REVIEW ARTICLE

Mood Disorders

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UNLABELED USE OF PRODUCTS/INVESTIGATIONAL USE DISCLOSURE:
Drs Rakofsky and Rapaport discuss the unlabeled/investigational use of buspirone, pramipexole, and thyroid hormone as adjuncts to an antidepressant in the treatment of major depression and ketamine for treatment-resistant patients who are depressed and suicidal.

ABSTRACT

PURPOSE OF REVIEW: **This article discusses the prevalence of the major mood disorders (major depressive disorder and bipolar disorder) in the community and within neurologic settings, articulates the steps taken to make a diagnosis of major depressive disorder or bipolar disorder, and reviews old and newer treatment options with proven efficacy for the treatment of these two conditions.**

RECENT FINDINGS: **New medications are available as treatment options for major depressive disorder and bipolar disorder, such as intranasal and IV ketamine, and somatic treatments, such as deep brain stimulation and vagal nerve stimulators, are being used to target treatment-resistant depression.**

SUMMARY: **Mood disorders are common in neurologic settings. They are disabling and increase morbidity and mortality. Clinicians should have a high index of suspicion if they suspect their patients seem more distressed or incapacitated than would be warranted by their neurologic disorders. If a patient does have a mood disorder, validating the patient's experience, initiating treatment, and, if necessary, referring the patient to a primary care physician or psychiatrist are appropriate steps.**

INTRODUCTION

Mood disorders are a group of psychiatric illnesses that can simultaneously affect one's emotions, energy, and motivation. The two most prominent examples are major depressive disorder and bipolar disorder, which are the focus of this article. Major depressive disorder is a psychiatric illness that has a lifetime prevalence of 16%,[1] while bipolar disorder has a lifetime prevalence of close to 5%, inclusive of all patients on the bipolar disorder spectrum.[2] Both conditions are associated with poor quality of life[3,4] and increased mortality,[5,6] and major depressive disorder is the second leading cause of disability in the world.[7] Within primary care settings, 13% to 17% of patients screen positive for symptoms of depression, while 33% of patients seen in a neurologic outpatient setting screen positive for depressive symptoms.[8] Thus, neurologists are likely to encounter patients with major depressive disorder or bipolar disorder and should be familiar with these diagnoses, their treatments, and the signs and symptoms that overlap neurologic illnesses.

EPIDEMIOLOGY AND COURSE OF ILLNESS

The median age of onset for major depressive disorder is 32 years of age.[9] The average duration of a recurrent episode is about 20 weeks.[10] Sixty percent of

patients will have a recurrence at some point after their first episode, while a 74% chance of a recurrence exists after a second episode and a 90% chance after a third episode (CASE 7-1).[11,12] Women are 1.7 times more likely to develop an episode of major depressive disorder than men, and the difference in prevalence is not influenced by socioeconomic status or country of origin. This suggests that hormonal and developmental differences in brain circuitry may contribute more to this ratio than socioeconomic disparities between the sexes.[13]

Major depressive disorder has a significant genetic component associated with its etiology. Genetic studies have revealed a heritability of 37% and a 2.8 times increased risk for developing this illness among first-degree relatives of probands with major depressive disorder.[14] Some individuals will have a seasonal onset of depressive episodes occurring every winter or every spring. For others, episodes are either triggered by stress or occur spontaneously independent of any physical or psychological stressor. Studies demonstrate that first-onset episodes are more likely to be related to a severe life event than recurrences.[15] Consistent with the data demonstrating that major depressive disorder is more prevalent in women than men are data linking changes in reproductive hormone levels and mood disorders: hormonal fluctuations are thought to be key to the pathogenesis of the premenstrual worsening of depression symptoms reported by some patients and the etiologies of postpartum onset of depression and perimenopause/postmenopause-onset depression.[13]

Bipolar disorder consists of several different types of mood episodes (depression, mania, hypomania, mixed episodes), which are described in more detail later in this article. Bipolar I disorder is a diagnosis reserved for those who have had manic episodes, while bipolar II disorder is used for those who have never had a manic episode but have had hypomanic episodes and at least one major depressive episode.[16] The mean age of onset is 18.2 years for bipolar I disorder and 20.3 years for those with bipolar II disorder.[2] Depressive episodes treated naturalistically (in a clinic setting, not as part of a clinical trial) have a median duration of 15 weeks, while the median duration is 7 weeks for manic episodes and 3 weeks for hypomania.[17] Over the course of their illness, patients will spend more time depressed than in elevated mood states.[18,19] Among patients who have recovered from their first manic episode, 40% will have a recurrence into depression or mania within the subsequent 2 years.[20] In contrast to major depressive disorder, in bipolar I disorder, women are just as likely to be affected as men, whereas in bipolar II disorder, women are twice as likely to be affected.[21]

Bipolar disorder is considered to be highly genetic, with a heritability of 89%.[22] Among first-degree relatives of a bipolar proband, the risk of having bipolar disorder is 8.7%.[23] Twin studies reveal monozygotic concordance rates of 40% compared to dizygotic concordance rates of 5.4%.[22] This suggests that while genetics play a large role in determining illness onset, environmental factors exist as well. Unlike major depressive disorder, bipolar disorder episodes, in particular mania and hypomania, can be triggered by events that impact circadian rhythms (eg, sleep deprivation, seasonal change, time zone travel) and exposure to rewarding stimuli (eg, falling in love, starting a creative project, a period of personal growth).[24]

COMORBIDITY

Nearly 75% of people with a lifetime history of major depressive disorder will have another psychiatric illness at some point in their lives.[1] Anxiety disorders

KEY POINTS

- Within primary care settings, 13% to 17% of patients screen positive for symptoms of depression, while 33% of patients seen in a neurologic outpatient setting screen positive for depressive symptoms.
- Genetic studies have revealed a heritability of 37% and a 2.8 times increased risk for developing major depressive disorder among first-degree relatives of probands with major depressive disorder.
- Among patients who have recovered from their first manic episode, 40% will have a recurrence into depression or mania within the subsequent 2 years.
- Nearly 75% of people with a lifetime history of major depressive disorder will have another psychiatric illness at some point in their lives.

are most prevalent, with nearly 60% of patients with depression meeting criteria for one of these conditions, while substance-use disorders are seen in as many 24% of patients with major depressive disorder.[1] Major depressive disorder is also highly comorbid with other medical conditions, including obesity, hypertension, diabetes mellitus, rheumatologic disorders, immune-mediated dermatologic disorders, and cardiovascular disease.[25] Depression is frequently observed in patients with neurologic disorders. The prevalence rates of comorbid depression are 30% to 50% for patients with Alzheimer disease, 20% to 72% for patients with stroke, 40% to 50% for patients with Parkinson disease (CASE 7-1), 19% to 54% for patients with multiple sclerosis (MS),[26] and 7% to 63% for patients with obstructive sleep apnea.[27]

