicality of psychotherapy are other areas needing improvement in combined therapy.

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# 22 Internet-Based Mindfulness-Based Cognitive Therapy for the Adjunctive Treatment of Major Depressive Disorder

Jennifer Apolinário-Hagen and Christel Salewski

## 22.1 Introduction

Depression is one of the leading causes of chronic illness and disability worldwide (Gotink et al. 2015; Kessler and Bromet 2013). World Health Organization (WHO) estimates accounted to 300 million people living with depression, with an increase of 18% within the past decade (2005 to 2015). Consequently, "Depression: Let's Talk" was chosen as the campaign motto of the WHO World Health Day 2017.[1] The aim of this self-help campaign was to engage more persons with depression to seek and get help. According to the Global Burden of Disease Study 2015, the incidence rates for depressive disorders ranged from 2.9% (Solomon Islands) to 5.9% (Australia), with an estimation of 4.4% of the global population suffering from depressive disorders (WHO 2017).

Among the different types of depressive disorders, major depressive disorder (MDD) is an ongoing global burden because of the relatively high lifetime prevalence (e.g., 16.9% in the United States), and its occurrence throughout regional, sociodemographic, or economic backgrounds (Kessler and Bromet 2013). According to the Diagnostic and Statistical Manual (DSM) V (American Psychiatric Association; APA 2013), MDD is characterized by depressed mood or a loss of interest or pleasure in everyday activities, with an unceasing or almost daily presence for 2 weeks or more, resulting in substantial psychological strain and impaired psychosocial, occupational, social, and educational functioning (Box 22.1).

**Box 22.1: DSM V Symptoms of MDD**

MDD diagnosis requires at least five of the following nine complaints:

(1) Depressed or nervous mood
(2) Reduced interest or pleasure in most activities
(3) Significant changes in weight or appetite, (4) sleep patterns, and/or (5) in psychomotor activity
(6) Emotional fatigue or loss of energy
(7) Feelings of worthlessness and/or excessive or inappropriate guilt
(8) Diminished concentration or increased indecisiveness
(9) Thoughts, intentions, or plans related to suicidality

[1] WHO International (2017). Depression: Let's Talk. Last accessed on 10 April 2017 under http://www.who.int/campaigns/world-health-day/2017/toolkit.pdf?ua=1. Archived under http://www.webcitation.org/6plZia43b.

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Treatment as usual (TAU) for MDD includes different types of antidepressant pharmacotherapy and psychological interventions, such as cognitive behavior therapy (CBT). Considering potential side effects of antidepressants as the main reason for nonadherence in the longer-term maintenance therapy and relapse prevention of recurrent MDD, psychological interventions have been endorsed as noninvasive, effective alternative. Mindfulness-based cognitive therapy (MBCT) has been developed as specialized group program for the relapse prevention of MDD (Teasdale et al. 2000; Segal et al. 2002). Systematic reviews and meta-analyses of randomized controlled trials (RCTs) have confirmed MBCT as effective compared to active and waiting list control groups in face-to-face settings in persons with current or past depression (MacKenzie and Kocovski 2016). However, several drawbacks can hamper the adherence to treatment or the longer-term maintenance of treatment effects, such as perceived inflexibility of group programs or high time constraints when implementing mindfulness practice into everyday routines (Kvillemo et al. 2016; Wahbeh et al. 2014). To overcome some of the obstacles of face-to-face group-based MBCT, web-based mindfulness-based interventions have been suggested as suitable self-help options in the adjunctive treatment and prevention of depression (Brown et al. 2016; Spijkerman et al. 2016). The interventions are delivered by computer, tablet, or smartphone and, in the latter case, via mobile health applications (mHealth apps). Due to the novelty of these developments, patients as well as health professionals require evidence-based recommendations regarding the usefulness of web-based mindfulness programs and apps.

To derive such recommendations for health professionals in practice and research, the purpose of this chapter is to provide a short overview of the evidence base on the efficacy of web-delivered MCBT self-help formats in the prevention or prophylaxis of MDD relapse in public health, based on the current state of knowledge about traditional face-to-face MBCT.

## 22.2 Mindfulness-Based Cognitive Therapy for Depression Relapse Prevention

Learning the skill of mindfulness (or awareness at the present moment) is a key strategy in the relapse prevention of MDD in MBCT (Box 22.2).

**Box 22.2: Defining Mindfulness as Multifacet Construct in the Context of MBCT**

Mindfulness is widely defined as "…the awareness that emerges through paying attention on purpose, in the present moment, and nonjudgmentally to the unfolding of experience moment by moment" (Kabat-Zinn 2003, p. 145).

In addition to this definition, Bishop et al. (2004, p. 234) understand "… mindfulness as a process or regulating attention in order to bring a quality of nonelaborative awareness to current experience and a quality of relating to one's experience within an orientation of curiosity, experiential openness, and acceptance."

Concerning MBCT: "(1) Mindfulness is a generic skill and so it can be praticised on many aspects of experience in many situations (…) (2) (…). Mindfulness training aims to make individuals fully aware of their thoughts and feelings, from moment to moment, whether those experiences are pleasant, unpleasant, or neutral (…) (3). The mindfulness state is characterised by direct experience of current reality in the moment, rather than elaborative, ruminative thinking about one's situation, and its origins, implications and associations. Mindfulness training appears to be associated with a reduction in the tendency to 'float away' into ruminative, elaborative thoughts throughout streams (…)" (Teasdale et al. 1995, p. 34).

Mindfulness skills are taught in manualized 8-week group programs under supervision of an expert instructor. Regarding the course contents, mindfulness courses vary across three main orientations: mindfulness-based stress reduction (MBSR), mindfulness-based cognitive therapy (MBCT), and acceptance and commitment therapy (ACT) (Kabat-Zinn 2003). In general, mindfulness-based interventions aim to change the function and context of maladaptive inner processes, such as negative feelings and automated thoughts (Hofmann et al. 2010; Kabat-Zinn 2003). Grounded on mindfulness meditation practice and tailored from Buddhist to Western culture, Kabat-Zinn developed MBSR as the first mindfulness-based training for patients with chronic pain in the late 1970s (Kabat-Zinn 2003). MBCT was developed by Segal in the 1990s for depressive patients as manualized 8-week group course (Strauss et al. 2014; van der Velden et al. 2015).

MBCT was first termed by Teasdale et al. (1995) as attentional control (mindfulness) Training that was based on information-processing analyses conducted to explain the mechanisms of action of cognitive therapy for effective prevention of MDD (see Teasdale et al. 1995). MBCT is based on both the principles of MBSR and CBT (Segal et al. 2002, 2012). Although MBSR and MBCT share their grounding and mediation exercises, their contents, targeted health conditions, and populations differ substantially. Since MBCT was designed as a specific mindfulness intervention for the relapse prevention of MDD (Teasdale et al. 2000), it is usually provided in homogenous group settings consisting of participants with similar health conditions (Meibert 2016), which is different from MBSR. The aim of MBCT training is to learn and regulate contrast between attention in the autopilot mode and mindfulness in daily activities (Teasdale et al. 1995). Another derivate of MBSR and CBT is ACT that has been developed by Hayes et al. (2006). While MBSR scopes on mindfulness-based meditation practice, MBCT has an additional focus on CBT exercises for depression, and ACT puts emphasis on experience-orientated techniques to train self-acceptance and a nonjudgmental attitude toward oneself (Keng et al. 2011). In practice, however, many mindfulness programs combine components of MBSR, MBCT, and ACT. Nonetheless, each mindfulness program starts from the premise that it is mandatory to develop and promote mindfulness systematically through regular practice in both the course group setting and in daily life (Kabat-Zinn 2003).

Regarding therapeutic indications, MBCT has a clear focus on MDD and related mental or somatic illnesses, whereas MBSR is applied to a broader spectrum of mental health conditions and populations (Cavanagh et al. 2014; Khoury et al. 2013). In some indications, such as bipolar disorder, acute depression, and social phobia, preliminary evidence suggested that MBCT may be even more effective than TAU (Keng et al. 2011). Contraindications for MBCT involve persons who are not capable of or willing to attending group programs and persons suffering from acute psychotic symptoms, suicidality, or a current life crisis (Keng et al. 2011; Meibert 2016).

Regarding its content and structure, MBCT is designed as an 8-week group course, with a maximal number of 12–14 participants. Since the first four of the eight modules of MBCT courses (i.e., lessons 1–4) are based on exercises to learn mindfulness meditation in the course setting and daily life, the second four (i.e., lessons 5–8) focus on the management of future negative or depressed mood on the basis of mindfulness (Meibert 2016). As mentioned above, MBCT usually consists of similar basic training components as MBSR. These elements can be differentiated in formal and informal mindfulness exercises. **Formal mindfulness exercises** include structured workouts like body scan, sitting meditation, and mindfulness body work or yoga exercises. Mindfulness exercises comprise a broad number of **informal mindfulness** practices aiming to bring awareness or "inner presence" to daily routines, such as breathing, eating, or walking. Informal exercises can be easily applied in everyday life (Meibert 2016).

## 22.3 Mechanisms of Change in MBCT

To understand why and how MBCT works, mechanisms of change have been investigated to identify who is most likely to benefit from MBCT (MacKenzie and Kocovski 2016). The theoretical model behind MBCT describes the impact of cognitive vulnerability on repetitive automated, negative thoughts in the relapse of MDD (MacKenzie and Kocovski 2016). According to this cognitive vulnerability model, repeated automated negative thoughts become associated with the depressed state. In turn, the number of depressive episodes increases the risk of depression relapse through the easier reactivation of implicit response patterns (Teasdale et al. 1995). In line with the diathesis-stress model, cognitive reactivity or vulnerability to stress is crucial for the onset, relapse, and recurrence of MDD symptoms. Therefore, cognitive reactivity is a central concept in MBCT that explains the frequent recurrence of MDD even after successful antidepressant therapy—at least in persons who are vulnerable during stressful situations (Scher et al. 2005). Within the process of internal maintenance of depression, so-called depressogenetic schematic models (cognitions that advance depressive thoughts and feelings) are synthesized. These emotional patterns of responses result in the "establishment of self-perpetuating processing configuration that continue to regenerate depressogenetic schematic models" (Teasdale et al. 1995, p. 28).

Bishop et al. (2004) assume that two processes are involved in the training of mindfulness: (1) regulation of mindfulness at the present moment and (2) orientation to the experience within daily activities. According to Shapiro et al. (2006), further elements are vital, namely, intention to practice and attitudes that affect meditation practice. These authors also state that multiple mechanisms may enable behavior changes in mindfulness interventions, namely, self-regulation, values clarification, cognitive behavioral flexibility, and exposure. They propose three axioms of mindfulness: (I) "on purpose" (intention), (II) "paying attention," and (III) "in a particular way" (attitude toward mindfulness qualities) (Fig. 22.1). These aspects represent interconnected stages of a cyclic process that occur simultaneously. Mindfulness is assumed to reflect this type of moment-to-moment process. These components appear to be relevant to understand mechanisms of change in MBCT.

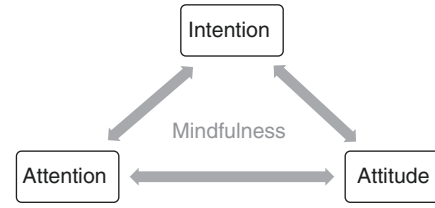


**Fig. 22.1** The three axioms of mindfulness: intention, attention, and attitude. Adapted from Shapiro et al. (2006), p. 375. According to Shapiro et al. (2006), these aspects represent no separate stages; instead they are interconnected aspects of a single cyclic process. They occur simultaneously. Mindfulness reflects this type of moment-to-moment process

Several predictors and mediators for the effectiveness of MBCT are discussed in the literature. For instance, in treatment-resistant MDD, Eisendrath et al. (2011) identified four mediators for the effectiveness of face-to-face MBCT: lower rumination, increased self-compassion, improved acceptance, and reduced avoidance. These and other factors have been investigated in several RCTs on the effectiveness of traditional MBCT group formats. Other studies suggest that MCBT is most likely to be effective (in terms of reduced relapse risk) in patients with three or more previous depressive episodes, childhood adversity (i.e., dysfunctional parenting), and earlier onset of the first MDD episode (Ma and Teasdale 2004). However, empirical evidence also suggests that two or more previous episodes increase the effectiveness of MBCT in the prevention of MDD relapse (Clarke et al. 2015).

## 22.4 Evidence Base for Face-to-Face MBCT

In face-to-face settings, mindfulness-based interventions have been shown to be as effective as CBT in reducing depression, stress, and anxiety

in different groups of patients (Hofmann et al. 2010; Khoury et al. 2013, Khoury et al. 2015). A systematic review by Fjorback et al. (2011) on five included reviews revealed that MBCT is effective in the relapse prevention of MDD. There is also evidence that MBCT is as effective as pharmacotherapy in the maintenance treatment of MDD (Clarke et al. 2015). Teasdale et al. (2000) investigated the effectiveness of MCBT (TAU provided by the family doctor versus TAU plus MBCT training) in 145 patients with two previous episodes of depression and found that TAU and MBCT were equally effective. Additionally, a first meta-analytic review by Strauss et al. (2014) on 12 RCTs targeting the effectiveness of MBIs in the relapse prevention of MDD showed significant effects in terms of reduced depressive symptom severity in patients with current MDD. Another review on 15 RCTs investigating mindfulness-based interventions (Cavanagh et al. 2014) identified small to medium effect sizes for depression outcomes. According to a systematic review of 23 reviews and meta-analyses (Gotink et al. 2015), data on 115 RCTs with 8683 participants confirmed that both MBCT and MBSR significantly improved depressive symptoms compared to TAU (i.e., help patients receive from a family doctor or other sources depressed patients usually seek help from) and waiting list control groups. In this review of reviews, three included reviews scoping on 17 RCTs on MBCT for depression (Chiesa and Serretti 2011; Coelho et al. 2007; Piet and Hougaard 2011) positive, but not significantly higher effects of MBCT compared to TAU were identified. Moreover, in an individual patient data meta-analysis (Kuyken et al. 2016), the efficacy of MBCT in the prevention of MDD relapse across ten included RCTs was confirmed. Patients receiving MBCT showed a reduced risk of MDE relapse within a 60-week follow-up period compared to the non-MBCT condition. Since there were no significant interaction effects between MBCT outcomes and individual characteristics (sociodemographic and illness-related variables), at least some evidence was found for the assumption that especially patients suffering from recurrent depressives episodes or profound residual symptoms are most likely to benefit from MBCT. In other words, more severe depressive symptoms at baseline were associated with larger effects of MBCT compared to other active treatments across RCTs (Kuyken et al. 2016).