Comorbidity is also very common in bipolar disorder. Approximately 75% of patients with bipolar disorder are diagnosed with an anxiety disorder at one time

CASE 7-1

A 68-year-old man with a 2-year history of Parkinson disease presented with symptoms of depression. He had experienced his first episode of depression in his early thirties after losing a job. This episode resolved after several months without any treatment. A second episode occurred in his early forties after his father passed away, with this episode lasting several months before the patient sought treatment from a psychiatrist, who started him on the antidepressant fluoxetine, titrating the dose to 40 mg/d. Within 6 weeks, his symptoms fully resolved. He stayed on fluoxetine for a full year without any additional depressive symptoms; at that time, he decided to taper off the medicine. Since being diagnosed with Parkinson disease, his motor symptoms had been well controlled with carbidopa/levodopa 25 mg/100 mg 3 times a day.

The patient stated that over the past month, he had been waking up feeling down in the morning. When he took his Parkinson medicine, it helped his mood a bit, but he still felt lower than normal. He was sleeping much later into the morning and was taking naps, both of which were unusual for him. He no longer was interested in spending time with his children and grandchildren, something he had always looked forward to in the past. He denied suicidal ideation, but he felt worthless and believed that he was no good to anyone. His wife reported that he had recently become forgetful. When it was explained to the patient that he might be experiencing a recurrence of depression, the patient stated that this felt different than the depression he experienced earlier in his life.

Neurologic examination showed a depressed affect. Examination was otherwise unremarkable other than his baseline signs of mild parkinsonism. Laboratory evaluation, including thyroid function tests, was normal. Brain MRI revealed mild nonspecific white matter hyperintensities. Neuropsychological assessment revealed slight deficits in executive function, memory, and attention. However, the report also indicated that the patient often said, "I can't do this" after being given instructions on a task. When gently pushed to continue, he performed as instructed.

in their life; 42.3% are diagnosed with a substance-use disorder and 62.8% with an impulse control disorder,[2] while approximately 60% are diagnosed with a personality disorder.[28] Medical illnesses, including asthma, type 2 diabetes mellitus, hypercholesterolemia, epilepsy, kidney disease, and thyroid disease, are up to 6 times more common among those with bipolar disorder than among healthy controls and those with major depressive disorder.[29] Neurologic illnesses among a sample of 1720 British patients with bipolar disorder included epilepsy (3.4%), dementia (2%), migraine (23.7%), MS (0.5%), Parkinson disease (0.6%), and stroke (2.5%).[29]

PATHOPHYSIOLOGY

Over many decades, researchers have developed several theories to explain the biological causes of major depressive disorder. It is now thought that our current

He was referred to a psychiatrist, who started him on bupropion XL 150 mg/d for 4 days, which was then increased to 300 mg/d. This led to some improvement in symptoms over the subsequent 4 weeks, but his depressed mood and excessive sleeping continued. The psychiatrist then increased the dose of bupropion XL to 450 mg/d, and within a month, the patient's mood and cognitive symptoms resolved completely. The psychiatrist convinced the patient to stay on the medicine for the long term to prevent recurrences.

COMMENT

This case exemplifies the diagnostic complexity faced by physicians when treating patients with neurologic illness and symptoms of depression. This patient had a history of major depressive disorder and had depressive episodes that predated the onset of his Parkinson disease by several decades. This patient had never had a manic or hypomanic episode, which rules out bipolar disorder as a cause of the depressive episodes. As is often the case, the patient had more than one episode of depression over the course of his life. It is possible that the onset of his Parkinson disease brought on a recurrence of depression, either from the psychological stress associated with it or from its effect on brain circuitry. This patient reported that his current episode of depression seemed different than his earlier episodes. Given this different presentation, his cognitive symptoms, and his comorbid parkinsonism, the neurologist was justified in ordering an MRI. The patient's performance, and, in particular, his tendency to avoid exerting full effort during the neuropsychological testing are typical for depressed patients.

Although fluoxetine, a selective serotonin reuptake inhibitor (SSRI), was helpful for the patient's depression in the past, now that the patient had Parkinson disease, the use of bupropion, a medicine that affects central dopamine release, was justified. The psychiatrist's recommendation that the patient take antidepressants for the duration of his life was made to help the patient prevent future depressive episodes. The patient had already had three depressive episodes and was likely to have more down the road.

KEY POINT

- It is now thought that our current construct of major depressive disorder encompasses a complex heterogeneous syndrome in which multiple different defects can lead to a cascade of events that cause the development of a depressive endophenotype.

construct of major depressive disorder encompasses a complex heterogeneous syndrome in which multiple different defects can lead to a cascade of events that cause the development of a depressive endophenotype. Investigations into the etiologies of major depressive disorder include studies at the genetic, epigenetic, cellular, synaptic, neurochemical, circuit, and systems level.

The monoamine hypothesis of depression was one of the first biologically based theories of the etiology of depression. It was developed based on the early observations that antidepressant medications increased synaptic levels of monoamines and that acute depletion of monoamines led to a depressivelike state in both human and nonhuman primate models of depression. The theory suggested that a reduction of monoamines in the central nervous system was the underlying cause of the illness.[30] However, this idea was challenged following studies that depleted brain serotonin and norepinephrine levels in healthy subjects and in those with major depressive disorder. Only the latter developed depressive symptoms, suggesting that acute monoamine perturbations were only part of the story of depression.[31] Postmortem and positron emission tomography (PET) imaging studies suggest increased levels of 5-hydroxytryptamine 1A (5-HT_{1A}) autoreceptors in the dorsal raphe neurons may play a role in the development of major depressive disorder by lowering the tonic level of serotonin within synapses.[32]

The neurotrophic hypothesis of the etiology of major depressive disorder represents a second line of investigation. Proponents postulate that depression results from a reduction in neurotrophins (eg, brain-derived neurotrophic factor [BDNF]) that leads to neuronal atrophy, loss of glia, decreased hippocampal neurogenesis, and impaired brain circuitry. Antidepressants have been shown to both increase BDNF levels and reverse the atrophy.[33] In line with the neurotrophic hypothesis, subanesthetic doses of ketamine rapidly reduce symptoms of depression and, within the same time frame, increase synaptogenesis by increasing dendritic spine function and number in the prefrontal cortex.[33] This cascade of intracellular signaling is believed to be initiated by ketamine's blockade of the *N*-methyl-D-aspartate (NMDA) receptor on inhibitory γ-aminobutyric acid–mediated (GABA-ergic) interneurons.[34]

Neuroinflammation has been implicated as a cause of major depressive disorder in a subset of patients.[35] A shift in the balance of proinflammatory and anti-inflammatory cytokines toward the former can have a number of central nervous system effects: (1) it can divert tryptophan metabolism away from serotonin production and toward the production of excitotoxic chemicals, such as quinolinic acid; (2) it may reduce glucocorticoid receptor sensitivity, leading to chronic cortisol release and hippocampal damage; and (3) it can create a greater number of reactive oxidative species and cell death in patients who may already have decreases in antioxidant capacity.[35,36]

These theories and others not discussed here are a reflection of the biological heterogeneity that is believed to underlie major depressive disorder. Many of these same theories have been used to explain the pathophysiology of bipolar disorder, including neuroinflammation,[37] reduced antioxidant capacity,[38] and the neurotrophic hypothesis.[39] One theory unique to bipolar disorder relates mood episode recurrences to desynchronized circadian rhythms and points to genetic polymorphisms on genes that affect the circadian timing system (eg, circadian locomotor output cycles kaput [*CLOCK*], glycogen synthase kinase 3 beta [*GSK3B*]); delays in melatonin secretion among people with bipolar

disorder; an inherent less-than-24-hour free-running circadian rhythm; and the ability of lithium and valproate, first-line treatments for bipolar disorder, to influence the rhythmic expression of circadian proteins and the rhythmic function of molecular clocks.[40]

DIAGNOSIS

The diagnostic criteria for major depressive disorder (TABLE 7-1) and the manic (TABLE 7-2) and hypomanic (TABLE 7-3) episodes of bipolar disorder can be found in the *Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition* (*DSM-5*).[16] The criteria for a major depressive episode are the same in bipolar disorder and major depressive disorder. Several symptoms must be present and other conditions must be ruled out to make the diagnosis. For major depressive

DSM-5 Diagnostic Criteria for Major Depressive Disorder[a]

TABLE 7-1

A Five (or more) of the following symptoms have been present during the same 2-week period and represent a change from previous functioning; at least one of the symptoms is either (1) depressed mood or (2) loss of interest or pleasure.

Note: Do not include symptoms that are clearly attributable to another medical condition.

1. Depressed mood most of the day, nearly every day, as indicated by either subjective report (eg, feels sad, empty, hopeless) or observation made by others (eg, appears tearful). (**Note:** In children and adolescents, can be irritable mood.)
2. Markedly diminished interest or pleasure in all, or almost all, activities most of the day, nearly every day (as indicated by either subjective account or observation).
3. Significant weight loss when not dieting or weight gain (eg, a change of more than 5% of body weight in a month), or decrease or increase in appetite nearly every day.
4. Insomnia or hypersomnia nearly every day.
5. Psychomotor agitation or retardation nearly every day (observable by others, not merely subjective feelings of restlessness or being slowed down).
6. Fatigue or loss of energy nearly every day.
7. Feelings of worthlessness or excessive or inappropriate guilt (which may be delusional) nearly every day (not merely self-reproach or guilt about being sick).
8. Diminished ability to think or concentrate, or indecisiveness, nearly every day (either by subjective account or as observed by others).
9. Recurrent thoughts of death (not just fear of dying), recurrent suicidal ideation without a specific plan, or a suicide attempt or a specific plan for committing suicide.

B The symptoms cause clinically significant distress or impairment in social, occupational, or other important areas of functioning.

C The episode is not attributable to the physiologic effects of a substance or to another medical condition.

D The occurrence of the major depressive episode is not better explained by schizoaffective disorder, schizophrenia, schizophreniform disorder, delusional disorder, or other specified and unspecified schizophrenia spectrum and other psychotic disorders.

E There has never been a manic episode or a hypomanic episode.

DSM-5 = Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition.

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disorder, the diagnostic criteria are nearly identical in *DSM-5* and the last iteration of the *DSM*, the *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, Text Revision* (*DSM-IV-TR*).[12] One refinement of the criteria in *DSM-5* is the elimination of an arbitrary rule that prevented clinicians from diagnosing major depressive disorder in an individual who presented with symptoms within the first 2 months after the death of a loved one.[41] For bipolar disorder manic and hypomanic episodes, the *DSM-5* now requires that a person must have both a mood state change (eg elevated, euphoric, irritable) and an increase in energy, whereas in earlier iterations of the *DSM*, only the mood state change was required.[16]

Increasingly, primary care, obstetric/gynecologic, and psychiatric practices across the country are using depression-screening instruments, including the Patient Health Questionnaire-2,[42] the Patient Health Questionnaire-9,[43] and the Quick Inventory of Depressive Symptomatology,[44] as recommended by the US Preventive Services Task Force.[45] This practice helps identify patients most likely to have major depressive disorder but on its own is insufficient to diagnose the illness. Similarly, some physicians use the Mood Disorders Questionnaire[46] to uncover prior histories of mania or hypomania, a requisite to make a bipolar disorder diagnosis. However, because of its sensitivity and specificity, full

TABLE 7-2 ***DSM-5* Diagnostic Criteria for Manic Episode**[a]

A **A distinct period of abnormally and persistently elevated, expansive, or irritable mood and abnormally and persistently increased goal-directed activity or energy, lasting at least 1 week and present most of the day, nearly every day (or any duration if hospitalization is necessary)**

B **During the period of mood disturbance and increased energy or activity, three (or more) of the following symptoms (four if the mood is only irritable) are present to a significant degree and represent a noticeable change from usual behavior:**

1. Inflated self-esteem or grandiosity
2. Decreased need for sleep (eg, feels rested after only 3 hours of sleep)
3. More talkative than usual or pressure to keep talking
4. Flight of ideas or subjective experience that thoughts are racing
5. Distractibility (ie, attention too easily drawn to unimportant or irrelevant external stimuli), as reported or observed
6. Increase in goal-directed activity (either socially, at work or school, or sexually) or psychomotor agitation (ie, purposeless non-goal-directed activity)
7. Excessive involvement in activities that have a high potential for painful consequences (eg, engaging in unrestrained buying sprees, sexual indiscretions, or foolish business investments)

C **The mood disturbance is sufficiently severe to cause marked impairment in social or occupational functioning or to necessitate hospitalization to prevent harm to self or others, or there are psychotic features**

D **The episode is not attributable to the physiologic effects of a substance (eg, a drug of abuse, a medication, other treatment) or another medical condition**

DSM-5 = Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition.

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diagnostic interviews are required to avoid false negatives or false positives, limiting its usefulness for psychiatrists.[47] A few of the major depressive disorder and mania/hypomania symptoms are discussed here since they may occur as part of neurologic illnesses and may confound the diagnosis of major depressive disorder or bipolar disorder. Suicide is discussed because of its relevance to patient safety.