Regarding mechanisms of change, a systematic review (Keng et al. 2011) identified increases in mindfulness, metacognitive awareness, acceptance, and behavioral self-regulation as important factors for the effectiveness of MBCT. In addition, a systematic review (van der Velden et al. 2015) on 23 studies identified that changes in mindfulness, rumination, worry, compassion, and meta-awareness were associated (in some studies with mediating effects) with improvements in depression-related outcomes.

Regardless of these promising findings on MBCT efficacy, empirical evidence further indicated that the therapeutic success of mindfulness-based trainings depends on active participant engagement and regular exercises of acquired mindfulness techniques in daily life (Cavanagh et al. 2013). Implementing mindfulness practice into daily life can be challenging for persons with recurrent depressive episodes. A potential solution to facilitate the access to mindfulness interventions could be the provision of web-based mindfulness interventions for adults with mental health issues (Mak et al. 2015).

## 22.5 Internet-Based MBCT as Novel Strategy

Mindfulness-based and acceptance-based treatments face a growing interest in patients and policy makers in general. There is also a recent expansion of web-delivered mindfulness-based interventions for depression (Brown et al. 2016). Web-based mindfulness interventions have been suggested as a further opportunity to enlarge self-help options (Spijkerman et al. 2016). The Internet provides additional pathways for the dissemination of evidence-based mindfulness-based interventions to a broader range of individuals (Kvillemo et al. 2016). Potential key advantages of Internet-based mindfulness interventions include the easy access and cost-effectiveness

(Brown et al. 2016). Preferred delivery modes of interventions should therefore be considered in the treatment and the relapse prevention of MDD. In a survey by Wahbeh et al. (2014), the majority of the 500 respondents preferred the Internet over traditional group courses as delivery mode for mindfulness interventions, because web-based programs can be attended with more convenience than face-to-face group formats.

Most of clinically tested web-based mindfulness interventions follow the structure of 8-week MBSR courses, and many provide at least a minimal professional support, including therapist assistance, individualized feedback, or coaching (Spijkerman et al. 2016). Examples for such web-delivered mindfulness programs and apps are the "Mindfulness" app from Sweden (Ly et al. 2014), "Mindfulness online" from the United Kingdom (Krusche et al. 2013), "iMind" from China (Mak et al. 2017), or "Mindful Mood Balance" from North America (MMB, Boggs et al. 2014). An example for a multicomponent nine-module program is "Deprexis" (Meyer et al. 2009) from Germany. This program combines CBT with acceptance-based and mindfulness-based modules for the self-help treatment of mild to moderate depressive symptoms. "Deprexis" uses behavioral activation, cognitive restructuring, mindfulness or acceptance, and social skill training.

Although 8 weeks is the standard duration time for MBSR and MBCT in face-to-face group formats, a review on 15 web-based mindfulness interventions has shown that their time span ranged from 2 to 12 weeks (Spijkerman et al. 2016). According to a systematic review with ten RCTs on the efficacy of eHealth versions of mindfulness-based ACT programs for mood and anxiety disorders (Brown et al. 2016), the intended duration time of web-delivered ACT programs ranged between 3 and 12 weeks. The number of sessions varied between 2 and 9 modules. Design features appeared to be associated with engagement and adherence to a program. Included web-based ACT interventions used different levels of mostly asynchronous communication and clinical assistance: While some interventions provided no human guidance or automated feedback via reminders or a system, others provided professional guidance from a trained psychologist or psychology graduate students. Clinical support was mostly delivered via email or telephone and could include the personalized feedback on the progress or completion of tasks, for instance, regarding tasks in an additional workbook targeting strategies to inform about mindfulness skills and self-acceptance in everyday life. Taken together, web-based mindfulness programs have become increasingly interesting for healthcare, and thus health professional should be informed about its chances and risks for patients with recurrent MDD.

## 22.6 Evidence Base for Internet-Based MBCT

In summary, preliminary evidence from RCTs suggested that Internet-based mindfulness interventions such as MBCT are effective in depression treatment across different populations (Fish et al. 2016; Jayewardene et al. 2017; Spijkerman et al. 2016). For instance, first evidence has demonstrated that hybrid group online mindfulness group programs with peer support are feasible alternatives to rather inconvenient and costly traditional group courses with expert teachers (see Kemper and Yun 2015). Most studies focused on nonclinical populations, but reported improvements in depressive symptoms after web-based or app-based mindfulness-based interventions nonetheless (e.g., Ly et al. 2014). In addition, brief online mindfulness-based interventions (shorter than 7 weeks) have also proved to be effective in reducing depressive symptoms in nonclinical populations (e.g., Cavanagh et al. 2013; Krusche et al. 2013; Mak et al. 2015).

However, the number of RCTs on web-based mindfulness interventions is still small, and most interventions use mild to moderate depressive symptoms and not relapse prevention of MDD as primary outcome. Often the scope is on MBCT for nonclinical populations (e.g., Ly et al. 2014) or on the effectiveness of other intervention types like ACT (e.g., Levin et al. 2014; Pots et al. 2016; Wolever et al. 2012) or MBSR (Kvillemo

et al. 2016; Mak et al. 2015) in nonclinical populations such as students and employees. One exception is a qualitative study conducted by Boggs et al. (2014) on the web-based MBCT program "Mindful Mood Balance" that proved to be effective in reducing residual symptoms of MDD and was endorsed as suitable for relapse prophylaxis. A study (Meyer et al. 2009) on the program "Deprexis" found significant improvements of current depressive symptoms at the 6-month follow-up assessment. Another web-based mindfulness intervention was also found to be effective in reducing residual symptoms of MDD (Dimidjian et al. 2014).

In addition to computerized programs, apps are a potential means to ease the implementation of mindfulness practice in daily life and to match habits and preferences of younger adults better than traditional programs. Different smartphone apps conveying MBCT and MBSR to depressed populations might also serve as useful self-help tools. In a study by Ly et al. (2014), an 8-week smartphone-delivered mindfulness app turned out to be as effective as a behavioral activation app in 40 middle-aged patients with symptoms of depression. This is an important finding because patient preferences to physical activity or mindfulness may differ. Thus, more options such as different types of effective apps can be provided for patients with depression. Although mHealth apps may provide an easily accessible delivery mode for mindfulness interventions, the usefulness of numerous services that are currently freely available in app stores can be considered as questionable. In line with a previous review (Plaza et al. 2013), Mani et al. (2015) confirmed in a systematic review of 23 iPhone apps a lack of evidence for the content quality and usefulness of the (mostly not evaluated) mindfulness apps to develop mindfulness. Likewise, many apps misleadingly suggested to target, but were only guided, meditation apps, timers, or reminders.

Adherence rates vary largely across web-based mindfulness interventions. According to a systematic review by Spijkerman et al. (2016), adherence (i.e., completion of five or more lessons) for the 15 included RCTs on web-based mindfulness interventions for depression, anxiety, and distress ranged between 39.5% and 92% across programs with an intended course length of 6–8 weeks. According to another systematic review on web-delivered ACT interventions (Brown et al. 2016) with 10 RCTs ($n$ = 5 RCTs targeting depression), adherence rates ranged from 48 to 100% across included studies. Improved adherence in guided interventions may imply that guidance is one or even the core component of the effectiveness of web-delivered mindfulness interventions, but more research is needed to support this assumption (Brown et al. 2016; Spijkerman et al. 2016). In addition, studies on web-based mindfulness interventions reveal severe differences in the construction, length, and delivery modes (Fish et al. 2016). Finally, application-oriented issues like implementation of web-based interventions into healthcare settings need to be discussed more detailed.