Sleep Changes

Patients with major depressive disorder often report insomnia or hypersomnia. Usually, the insomnia is characterized by problems falling asleep, middle of the night awakenings, or early morning awakenings. Hypersomnia is defined as an increase in total sleep time of 2 or more hours as compared to one's baseline. Polysomnographic studies of patients with major depressive disorder revealed decreased sleep efficiency, reduced slow-wave sleep, and increased rapid eye movement (REM) pressure.[48] All these sleep abnormalities will resolve with effective treatment of depression. However, polysomnography is only ordered in

DSM-5 Diagnostic Criteria for Hypomanic Episode[a] TABLE 7-3

A **A distinct period of abnormally and persistently elevated, expansive, or irritable mood and abnormally and persistently increased activity or energy, lasting at least 4 consecutive days and present most of the day, nearly every day.**

B **During the period of mood disturbance and increased energy and activity, three (or more) of the following symptoms (four if the mood is only irritable) have persisted, represent a noticeable change from usual behavior, and have been present to a significant degree:**

1. Inflated self-esteem or grandiosity
2. Decreased need for sleep (eg, feels rested after only 3 hours of sleep)
3. More talkative than usual or pressure to keep talking
4. Flight of ideas or subjective experience that thoughts are racing
5. Distractibility (ie, attention too easily drawn to unimportant or irrelevant external stimuli), as reported or observed
6. Increase in goal-directed activity (either socially, at work or school, or sexually) or psychomotor agitation
7. Excessive involvement in activities that have a high potential for painful consequences (eg, engaging in unrestrained buying sprees, sexual indiscretions, or foolish business investments)

C **The episode is associated with an unequivocal change in functioning that is uncharacteristic of the individual when not symptomatic.**

D **The disturbance in mood and the change in functioning are observable by others.**

E **The episode is not severe enough to cause marked impairment in social or occupational functioning or to necessitate hospitalization. If there are psychotic features, the episode is, by definition, manic.**

F **The episode is not attributable to the physiologic effects of a substance (eg, a drug of abuse, a medication, other treatment).**

DSM-5 = Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition.

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cases in which the physician suspects that a primary sleep disorder may be present in addition to major depressive disorder. During mania/hypomania, reduced sleep can be both a trigger and a symptom of the mood episode. Similar to patients with major depressive disorder, polysomnographic studies of both manic and depressed patients with bipolar disorder reveal reduced REM latency, increased REM density, and low sleep efficiency.[40] Euthymic patients with bipolar disorder continue to demonstrate increased REM density and reduced sleep efficiency, along with greater night-to-night variability of sleep patterns and increased anxiety and fear about poor sleep.[49]

For depressed patients with bipolar disorder or patients with major depressive disorder, sleep deprivation as a therapeutic intervention provides immediate but temporary relief of depressive symptoms in some individuals; it can also induce mania/hypomania in patients with bipolar disorder. The improvement in depressive symptoms disappears with a night of recovery sleep.[48,49]

Cognitive Symptoms

Patients with major depressive disorder will often report an inability to maintain their concentration on tasks and make simple decisions. These cognitive symptoms are a major cause of functional disability and interfere with patients' ability to work productively and efficiently when experiencing a depressive episode.[50] Cognitive impairment is present during and between episodes of depression and is seen more often in those with multiple episodes or chronic depression.[50,51] Neuropsychological assessment during depressive episodes frequently reveals deficits in executive function, memory, and attention.

Patients with major depressive disorder who are older may demonstrate pseudodementia, or what is now referred to as *depression with reversible dementia*. During testing, these patients may answer questions with "I don't know" (**CASE 7-1**), will demonstrate variable performance on tests of similar difficulty, and will have equal deficits in remote and recent memory.[52] However, epidemiologic studies have found that patients with a history of depression have a twofold greater risk of developing irreversible dementia,[53] and a large number of those with depression with reversible dementia will progress to irreversible dementia within 2 to 3 years.[54] Thus, an interplay clearly exists between either an increased risk of developing a dementing illness associated with major depressive disorder or the possibility that the stress of an episode leads to a temporary dementialike condition that is actually a harbinger of future events.

During mania/hypomania, patients with bipolar disorder become highly distractible, and during depressive episodes, they can develop concentration problems similar to patients with major depressive disorder. A 2015 study of cognition in subjects with bipolar disorder revealed worse verbal memory, working memory, psychomotor speed, verbal fluency, attention/speed of information processing, and executive function/problem-solving abilities compared to healthy controls. In particular, patients with bipolar disorder who were manic performed worse than patients with bipolar disorder who were depressed, mixed, or euthymic, and low cognitive performance was associated with a predominance of manic episodes.[55]

Fatigue

Physical fatigue is another symptom commonly reported by patients with major depressive disorder or bipolar disorder, and it can present as low energy,

decreased physical endurance, tiredness, increased effort with physical tasks, weakness, or sluggishness.[56] This should be distinguished from the sleepiness that occurs from insomnia, discussed earlier in this article. Fatigue is more likely to present in women with major depressive disorder than in men[57] and is a common prodromal symptom in a patient's first episode of major depressive disorder.[58] Reduced activity of the hypothalamic-pituitary-adrenal axis, as seen among the atypical subtype of depression (a symptom profile including hypersomnia, hyperphagia, extreme fatigue, and rejection sensitivity [a tendency to overreact to social rejection]),[59] and the presence of proinflammatory cytokines that decrease presynaptic dopaminergic inhibition of basal ganglia dopaminergic activity[60] have both been postulated as explanations for major depressive disorder–associated fatigue. A 2016 study of both patients with major depressive disorder and patients with bipolar disorder who were depressed demonstrated that elevated plasma C-reactive protein levels, a marker of inflammation, predicted decreased dorsal striatal to ventromedial prefrontal cortex and presupplementary motor area connectivity, which was correlated with decreased motor speed and increased psychomotor slowing.[61]

Fatigue is a common persistent residual symptom of major depressive disorder, with 10% to 35% of patients in remission still reporting life-altering problems with fatigue.[62] It is always important to consider the many other etiologies of fatigue, such as comorbid neurologic and medical disorders, occult neoplasm, obesity, sleep disorders, and the adverse effects of many different classes of medications.