## 22.7 Implementation of Internet-Based MBCT

Currently, the process of disseminating and implementing web-based mindfulness-based interventions successfully into public health settings is a key challenge in this developing field. Regarding the implementation into care, a meta-analytic review on the efficacy of mindfulness-based interventions in primary care (Demarzo et al. 2015) with six trials suggests that the interventions can be effectively provided in healthcare and can help to improve mental health and quality of life in patients. However, as a scoping review (Drozd et al. 2016) revealed, little attention has been placed so far the (both successful and unsuccessful) implementation of web-based interventions for depressive disorders.

Different barriers and facilitators related to the implementation of web-based intervention are discussed (Hennemann et al. 2016). For instance, in an 8-week web-based self-administered mindfulness intervention using automated reminders from Sweden (Kvillemo et al. 2016), the program's anonymity and flexibility in terms of time and location were endorsed as advantageous

program features by the participating students. Positive attitude to mindfulness practice and perceiving the program as helpful and meaningful improved the likelihood for completion. In a qualitative study on the web-based MBCT program "Mindful Mood Balance" for relapse prophylaxis, participants' comments indicated some other important topics, such as time management as challenge for program completion and home practice of mindfulness and flexibility and reduced time commitment as benefits of the Internet delivery mode (Boggs et al. 2014). Both less time commitment and more flexibility appear to be important benefits of brief web-based mindfulness interventions. As some pilot studies have indicated, brief web-based mindfulness interventions (7 weeks or less) have been shown to be effective, although it should be noted that some nonclinical prevention studies involved high attrition rates (see Cavanagh et al. 2013; Kvillemo et al. 2016; Mak et al. 2015, 2017).

## 22.8 Implications for Practice and Research

Overall, the evidence base on the effectiveness and acceptability of face-to-face MBCT group formats in MDD relapse prevention is promising (Fjorback et al. 2011; Hofmann et al. 2010; Khoury et al. 2013; Strauss et al. 2014). Mindfulness-based group interventions have proved to be effective as adjunctive treatment and prevention options across different conditions, populations, and primary care settings (Demarzo et al. 2015). Concerning the relapse prevention of MDD, regular home meditation practice can turn out as challenge for some patients (Crane et al. 2014). Thus, web-based interventions could be a convenient alternative for hard-to-reach populations such as young adults and males who are unlikely to attend face-to-face group courses (Jayewardene et al. 2017; Khoury et al. 2013, Khoury et al. 2015).

However, to date the evidence base for web-based delivery of MBCT is still insufficient to derive comprehensive or definitive conclusions on the helpfulness of online mindfulness interventions for different populations (Spijkerman et al. 2016). In addition, most web-based interventions report high attrition rates (e.g., Dimidjian et al. 2014; Mak et al. 2015). It must also be considered that several RCTs on MBCT involve limitations, such as heterogeneous patient groups, publication bias, and a lack of studies on long-term effects and follow-up periods (Fish et al. 2016; Gotink et al. 2015). Due to the lack of high-quality and longitudinal studies, more research is needed to derive recommendations for the use of MBCT in different populations with past or current depressive symptoms. Open questions include the clarification of mechanisms of change and the cost-effectiveness of MBCT programs in mental healthcare (Gotink et al. 2015). Therefore, determinants of the effectiveness or mechanisms of change need to be explored for different delivery modes of MBCT. There is a lack of mediation model analyses in the MBCT effectiveness research literature to identify pathways of change in mindfulness interventions (Gu et al. 2015; Shapiro et al. 2006; van der Velden et al. 2015) that needs to be addressed in future studies. Available evidence also suggests the need for research to determine effective motivational features in online self-help, such as the application of persuasive design (Kelders et al. 2012, 2013). More studies using mixed methods, including in-depth interviews and participatory approaches going beyond the exploration of the effectiveness, are required to identify important features in web-based programs (Yardley et al. 2015).

Theory-driven strategies are needed to generate meaningful contents of motivational messages based on health behavior change models and to improve adherence in web-based mindfulness interventions subsequently (Mak et al. 2015). However, poor eHealth literacy or e-awareness, low technology acceptance, and negative attitudes toward web-based self-help treatments can turn out as obstacle to use such services (Hennemann et al. 2016). To understand the conditions for an effective dissemination of MBCT, differences in delivery modes as well as contextual and individual factor need to be studied in more depth, especially before implementing innovative strategies into primary care. It should also be considered

that, outside of clinical trials, evidence-based web-based mindfulness interventions are currently inaccessible for the public in various countries (Kvillemo et al. 2016). Furthermore, it should be noted that the helpfulness of mindfulness apps remains unclear at present (Mani et al. 2015; Plaza et al. 2013). The role of system features like automated reminders with regard to the effectiveness of web-delivered mindfulness-based or acceptance-based interventions appears still unclear (Brown et al. 2016). Finally, there is an overall scarcity of RCTs on web-based mindfulness interventions in clinical populations (Fish et al. 2016). Future studies should aim to fill these research gaps, especially in terms of web-based and app-delivered MBCT formats in different populations worldwide. Fish et al. (2016) recommended a number of components to standardization of mindfulness interventions delivered by technology: They should last at least 4 weeks, contain 30 min of practice for 6 days per week, and use a different media (e.g., audio, video, and text material).

### Conclusions

In this chapter, we reviewed the evidence base on the effectiveness of both face-to-face MBCT and Internet-based MBCT for MDD relapse prevention. Research results suggest that both traditional and web-based mindfulness programs are effective in reducing symptoms of depression, although data on the role of different factors such as guidance and delivery modes is still not sufficient to derive definitive conclusions. To provide support for informed decisions, health professional can assist patients to find appropriate mindfulness programs. However, several challenges for the successful implementation of web-delivered MBCT programs remained open that need to be addressed in the future.

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# 23 Current Research on Complementary and Alternative Medicine (CAM) in the Treatment of Depression: Evidence-Based Review

Karen Pilkington

## 23.1 Introduction

Complementary and alternative medicine (CAM) is the term used to describe a range of treatments, therapies and practices that are not considered part of conventional medicine. These approaches are used alongside conventional treatment (complementary use) or, in some cases, in place of this (alternative use). While certain practices and treatments are part of medical practice in some countries, they may be classed as CAM in other countries. For example, acupuncture traditionally used in East Asian countries and widely used in standard care is viewed as CAM in Western healthcare contexts. Similarly, views on practices change over time so that herbal medicine, a part of traditional medicine in many countries, is generally considered to be CAM in Western contexts. Nevertheless, the use of CAM is widespread.

## 23.2 Use of CAM for Depression

Surveys of CAM use have consistently revealed frequent use by those with depression. In a study in the United States (USA), people meeting the criteria for major depression were significantly more likely to use alternative medicine than those without this disorder (Unützer et al. 2000). While over 50% of those with severe depression reported using CAM to treat their condition, less than 20% visited a CAM therapist, suggesting a high proportion of self-diagnosis and self-treatment (Kessler et al. 2001). In an Australian survey, participants reported using CAM less frequently than prescription medications to treat depressive symptoms (Parslow and Jorm 2004). CAM users suffered from worse mental health including more depressive and anxiety symptoms than those who took neither CAM nor prescribed medication. In Europe, 18% of people with anxiety/depression consulted a CAM provider at least once in the previous 12 months, while 12% had attended psychiatric outpatient services, and 2.5% visited both (Hansen and Kristoffersen 2016). Women and those with higher levels of education were more likely to visit CAM providers compared with men and those with lower educational achievement, but severity of depression did not predict extent of use.

Frequent use of CAM has also been identified in Asian populations although few studies have been published. A small survey of adult inpatients in Taiwan found that nearly 70% of those with depression reported using at least one form of CAM in the past 12 months (Hsu et al. 2008). Herbal medicines, spiritual healing and folk remedies were used most frequently, and mild to moderate depression was a stronger predictor of use than severe depression. As is common with CAM, only 35% had discussed CAM use with their psychiatrist. CAM use, most frequently

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involving Chinese herbal medicines, was also reported by over 40% of a nationally representative sample of older adults in Singapore (Feng et al. 2010).

Forty-five surveys of CAM use for depressive disorders have been collated (Solomon and Adams 2015). Twenty-three studies were conducted in the United States, five in Australia and at least one from each of 14 other countries. Prevalence varied significantly due to variation in study methodology, population and the definition of CAM used. A wide range of therapies are reported to be used for depression, but those that are self-directed including herbal medicine and dietary supplements were most prevalent. Other self-prescribed therapies that are sought include aromatherapy and mind-body approaches such as meditation, relaxation and yoga. Therapies provided by practitioners such as acupuncture, homeopathy, massage and Chinese medicine are also popular (Solomon and Adams 2015).

In general, typical CAM users appeared to be 40–59 years of age with medium-level education and a higher income and socioeconomic status than non-users. Comorbidity is common with greater perceived mental health needs than non-CAM users (Solomon and Adams 2015).

## 23.3 General Comments About Research on CAM for Depression

Clinical trials of various forms of CAM have been conducted, and these have been compared with trials of antidepressants (Freeman et al. 2010). Participants in CAM trials were more likely to be female and lower placebo response rates were seen compared with those in the antidepressant trials (Freeman et al. 2010). Depression severity was, however, similar. For therapies that require considerable interaction between the practitioner and patient and where placebo controls are not feasible, selection of appropriate control interventions is challenging. The fact that blinding in clinical trials is not possible for most complementary therapies is a point of particular significance when assessing an outcome such as depression which is subjective and based on self-assessment. It is also relevant because expectations of and preference for CAM may influence results of clinical trials.

## 23.4 Approach to the Literature

In the following sections, brief summaries are presented of the evidence from research on each of the therapies. The focus is on providing an overview of the 'best available evidence' which is primarily based on systematic reviews and randomised controlled trials (RCTs). These were identified through searches of the Cochrane Library including the Cochrane Database of Systematic Reviews for 'gold' standard systematic reviews, the Database of Abstracts of Reviews of Effects for quality appraised reviews and the Cochrane Central Register of Controlled Trials. In addition, searches were carried out on PubMed.

Many trials use depression as an outcome measure whether the condition being treated is psychological, physical or medical. In cases of comorbidity, it is possible that any effect on depression is indirect. For example, chronic pain may be relieved by treatment and, thus, depression due to the pain may also be relieved. Therefore, the focus in the summaries is on trials in depressive disorder as the primary condition. Those in which depression was measured as one of a whole range of outcomes, and where the main target for treatment was a medical or physical condition, were excluded.

The therapies addressed include those most frequently used or researched: acupuncture, aromatherapy and massage, dietary supplements, herbal medicines, homeopathy, hypnotherapy, meditation, relaxation, yoga and other mindful exercises.

## 23.5 Evidence on Specific Therapies

### 23.5.1 Acupuncture

Acupuncture involves the stimulation of specific points of the body usually by inserting fine needles. Points may be stimulated manually or by the application of a small electric current (electroacupuncture). The selection of points depends on a number of factors including the training and

background of the acupuncturist and the condition being treated. There are two main approaches: traditional Chinese and 'Western' or 'medical' acupuncture. In traditional Chinese medicine, acupuncture is often used in conjunction with other therapies such as herbs. The diagnostic system is different from that used in conventional medicine. Disease is considered to result from imbalance of a vital force or energy known as 'qi'. Acupuncture points are considered to lie along energy channels called meridians through which qi flows. In contrast, Western or medical acupuncture is based on conventional anatomy and physiology and often focused on pain relief.

A large number of trials have been conducted of acupuncture in depression, many of which have been carried out in China. Thirty clinical trials are included in the Cochrane systematic review (Smith et al. 2010). Acupuncture delivered in the trials varied in terms of point selection, frequency of treatments and total number of treatments administered. Most trials compared acupuncture with drug treatment, and, consequently, there was a high risk of bias due to lack of blinding. In addition, the quality of reporting was poor with limited data on adverse effects. Trials in post-stroke depression were included, in which it is possible that stimulation had an effect on stroke-related dysfunction and, thus, indirectly relieved depression.

More recently, beneficial effects were reported in a systematic review of acupuncture as an adjunctive treatment based on the standardised mean difference (SMD) in scores on the 17-item Hamilton Rating Scale for Depression (HAMD) (−2.52; 95% CI, −4.12 to −0.92; $p < 0.01$) in week 6 (Chan et al. 2015). The treatment was found to be well tolerated, but the lack of a placebo control means that the findings are not conclusive. The most recent review included 18 studies: 11 as monotherapy and 7 as adjunct treatment (Sorbero et al. 2016). As with previous reviews, interventions and comparators varied and the evidence was judged to be weak and inconclusive.

### 23.5.2 Aromatherapy and Massage

Oils extracted from various parts of plants are used in aromatherapy. These 'essential oils' may be inhaled, applied to the skin or used in combination with massage. In most cases, dilution of the oils is required prior to use. Effects of aromatherapy are thought to be due to psychological responses to the odour and the effects of inhaled volatile compounds on the limbic system (Cavanagh and Wilkinson 2002). Few trials have been carried out into the effects of essential oils in depression. One small study compared aromatherapy massage with massage alone in 32 inpatients and outpatients at a UK hospital suffering from depression and/or anxiety (Lemon 2004). The oils were selected according to physical and psychological symptoms. The control group received massage without the essential oils in an identical environment to the test group. Aromatherapy massage was found to have greater effects, but a lack of blinding may have influenced the results. Citrus fragrance by inhalation has also been investigated with positive results reported (Komori et al. 1995) as has aromatherapy massage with oils including sweet orange, geranium and basil (Okamoto et al. 2005). Both trials were small and uncontrolled so the findings can be considered preliminary at best.

The effects of inhalation aromatherapy have been compared with aromatherapy massage. Twelve RCTs were located, five involving inhaled aromatherapy and seven massage aromatherapy (Sánchez-Vidaña et al. 2017). Seven studies showed improvement in depressive symptoms, but the study populations were varied and not all were depressed. Of those studies using aromatherapy inhalation, only two involved participants who were actually depressed—one in cancer patients and one in postnatal depression—and the results were contradictory. The trials focused on aromatherapy massage involved diverse populations. This, together with the varied administration methods and outcome measures, complicated interpretation. The authors concluded that the evidence on aromatherapy massage was stronger than that for aromatherapy inhalation.

These findings suggest that it is the massage component from which those treated derive the most benefit. Four trials in depression or dysthymia were included in a systematic review of massage in depression (Coelho et al. 2008). In three trials, massage was compared with relaxation, but the evidence was judged to be inconclusive. A subsequent meta-analysis included 17 trials involving

participants with differing conditions and ages (Hou et al. 2010). Significant differences between massage and control treatments were reported. Trials were reported to be of moderate quality, but quality scores did not appear consistent with the assessment tool used. This causes some uncertainty as to the reliability of the conclusions.