Suicidal Ideation/Suicide

A suicide attempt is the act of intentionally harming oneself with the objective of ending one's life. The clinician should distinguish suicide attempts from other acts of self-harm in which the intent is not death but another purpose, such as the elimination of anxiety, resolution of a sense of emptiness, a desire for a sense of control, or mitigating a feeling of intense rage. Wishes for death that eventually result in suicide attempts or suicide are a common symptom in major depressive disorder. Of patients with major depressive disorder, 30% to 40% will attempt suicide,[63] while 6.67% of men and 3.77% of women will die by suicide.[64] In bipolar disorder, 25% to 50% will attempt suicide, while 15% to 20% of patients die by suicide.[65,66] The suicide attempts of patients with bipolar disorder tend to be more lethal than attempts in the general population.[66] Overlapping risk factors are associated with suicide attempts and suicide completions. Risk factors associated with attempted suicide include female sex (major depressive disorder only), previous suicide attempts, high severity of depressive symptoms, young age, comorbid substance-use disorders, anxiety disorders, Cluster B personality disorders as described in *DSM-5* (ie, antisocial personality disorder, borderline personality disorder, narcissistic personality disorder, histrionic personality disorder), hopelessness, and impulsive-aggressive traits. Risk factors associated with completed suicide include the same risk factors except male instead of female sex (major depressive disorder only), recent discharge from hospitalization, adverse life events (eg, trauma, relationship loss, homelessness), and, in the elderly, concurrent physical illness and depressive and dysphoric-irritable mood states (bipolar disorder only).[63,66] Increased risks of suicide attempt and completion have been reported for patients with neurologic illnesses such as MS, epilepsy, Huntington disease, dementia, traumatic brain injury, and migraine with

KEY POINTS

- One refinement of the criteria in the *Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition* (*DSM-5*) is the elimination of an arbitrary rule that prevented clinicians from diagnosing major depressive disorder in an individual who presented with symptoms within the first 2 months after the death of a loved one.
- Polysomnography is only ordered in cases in which the physician suspects a primary sleep disorder may be present in addition to major depressive disorder.
- Patients with a history of depression have a twofold greater risk of developing irreversible dementia, and a large number of those with depression with reversible dementia will progress to irreversible dementia within 2 to 3 years.
- Physical fatigue is a symptom commonly reported by patients with major depressive disorder or bipolar disorder, and it can present as low energy, decreased physical endurance, tiredness, increased effort with physical tasks, weakness, or sluggishness.
- The clinician should distinguish suicide attempts from other acts of self-harm in which the intent is not death but another purpose, such as the elimination of anxiety, resolution of a sense of emptiness, a desire for a sense of control, or mitigating a feeling of intense rage.

KEY POINTS

- Increased risks of suicide attempt and completion have been reported for patients with neurologic illnesses such as multiple sclerosis, epilepsy, Huntington disease, dementia, traumatic brain injury, and migraine with aura, while Parkinson disease has been associated with increases in suicidal ideation but not attempts.
- Several neurologic illnesses can induce symptoms by their impact on mood regulatory components of the brain and monoamine production.

aura, while Parkinson disease has been associated with increases in suicidal ideation but not attempts.[67] The risk of suicide attempts or completions in these illnesses has been strongly associated with depression, hopelessness, and social isolation.[67]

Acute hospitalization is an appropriate intervention to monitor patients felt to be at high risk of killing themselves and to prevent them from attempting to kill themselves. Encouraging patients and their families to temporarily remove firearms, other weapons, and unnecessary medications from the home is an important step to reduce harm in those unpredictable moments of despair that lead to suicide attempts.

Neurologic Medications That Can Induce Mood Symptoms

DSM-5 stipulates that before making a diagnosis of any mood disorder, one must discern if the symptoms observed developed coincident with the use of substances or medications that might cause mood symptoms.[16] Some medications used to treat neurologic disorders have been associated with depressive symptoms (TABLE 7-4). These include steroids for MS, opioids for severe pain disorders, and cholinesterase inhibitors for dementia. While the risk for depressive symptom induction from these medicines is relatively low, if symptoms emerge after starting these medicines, it is possible that the medicines are the cause or may be contributing to the severity of the symptoms. It is also important to recognize that medications may frequently worsen the neurocognitive symptoms associated with major depressive disorder and bipolar disorder. Some medications have also been associated with symptoms of mania/hypomania (TABLE 7-4), including steroids for MS, tricyclic antidepressants for various neurologic syndromes, and pramipexole for Parkinson disease.

Neurologic Illnesses That Can Induce Mood Symptoms

DSM-5 also requires that clinicians rule out medical illnesses that can cause depressive symptoms or a depressionlike syndrome before making a diagnosis of major depressive disorder or symptoms of mania/hypomania before making a diagnosis of bipolar disorder. Several neurologic illnesses can induce symptoms by their impact on mood regulatory components of the brain and monoamine production. Examples include MS, obstructive sleep apnea, stroke, Parkinson disease, dementia, Huntington disease, traumatic brain injury, and seizures. Treatment of the underlying condition may sometimes ameliorate the mood symptoms, as is the case in Parkinson disease, MS, and obstructive sleep apnea. The disinhibition exhibited by patients with frontotemporal dementia can lead a clinician to mistakenly suspect mania and make a diagnosis of bipolar disorder.

Mental Status Examination

When conducting a diagnostic interview, psychiatrists pay close attention to the form, volume, and content of speech along with a patient's appearance and movements. Such information composes the mental status examination, which is combined with the patient's history of illness to make the diagnosis. Although the mental status examination items assessed vary among psychiatrists, they often include appearance, attitude, behavior, speech, mood, affect, thought process, thought content (hallucinations, delusions, ruminations), cognition (orientation, concentration, immediate and delayed recall), insight, judgment, and gait. No

Medications That Can Induce Mood Symptoms

TABLE 7-4

Medication/Class	Possible Use(s)	Mood Symptoms That May Be Induced
Antiepileptics	Epilepsy, bipolar disorder	Depression
Beta-blockers	Hypertension, tremor	Depression
Cholinesterase inhibitors	Alzheimer dementia	Depression
Dopamine agonists	Parkinson disease	Mania
Efavirenz	Human immunodeficiency virus (HIV)	Depression, mania
Integrase strand transfer inhibitors	HIV	Depression
Interferons	Hepatitis C, multiple sclerosis	Depression
Isotretinoin	Acne	Depression
Mefloquine	Malaria	Depression
Methyldopa	Hypertension	Depression
Montelukast	Allergies, asthma	Depression
Oral contraceptives	Birth control	Depression
Opioids	Pain control	Depression
Reserpine	Hypertension	Depression
Rilpivirine	HIV	Depression
Selegiline	Parkinson disease	Mania
Steroids	Multiple sclerosis	Depression, mania
Tricyclic antidepressants	Migraine prophylaxis, neuropathic pain	Mania
Vigabatrin	Epilepsy	Depression
Zidovudine	HIV	Mania

typical mental status examination profile exists for a patient with major depressive disorder; however, patients with more severe symptoms (eg, melancholic subtype) may be unkempt, demonstrate behavior characterized as either psychomotor agitation or extreme slowness, and may speak softly and sparingly. Their thought process may be perseverative and their affect constricted and sad. Many of these findings, such as perseverative thought process, soft speech, and slow movements, can be seen among neurologic patients who do not have major depressive disorder. Thus, the psychiatric mental status examination is only one small part of the data that should be gathered to make an accurate diagnosis of major depressive disorder.