### 23.5.3 Dietary Supplements

Several vitamins and minerals and the dietary supplements, inositol, tryptophan and 5-hydroxytryptophan, omega-3 fatty acids, S-adenosylmethionine (SAMe) and turmeric, have all been assessed as potential treatments in depression.

#### 23.5.3.1 Vitamins (Folate/Folic Acid/ Vitamin B9 and Vitamin D)

A Cochrane review based on three RCTs, two of which assessed folate as an adjunctive treatment, concluded that the 'limited available evidence suggests folate may have a potential role as a supplement to other treatment for depression' (Taylor et al. 2003). There was insufficient evidence to confirm whether this was true for those with normal levels and with folate deficiency. Few trials have been published subsequently, but a subsequent meta-analysis reported a non-significant difference from placebo (Sarris et al. 2016).

Vitamin D deficiency has been associated with depression, but several systematic reviews of its therapeutic use have produced mixed conclusions. The most recent review focused specifically on adjunctive use and, based on two trials, suggested there was supportive evidence for the use of vitamin D with antidepressants (Sarris et al. 2016). As with folate, it is unclear whether this is true regardless of physiological levels in the body.

#### 23.5.3.2 Minerals (Magnesium and Zinc)

While there have been investigations into a possible correlation between magnesium levels and/or intake and depressive disorders (e.g. Yary et al. 2016), only zinc has undergone a series of clinical trials for depressive disorders. Four small trials examined the effects of zinc supplementation on depressive symptoms (Lai et al. 2012). Substantial heterogeneity was present, but the evidence indicated a potential benefit of zinc supplementation either as a stand-alone or adjunctive treatment. A subsequent trial illustrated the complexity of interpreting the findings of such studies as baseline levels, intake of zinc and other nutrients and antidepressants may all influence results (Ranjbar et al. 2013). Further research is needed to fully confirm the role of both minerals.

#### 23.5.3.3 5-HT (Hydroxytryptophan)/ Tryptophan

Tryptophan, an amino acid and component of a normal diet, is converted to 5-HT in the body (Shaw et al. 2002). Tryptophan and 5-HT can cross the blood-brain barrier where conversion to the neurotransmitter, serotonin, takes place. Thus, there has been interest in a potential antidepressant effect. A large number of trials were located for a Cochrane review in 2002, but only two (64 participants) were of sufficient quality for inclusion (Shaw et al. 2002). Very little subsequent research activity has taken place, possibly because of an outbreak of eosinophilia-myalgia syndrome linked to the supplement but which was subsequently found to be due to contaminated batches of L-tryptophan.

#### 23.5.3.4 Inositol

Inositol, a naturally occurring isomer of glucose, is consumed in many foods but is also available as a dietary supplement. It is involved in cell signalling via neurotransmitters including serotonin (Taylor et al. 2004). The Cochrane review in 2004, which included four short-term trials with a total of 141 participants, did not show 'clear evidence of a therapeutic benefit'. Little research interest has been shown subsequently.

#### 23.5.3.5 Omega-3 Fatty Acids (n-3 Polyunsaturated Fatty Acids)

An increasing prevalence of depressive disorders combined with reduced dietary intake of omega-3 fatty acids suggested a possible link between the two (Appleton et al. 2015). Consequently, large numbers of trials of omega-3 fatty acids have been conducted. Twenty-six trials, of which 25 (1438 participants) were placebo controlled, were included in a Cochrane review (Appleton et al.

2015). A 'small-to-modest' benefit was shown for the supplement, but the evidence was judged to be very low quality. Additionally, the effect did not appear to be clinically significant as the difference was equivalent to 2.1 points on the Hamilton Rating Scale for Depression with a 95% confidence interval of 0.7–3.5. Thus, as with other supplements, further research was recommended to fully assess effects, both positive and negative. Other reviews have, however, provided more positive interpretations (e.g. Sarris et al. 2016).

#### 23.5.3.6 SAMe (S-Adenosylmethionine)

SAMe is an active cofactor of methylation involved in the synthesis and metabolism of neurotransmitters (Galizia et al. 2016). It is synthesised from adenosine triphosphate and the amino acid, methionine. It is in clinical use in some European countries and available as a dietary supplement in others. A Cochrane review in 2016 included eight trials of SAMe as monotherapy or as add-on therapy to SSRIs. No differences were found between SAMe and placebo or antidepressants, and based on the absence of high-quality evidence, it was not possible to draw firm conclusions as to its effectiveness.

### 23.5.4 Herbal Medicine

Various plant-based treatments have been used as part of traditional medicine on a global basis and over millennia. Several of these have been investigated for measurable effects in depression based on reported psychopharmacological actions such as inhibition of monoamine reuptake and breakdown, effects on serotonin receptors and GABAergic effects (Sarris et al. 2011). Those that have received particular attention include *Crocus sativus* (saffron), *Echium amoenum* (borage), *Hypericum perforatum* (St John's wort), *Lavandula angustifolia* (lavender), *Panax ginseng* and *Rhodiola rosea* (roseroot).

#### 23.5.4.1 Hypericum perforatum (St John's Wort)

One herb that has generated a significant amount of research attention is *Hypericum perforatum* (St John's wort). A small, herbaceous perennial found in Europe and Asia, it is widely used in Europe and prescribed in countries such as Germany. Extracts of the plant, a member of the Hypericaceae family, have been shown to contain constituents with actions relevant to depression. Reuptake of several neurotransmitters including serotonin, dopamine and gamma-aminobutyric acid (GABA) is inhibited by extracts and specifically by one constituent, hyperforin (Russo et al. 2014). However, clinical efficacy has also been reported when hyperforin is absent (Schrader 2000), and a single mechanism of action has not been determined.

Thirty-seven trials were included in a Cochrane systematic review (Linde et al. 2005). Subsequently, the inclusion criteria were adjusted resulting in the exclusion of nearly half of these trials when the review was updated 3 years later. The current version includes 29 trials involving a total of 5489 patients (Linde et al. 2008). Hypericum has been compared with placebo and standard antidepressants and shown to have modest effects over placebo and comparable effects to antidepressants with fewer adverse effects. Most trials (19) addressed mild to moderate rather severe depression, but few included long-term follow-up with a maximum duration of 12 weeks. While rigorously conducted, the review revealed marked heterogeneity between placebo-controlled trials and more favourable findings in trials from German-speaking countries. The latter was not readily explained and thus complicated the interpretation of the findings.

Subsequent systematic reviews have reported similar findings: a meta-analysis of 27 trials (3808 patients) comparing hypericum with selective serotonin reuptake inhibitors (SSRIs) found comparable response and remission rates and a lower rate of discontinuation with hypericum (Ng et al. 2017). Evidence on long-term outcomes and in severe depression was still insufficient. A systematic review including 35 studies and 6993 patients also reached similar conclusions (Apaydin et al. 2016). Systematic differences were not found in outcomes based on the extract used, and an extract containing 0.3% hypericin and 1–4% hyperforin was used in the highest number of trials. Economic evaluation indicates that it is a cost-effective option (Solomon et al.

2013). Hypericum extracts, however, have an effect on the cytochrome P450 system, inducing metabolism and, hence, reducing the plasma levels of a wide range of clinically important drugs (Henderson et al. 2002). Concerns regarding potential interactions have affected recommendations on use in some countries.