A patient with bipolar disorder, while depressed, could have a mental status examination similar to that of a patient with major depressive disorder. However, when manic/hypomanic, patients may demonstrate agitation, distractibility, or fast and pressured speech or may use rhymes or move from topic to topic, and their conversational content may reveal grandiose delusional beliefs about themselves.

Threshold for Brain Imaging

A wealth of neuroimaging data exists demonstrating abnormalities among people with major depressive disorder. This includes results from structural MRI studies that show reduced gray matter volume in the anterior cingulate, insula, thalamus, and hippocampus; diffusion tensor imaging studies that reveal reduced white matter integrity in frontosubcortical areas of the brain; resting-state functional MRI (fMRI) studies that show hyperactivity of the default mode network (a collection of brain regions with activity that is highly intercorrelated during states of wakeful rest); and PET studies showing lower glucose metabolism in the basal ganglia, limbic system, and insula.[68]

In patients with bipolar disorder, fMRI studies reveal abnormally decreased ventrolateral prefrontal cortex activity during emotion processing/regulation tasks; abnormally increased activity in the amygdala, striatum, and medial prefrontal cortex and decreased connectivity between the amygdala and prefrontal cortex in response to positive emotional stimuli; increased amygdala, orbitofrontal cortex, and temporal cortical activity during nonemotional cognitive tasks; and increased left ventrolateral prefrontal cortex, orbitofrontal cortex, and ventral striatum activity when exposed to reward. Structural imaging studies reveal decreased cortical gray and white matter volume; decreased cortical thickness in prefrontal, anterior temporal, and insular cortices; decreased gray matter volume in the right ventrolateral prefrontal cortex and orbitofrontal cortex; and decreased amygdala and hippocampus volumes. Diffusion imaging studies are similar to those in major depressive disorder and report decreases in white matter tracts linking the prefrontal and subcortical brain regions.[69]

Despite these findings, psychiatrists do not routinely order brain imaging studies when trying to diagnose mood disorders. This is because the findings listed often lack sensitivity and specificity when applied to individuals with major depressive disorder or bipolar disorder. A lack of standardization also exists in the imaging and analytic protocols used in neuroimaging research studies. Practices must be standardized at the research level before they can be employed clinically to ensure reliable findings.[70]

Brain imaging becomes a consideration when trying to rule out a neurologic illness or trying to distinguish major depressive disorder or mania from a neurodegenerative disease.[71] Late age of onset of major depressive disorder or

symptoms of mania/hypomania or the simultaneous occurrence of neurologic symptoms may suggest the need for brain imaging.

TREATMENT

First-line treatments for major depressive disorder include depression-focused psychotherapy, pharmacotherapy, the combination of psychotherapy and medications, or somatic treatments, such as bright light therapy.[72] About two-thirds of patients will respond to either medication or psychotherapy with a 50% or greater reduction in symptoms, but only 30% to 40% will have a full remission with the first treatment intervention.[73] Although these treatments have demonstrated efficacy among large groups of patients with major depressive disorder, some patients will respond to only one of these treatments and not the other.[74] At this point, no accepted ways are known to predict which treatment will help an individual patient. However, some exciting preliminary neuroimaging findings suggest that resting-state functional connectivity of the left anterior ventrolateral prefrontal cortex/insula, the dorsal midbrain, and the left ventromedial prefrontal cortex brain regions can predict treatment outcome with cognitive-behavioral therapy versus antidepressant medication.[75] The somatic treatments, which include bright light therapy and other forms of neurostimulation, are gaining more attention and are often considered when psychotherapy and multiple trials of medications are ineffective.

For bipolar disorder, the first-line treatment is either pharmacotherapy or a combination of psychotherapy and medication but never psychotherapy alone. Treatment options will vary depending on the patient's current mood state and ability to tolerate the medication. The medications used are categorized as antimanic, antidepressant, and mood stabilizing (eg, lithium), which have efficacy in preventing new bipolar disorder mood episodes. While treatment response prediction is also limited in bipolar disorder, a 2017 study has shown that the neurons of patients who are lithium-responsive demonstrate a unique electrophysiologic profile as compared to those who do not respond to lithium,[76] while another 2017 study reported that elevated peripheral cytokines in patients with bipolar disorder predict treatment nonresponse to an antidepressant intervention.[77]

Neurologists may or may not choose to initiate pharmacologic treatment for a patient's major depressive disorder. Those who identify the illness in a patient and choose not to treat should, at minimum, provide psychoeducation to the patient (teach the patient about the illness, in particular that it is a brain illness that is treated medically and not a sign of moral failure), normalizing the major depressive disorder symptoms in the context of having a neurologic illness (explain to the patient that it is not uncommon for people with neurologic illnesses to also experience symptoms of major depressive disorder). Following this discussion, they should refer the patient to a primary care physician or psychiatrist for treatment. On the other hand, if the neurologist suspects a patient has undiagnosed bipolar disorder, the patient should always be referred to a psychiatrist.

Psychotherapy

Psychotherapy is a talking-based intervention performed by a social worker, psychologist, mental health counselor, or psychiatrist. Many different psychotherapies are effective for the treatment of major depressive disorder,

KEY POINTS

- The mental status examination is only one small part of the data that should be gathered to make an accurate diagnosis of major depressive disorder.
- First-line treatments for major depressive disorder include depression-focused psychotherapy, pharmacotherapy, the combination of psychotherapy and medications, or somatic treatments, such as bright light therapy.
- Neurologists may or may not choose to initiate pharmacologic treatment for a patient's major depressive disorder. Those who identify the illness in a patient and choose not to treat should, at minimum, provide psychoeducation to the patient, normalizing the major depressive disorder symptoms in the context of having a neurologic illness.
- After psychoeducation, neurologists should refer patients with major depressive disorder to a primary care physician or psychiatrist for treatment.
- If the neurologist suspects a patient has undiagnosed bipolar disorder, the patient should always be referred to a psychiatrist.

including cognitive-behavioral therapy, interpersonal psychotherapy, psychodynamic psychotherapy, and problem-solving therapy (TABLE 7-5).[72] Recently, a third wave of newly developed psychotherapies have shown some efficacy in major depressive disorder. These include mindfulness-based cognitive-behavioral therapy, acceptance and commitment therapy, and extended behavioral activation.[78] Each of these therapies was developed from different models of how the mind functions when a person is depressed. The unique techniques and strategies employed during these therapies reflect the differences in these conceptualizations of the mind and are time-limited in duration (months versus years). Psychotherapy is particularly useful for individuals with major depressive disorder who cannot tolerate medications and who may also be dealing with the losses (eg, independence, functioning) that come with comorbid neurologic illnesses. Additionally, the benefits of psychotherapy may be more enduring than pharmacotherapy when