#### 23.5.4.2 Crocus sativus (Saffron)

Saffron, the dried stigma from *Crocus sativus*, has been used in many cultures as a spice and medicine. Many medicinal properties including serotonergic and hypothalamus-pituitary-adrenal (HPA) axis-modulating effects have been observed. The dried stigmas have been used in clinical trials as have a less expensive product, the dried petals. Lopresti and Drummond (2014) identified six trials, two placebo-controlled and four versus antidepressants, while the meta-analysis by Hausenblas et al. (2013) included five trials. Both came to positive conclusions: 'initial support for the use of saffron for the treatment of mild-to-moderate depression' (Lopresti and Drummond 2014) and 'saffron may improve the symptoms and the effects of depression' (Hausenblas et al. 2013). A series of clinical trials has followed all conducted by research teams in Iran and investigating different patient populations. The small sample size of many has been identified as a limitation with recommendations for large, well-powered trials to confirm results.

#### 23.5.4.3 Echium amoenum (Borage)

Dried flowers from this plant are used in Iran to make a tea for use as an anxiolytic and mood enhancer (Sayyah et al. 2006). A preliminary, randomised, placebo-controlled trial (35 patients with mild to moderate depression) suggested some beneficial effects after 4 weeks in reducing depression symptoms. However, the effects were not maintained at 6 weeks. Further studies confirming these findings are not available.

#### 23.5.4.4 Lavandula angustifolia Miller (Lavender)

Lavender is widely promoted for use in insomnia, but other uses have been investigated. In particular, there had been interest in lavender used orally for major depression and mixed anxiety and depression. To date there has only been limited research. A small, preliminary RCT found tincture prepared from lavender flowers to be less effective than imipramine in the treatment of mild to moderate depression although patients in both groups improved from baseline (Akhondzadeh et al. 2003). A combination of imipramine and tincture was more effective than imipramine alone ($P < 0.0001$) possibly due to a synergistic effect or a result of the lack of blinding. Lavender oil capsules have been tested more recently: eight patients with major depressive disorder and symptoms of anxiety, insomnia and psychomotor agitation were included in a case series (Fißler and Quante 2014). Six cases responded to a combination of lavender and antidepressant. An oral form of lavender was also tested against placebo in mixed anxiety and depression (Kasper et al. 2016). The trial recruited 318 adult outpatients based on ICD-10 criteria. Significantly greater reductions in anxiety and depression were recorded with lavender. Further replication is needed to confirm these findings.

#### 23.5.4.5 Panax ginseng (Asian, Chinese, Korean Ginseng)

Ginseng, traditionally used in Asia for a range of medical conditions, was tested as an adjuvant treatment for women with residual depression symptoms. After 8 weeks, reduced depressive symptoms were reported, but, as no control group was included, it is not clear whether the improvement was due solely to the herbal treatment (Jeong et al. 2015).

#### 23.5.4.6 Rhodiola rosea (Roseroot or Goldenroot)

Rhodiola has traditionally been used in Russia and Scandinavia for various indications including depression and fatigue (Dwyer et al. 2011). Two RCTs investigated the effects of rhodiola in depression. Both were three-arm trials: one compared two different doses of a standardised extract of rhodiola rhizome against placebo (Darbinyan et al. 2007), and the other compared rhodiola with sertraline and placebo (Mao et al. 2015). According to the first trial, rhodiola performed significantly better than placebo in reduc-

ing mild to moderate depression after 6 weeks of treatment. Improvements in insomnia, emotional instability and somatisation were also reported. In contrast, the second trial demonstrated modest but non-significant reductions in depression scores with no significant differences between groups. Both trials were blinded, but different antidepressants were used, and the second trial was not powered to detect small differences between groups which may explain the contrasting results. Less adverse effects were reported with rhodiola leading the researchers to conclude that, though less effective than sertraline, rhodiola may provide a better risk-to-benefit ratio in mild to moderate depression.

#### 23.5.4.7 Curcuma longa (Turmeric)

Turmeric, a member of the ginger family, is a commonly used spice containing curcuminoids which are yellow chemicals used as food colourants. Used in Indian Ayurvedic medicine for various health conditions, curcumin had been reported to increase serotonin and dopamine levels while inhibiting monoamine oxidase enzymes (Kulkarni et al. 2008). Several clinical trials followed which were collated in a systematic review (Al-Karawi 2016). Trials originated from several countries and treatment was for a maximum of 8 weeks. Reduction in depression was seen in comparison with placebo. Statistically significant differences between curcumin and placebo were also reported in the second meta-analysis (Ng et al. 2017). The clinical significance is not entirely clear.

#### 23.5.4.8 Chinese Herbal Medicine

The 'herbs' used in traditional medical systems in Asia, such as Chinese herbal medicine, include animal and mineral substances in additional to those sourced from plants. These are usually used in various combinations (or formulae) which are prescribed on an individual basis based on diagnostic 'patterns'. Certain formulae have been promoted at being particularly suitable for depression, one of which Xiao Yao San and a modification of this, Free and Easy Wanderer Plus. An overview of the evidence on Chinese medicine for depression found that most clinical research had focused on these formulae (Butler and Pilkington 2013). Positive results were reported including no significant differences compared with medication, greater effect than medication or placebo and reduction in adverse event rates when used as additive therapy. Limitations in reporting and in methodology, and differing formulae and control interventions, prevented any reliable conclusions being presented. A subsequent review attempted to assess which herbal formulae were most frequently used for the 'patterns' matching a diagnosis of depression (Yeung et al. 2015). This confirmed that Xiaoyao decoction and Chaihu Shugan were the two formulae most frequently used, while Bai Shao (*Paeonia lactiflora* Pall.) and Chai Hu (*Bupleurum chinense* DC.) were the most commonly used individual herbs. The rationale underlying herb selection was seldom provided, and comparative efficacy could not be assessed due to the small number of good-quality studies.

### 23.5.5 Homeopathy

Homeopathy is a system of medicine based on the principle of *similia similibus curentur* or 'let like be treated by like'. Homeopathic remedies are prepared from various substances—animal, mineral and plant derived—in extremely dilute (ultramolecular) solutions. Interventions investigated in clinical trials of homeopathy may involve the whole system including a consultation with prescription of individualised remedies or involve only the remedies. Few RCTs have been carried out on homeopathy or homeopathic remedies for depressive disorders (Pilkington et al. 2005). While uncontrolled and observational studies have reported positive results including high levels of patient satisfaction and response, these results have not been replicated in rigorous RCTs. One trial in Brazil involving 91 outpatients with DSM-IV diagnosis of moderate to severe depression reported non-inferiority of individualised homeopathy compared with fluoxetine (Adler et al. 2011). Further investigation of these reported results in Europe was not successful. The aim was to assess the specific clinical benefit of the homeopathic consultation in addition to that of homeopathic remedies in depression

(Adler et al. 2013). Recruitment problems were encountered with only 44 from 228 planned patients randomised. Thus the trial was underpowered, and no consistent or clinically relevant results were observed for comparisons between homeopathic remedies and placebo or between homeopathic and conventional consultations.

### 23.5.6 Hypnosis/Hypnotherapy

Hypnosis has received relatively limited attention in terms of research on its effects in depressive disorders. A review of the research included six trials (258 participants) (Shih et al. 2009). The control conditions were not reported and all trials were categorised as poor quality. Considerable heterogeneity was apparent in the participants (cancer patients, postnatal women, students and volunteers) and interventions. Thus, the authors' conclusion that hypnosis 'appears to be a viable nonpharmacologic intervention for depression' appears to be premature.