TABLE 7-5 **Evidence-based Psychotherapies for Major Depressive Disorder and Bipolar Disorder**

Psychotherapy	Strategy
Acceptance and commitment psychotherapy	Helps patients accept unwanted thoughts and feelings; helps patients set goals according to their values and commit to meeting them
Cognitive-behavioral therapy for major depressive disorder or bipolar disorder	Identifies and modifies distorted cognitions; changes maladaptive behaviors
Extended behavioral activation	Increases environmental reinforcement and reduces punishment to improve engagement in behaviors that will enhance mood
Family-focused therapy for bipolar disorder	Provides psychoeducation about bipolar disorder to family members and improves communication patterns and conflict resolution within the family system
Interpersonal therapy	Improves patient's communication skills within interpersonal relationships to improve management of current stressors and losses
Interpersonal and social rhythm therapy	Helps strengthen the vulnerable circadian rhythms of patients with bipolar disorder by promoting regularity of daily routines and managing current interpersonal stressors
Mindfulness-based cognitive-behavioral therapy	Combines cognitive-behavioral techniques with mindfulness and mindfulness meditation
Problem-solving therapy	Addresses negative assessments and uses focal problem solving
Psychodynamic therapy	Identifies and modifies unconscious conflicts related to causes of depression

pharmacotherapy is stopped after a year.[73] For psychotherapy to be effective, the patient must have intact cognition in order to fully engage and must have some ability to be introspective.

Psychotherapies have also been developed specifically for patients with bipolar disorder, including cognitive-behavioral therapy for bipolar disorder, Interpersonal and Social Rhythm Therapy (IPSRT), and family-focused therapy for bipolar disorder. A large-scale effectiveness study demonstrated that patients with bipolar disorder who are depressed recovered faster from their depressive episode when receiving any of these adjunctive psychotherapies as compared to a 3-week psychoeducation collaborative care program.[79] Psychotherapies that promote medication adherence and early recognition of symptoms have a greater effect on mania, while those that teach cognitive and interpersonal coping strategies are more effective for the depression pole of the illness.[80]

Medications

A variety of medications have demonstrated efficacy in treating major depressive disorder (TABLE 7-6). The majority of these increase synaptic levels of monoamines or act as agonists or antagonists at monoamine receptors. The different classes of antidepressants include selective serotonin reuptake inhibitors (SSRIs), serotonin norepinephrine reuptake inhibitors (SNRIs), atypical antidepressants, tricyclic antidepressants, and monoamine oxidase inhibitors (MAOIs). SSRIs, SNRIs, and atypical antidepressants (specifically bupropion and mirtazapine) may be used as first-line treatments, while tricyclic antidepressants and MAOIs, because of their adverse event profile, are reserved for patients who are treatment resistant.[72] Tricyclic antidepressants have been associated with seizures, tremors, delirium, QT interval prolongation, cardiac arrhythmias, and anticholinergic adverse effects at higher blood levels, while MAOIs can result in serotonin syndrome and hypertensive crises if drug or food interactions with the MAOI occur.

When a patient's symptoms respond only partially to an antidepressant, augmentation strategies may be used. These strategies include adding psychotherapy, lithium, thyroid hormone, buspirone, an antidepressant from a different class, or second-generation antipsychotics to the antidepressant.[72] All the medications listed can introduce neurologic side effects, but second-generation antipsychotics, in particular, are commonly associated with extrapyramidal side effects.[81] These effects include parkinsonism, dystonic reactions, akathisia, and tardive dyskinesia. SSRIs may also induce extrapyramidal symptoms; however, this occurs more often in patients who are elderly and in those with Parkinson disease, and they occur less commonly overall as compared to second-generation antipsychotics.[82]

The first-line medications used in bipolar disorder are mood stabilizers, which include lithium, and the anticonvulsants valproate, carbamazepine, and lamotrigine. Two second-generation antipsychotics, lurasidone and quetiapine, and the combination of olanzapine and fluoxetine are all US Food and Drug Administration (FDA)–approved to treat bipolar depression. Antidepressants are used with caution in patients with bipolar disorder, almost always in combination with a mood stabilizer to prevent manic induction. Both first- and second-generation antipsychotics can be used on their own or in combination with mood stabilizers to treat manic episodes. For patients with frequent manic

KEY POINTS

- **Psychotherapy is particularly useful for individuals with major depressive disorder who cannot tolerate medications and who may also be dealing with the losses (eg, independence, functioning) that come with comorbid neurologic illnesses.**
- **The different classes of antidepressants include selective serotonin reuptake inhibitors (SSRIs), serotonin norepinephrine reuptake inhibitors (SNRIs), atypical antidepressants, tricyclic antidepressants, and monoamine oxidase inhibitors (MAOIs)**
- **The first-line medications used in bipolar disorder are mood stabilizers, which include lithium, and the anticonvulsants valproate, carbamazepine, and lamotrigine.**