### 23.5.7 Meditation and Mindfulness

Meditation refers to practices that involve training and regulating the attention and encompasses a range of practices including concentrative methods, transcendental meditation and mindfulness techniques. While little research exists on practices such as transcendental meditation, there has been considerable clinical and research interest in mindfulness techniques. This is confirmed by a review in 2015 which identified 18 studies relating to 7 distinct techniques of which mindfulness-based cognitive therapy (MBCT) comprised the largest proportion of studies (Jain et al. 2015). In fact, the other studies included in this review represented meditation as part of practices such as yoga and tai chi, and only one trial was of meditation per se. Mindfulness when combined with cognitive behavioural therapy as MBCT has been the subject of a large number of rigorous RCTs prompted by a trial in 2000 reporting successful prevention of recurrence/relapse (Teasdale et al. 2000). It is currently seen as one of the 'third wave' cognitive and behavioural therapies widely used in the treatment of psychological problems (Churchill et al. 2013). Evidence of its effects in acute depressive episodes is still required.

### 23.5.8 Relaxation Therapies

Progressive muscle relaxation, relaxation imagery and autogenic training are all forms of relaxation therapy. Fifteen trials involving people diagnosed with depression or symptoms of depression were analysed and collated for a Cochrane review (Jorm et al. 2008). These techniques were found to be more effective than no or minimal treatment, but only when symptoms were self-rated: effects based on clinician ratings were less conclusive.

### 23.5.9 Yoga

Yoga, a traditional Indian practice comprising spiritual, moral and physical practices, became popular in the West in the 1960s. Yoga, as practised in the West, generally involves the asanas (postures and stretches), breathing techniques and meditation. The practice is intended to improve physical aspects such as flexibility, strength and balance while also helping to focus the mind. Effects on the autonomic nervous system and relaxation response are proposed as the main mechanisms of action (Riley 2004). The clinical research on yoga for depression was first reviewed in 2005, at which point five RCTs ($n$ = 183) were identified (Pilkington et al. 2005). Further research was recommended and, by 2013, 12 RCTs were located ($n$ = 619) (Cramer et al. 2013). These included patients with depressive disorders and those with raised levels of depression. Moderate evidence was found for short-term effects of yoga compared to usual care but limited evidence compared to relaxation and aerobic exercise. Data on long-term and adverse effects were insufficient for analysis although a review of safety indicates that exercise is similar in this respect to usual care and exercise (Cramer et al. 2015). When trials were restricted to those diagnosed with major depres-

sive disorder, no differences were found in the short term between yoga and aerobic exercise and antidepressants (Cramer et al. 2017). The risk of bias was unclear for the majority of trials, but there was some evidence of effects beyond placebo and comparable to standard treatments.

### 23.5.10 Qigong and Tai Chi

Other mindful forms of exercise that have generated interest are qigong and tai chi. A series of systematic reviews have been published on each, but conclusions vary, possibly due to differences in inclusion criteria. For example, one review concluded qigong appeared beneficial in reducing depressive symptom severity (Liu et al. 2015), while another reported inconclusive results (Oh et al. 2013). Both included two trials in depressive disorder.

A summary of key results from all the relevant Cochrane reviews is presented in Table 23.1.

**Table 23.1** Cochrane reviews of complementary and alternative (CAM) for depression

| Author, year | Therapy | No. trials (no. patients) | Main comparisons | Results of meta-analysis (SMD [95%CI] unless stated) |
|---|---|---|---|---|
| Smith 2010 | Acupuncture | 1–3 (41–175) | Manual vs<br>• Wait list control<br>• Sham acupuncture<br>• Non-specific acupuncture<br>• Amitriptyline<br>• SSRI (monotherapy)<br>• SSRI (add-on) | Non-significant (NS) differences except for wait list control −0.73 [−1.18, –0.29]<br>SSRIs (add-on) −1.06 [−1.69, −0.43] |
| | | 1–6 (42–853) | Electroacupuncture vs<br>• Amitriptyline<br>• SSRIs (monotherapy)<br>• SSRI (add-on) | NS except for SSRIs (add on) −0.70 [−1.32, −0.07] |
| | | 1 (26) | Laser acupuncture vs sham | MD −7.3 [−12.68, −1.92] |
| Taylor 2003 | Folate | 2 (151) | Placebo (add-on) | MD −2.65 [−0.38, −4.93] |
| | | 1 (96) | Trazodone | – |
| Taylor 2004 | Inositol | 1 (28) | Placebo (monotherapy) | −0.71 [−1.48, 0.06] |
| | | 3 (85) | Placebo (add-on) | 0.12 [−0.31, 0.55] |
| Appleton 2015 | Omega-3 fatty acids | 25 (1373) | Placebo | −0.30 [−0.10, −0.50] |
| | | 1 (40) | Fluoxetine | – |
| Joyce 2015 | Reiki | 2 (84) | Wait list control | – |
| | | 1 (40) | Relaxation | – |
| Jorm 2008 | Relaxation | 5 (136) | Wait list, minimal or no treatment | −0.59 [−0.94, −0.24] |
| | | 9 (286) | Psychological (CBT) | 0.38 [0.14, 0.62] |
| Galizia 2016 | S-Adenosylmethionine | 2 (142) | Placebo (monotherapy) | −0.54 [−1.54, 0.46] |
| | | 4 (619) | Imipramine | −0.04 [−0.34, 0.27] |
| | | 1 (129) | Escitalopram | MD 0.12 [−2.75, 2.99] |
| | | 1 (73) | Placebo (add-on) | MD −3.90 [−6.93, −0.87] |
| Linde 2008 | St John's wort | 18 (3064) | Placebo | RR 1.48 [1.23, 1.77] |
| | | 17 (2810) | Antidepressants | RR 1.01 [0.93, 1.09] |
| Shaw 2002 | Tryptophan and 5-hydroxytryptophan | 2 (46) | Placebo | OR 4.10 [1.28, 13.15] |

## Conclusions

CAM use for depression is widespread and involves a range of treatments, practices and therapies. These have been tested in clinical trials, but results in many cases have to be interpreted with caution due to lack of blinding. This is particularly relevant in a condition such as depressive disorder which is assessed based on self-report of subjective measures. Many more studies have been conducted in which depression is one of the measured outcomes than in diagnosed depressive disorder. Therapies that have received most research attention include acupuncture, Chinese herbal medicine, hypericum (St John's wort), omega-3 supplements, mindfulness, relaxation techniques and exercise-based approaches. For many therapies, few RCTs have been performed and those that have tend to be relatively small and, therefore, inconclusive. Systematic review of the research further reveals the limitations of studies including short timescales and a lack of systematically collated data on adverse effects. Based on this review, the most promising evidence appears to be for hypericum (but concerns with adverse effects and interactions), omega-3, mindfulness, relaxation and yoga. Even where there is a strong evidence base, there may be factors preventing wider adoption for clinical use. This includes potential adverse effects and interactions with herbs and other supplements and a lack of consensus on appropriate practice or components of practice of, for example, yoga. Effects may also be relatively small. Nevertheless, CAM is sought by those with depressive disorders, and a need for decision-making based on reliable information on effectiveness and safety implies that further research is needed. This is particularly relevant as it appears that there is a significant prevalence of self-diagnosis and self-treatment. Several therapies are identified as worthy of further investigation, but future research needs to take account of patient preferences and expectations. It will also be important to consider whether the primary focus should be on comparative effectiveness or safety and whether the complete intervention should be tested or efforts made to 'unravel' the most effective component of these complex interventions.

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# Erratum to: Ketamine: A Promising Rapid-Acting Antidepressant

Samuel T. Wilkinson, Robert B. Ostroff, Rachel B. Katz, and John H. Krystal

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