TABLE 7-6 **Antidepressants Used in Major Depressive Disorder**

Class/Drug	Mechanism of Action	Possible Adverse Effects
Selective serotonin reuptake inhibitors (SSRIs)		
Fluoxetine, paroxetine, sertraline, citalopram, escitalopram, fluvoxamine	Blocks the 5-HT reuptake transporter	Headache, nausea, yawning, sweating, fatigue, insomnia, anxiety, sexual dysfunction, tremors, hyponatremia, serotonin syndrome
Vortioxetine	Blocks the 5-HT reuptake transporter and blocks 5-HT_7, 5-HT_3, and 5-HT_{1D} receptor; agonizes 5-HT_{1A} receptor; partial agonist at 5-HT_{1B}	Headache, nausea, yawning, sweating, fatigue, insomnia, anxiety, sexual dysfunction, tremors, hyponatremia, serotonin syndrome
Vilazodone	Blocks the 5-HT reuptake transporter and is a 5-HT_{1A} receptor partial agonist	Headache, nausea, yawning, sweating, fatigue, insomnia, anxiety, sexual dysfunction, tremors, hyponatremia, serotonin syndrome
Serotonin norephinephrine reuptake inhibitors (SNRIs)		
Venlafaxine, desvenlafaxine, duloxetine, levomilnacipran	Blocks 5-HT and norepinephrine reuptake transporters	Headache, yawning, fatigue, insomnia, anxiety, decreased libido, tremors, hypertension, nausea, diarrhea, sweating
Atypical antidepressants		
Bupropion	Dopamine- and norepinephrine-releasing agent	Seizures, headaches, tremors, insomnia, decreased appetite
Nefazodone	Blocks 5-HT_{2A} receptor; weak 5-HT reuptake inhibition	Sedation, hepatotoxicity
Mirtazapine	Blocks 5-HT_{2A}/5-HT_{2C} receptors, alpha 2A hetero- and autoreceptors, and histamine receptors	Weight gain, sedation
Trazodone	Blocks 5-HT_{2A} receptor and alpha 1 receptor; inhibits 5-HT reuptake transporter and blocks 5-HT_{2C} receptor at high doses; partial 5-HT_{1A} receptor agonism	Sedation, orthostatic hypotension, priapism
Tricyclic antidepressants		
Nortriptyline, amitriptyline, imipramine, desipramine, clomipramine	Blocks 5-HT and norepinephrine transporters and acetylcholine, alpha adrenergic, and H1 receptors	Headache, yawning, fatigue, sedation, insomnia, anxiety, decreased libido, tremors, seizures, delirium, arrhythmias, orthostasis, dry mouth
Monoamine oxidase inhibitors		
Tranylcypromine, phenelzine	Inhibits monoamine oxidase A and B	Serotonin syndrome, weight gain, insomnia, sexual dysfunction, hypertensive crisis, orthostatic hypotension
Selegiline	Selectively inhibits monoamine oxidase B at doses <20 mg; inhibits monoamine oxidase A and B at doses ≥20 mg	Serotonin syndrome, weight gain, insomnia, sexual dysfunction, hypertensive crisis, orthostatic hypotension

5-HT = 5-hydroxytryptamine (serotonin).

recurrences and poor medication adherence, long-acting injectable preparations of antipsychotics may be considered.[83]

For patients with Parkinson disease and depression, use of bupropion as a first-line strategy may be advised given its dopaminergic effects,[84,85] although it has never been studied for this indication in a randomized clinical trial. Additionally, SSRIs may exacerbate Parkinson tremors and failed to demonstrate superiority against placebo in a systematic review and meta-analysis (**CASE 7-1**).[86,87] Regardless of the antidepressant selected, one must be careful about adding an antidepressant to a Parkinson disease regimen that already includes a high dose of the MAOI selegiline as serotonin syndrome or hypertensive crises could ensue. Pramipexole, a D2/D3 receptor agonist used in the treatment of Parkinson disease, can be used to augment an antidepressant in addition to the options listed above and should be considered in patients with Parkinson disease.[88] When treating patients with epilepsy, antidepressants that lower the seizure threshold, including tricyclic antidepressants and bupropion, should be avoided.

Interest in the use of intranasal and IV forms of ketamine has increased since the publication of several clinical trials demonstrating its rapid salutary effects in patients with treatment-resistant depression or suicidality.[89] Side effects during ketamine administration may include dissociation, perceptual disturbances, and transient increases in blood pressure, while long-term use has raised concerns for the development of memory impairment and cystitis.[90]

Use of Pharmacogenetic Markers for Treatment Selection

Many medication options are available to treat mood disorders; however, some may be more effective or more tolerable for a given patient than others. Several companies have developed genetic testing services that can identify the presence or absence of alleles relevant to the pharmacokinetics and pharmacodynamics of psychotropic agents. These companies claim that this genetic information can predict a medication's efficacy and risk for an individual patient and thus guide the clinician's choices. Once the genetic testing is complete, these companies provide reports identifying psychotropic agents that can be used without concern and those that should only be used with caution. This service becomes attractive to patients who are desperate to get better quickly and to clinicians who feel overwhelmed by the number of psychotropic options available. The literature to date, however, does not support the use of this testing.[91] Only two small randomized trials[92,93] have studied the use of pharmacogenetics-informed treatments versus treatment as usual. Although both showed increased remission rates among patients whose clinicians relied on pharmacogenetic testing, only one achieved statistical significance.[93] This is a promising area of research as psychiatry, like other fields of medicine, moves closer to personalized treatments.

Somatic Treatments

For patients with major depressive disorder or bipolar disorder who receive no benefit from psychotherapy and medications or cannot tolerate them, somatic therapies should be considered. Somatic treatments are nonpharmacologic interventions that involve the application of physical forces (eg, light, electricity, magnetism) to induce neurochemical changes within specific regions of the brain.

Electroconvulsive therapy involves application of a brief electrical current to the patient's scalp to induce a generalized seizure while the patient is fully

KEY POINTS

- Regardless of the antidepressant selected, one must be careful about adding an antidepressant to a Parkinson disease regimen that already includes a high dose of the monoamine oxidase inhibitor selegiline, as serotonin syndrome or hypertensive crises could ensue.
- When treating patients with epilepsy, antidepressants that lower the seizure threshold, including tricyclic antidepressants and bupropion, should be avoided.
- Somatic treatments are nonpharmacologic interventions that involve the application of physical forces (eg, light, electricity, magnetism) to induce neurochemical changes within specific regions of the brain.

anesthetized. This procedure is safe and effective and should be offered to patients with a high suicide risk, those with late-life depression (onset after 60 years of age), or those who are catatonic or psychotic.[94] Interestingly, this procedure may benefit the mood and motor symptoms of patients with Parkinson disease who are depressed.[94] Repetitive transcranial magnetic stimulation involves the application of an electromagnetic coil above the scalp to stimulate neurons in regions of the brain involved in mood regulation, such as the prefrontal cortex. Patients receive treatments 5 days per week for a period of 4 to 6 weeks.[95] Vagal nerve stimulators, also used for refractory epilepsy, are implanted in the chest wall and connect to and stimulate the vagus nerve. This modulates signals sent from the vagus nerve to cortico-limbic-thalamic-striatal regions of the brain involved in mood regulation.[96] Deep brain stimulation, originally pioneered to treat Parkinson disease, involves the implantation of a pacemakerlike device in the chest wall that sends pulses to electrodes surgically placed in regions of the brain that influence mood-related circuitry. Currently considered experimental, this has been particularly promising for patients with treatment-resistant major depressive disorder or bipolar disorder.[97,98]

Transcranial direct current stimulation applies a low-frequency electrical current over the scalp and can improve symptoms of non–treatment-resistant major depressive disorder but not treatment-resistant major depressive disorder.[99] It can improve symptoms of bipolar disorder as demonstrated in multiple open-label studies, but randomized controlled trials are needed to validate this.[100] It is associated with few side effects and is portable and inexpensive.[99] Finally, bright light therapy requires patients to sit in front of a light box of at least 10,000 lux daily for 2 to 5 weeks. The light is expected to modulate the patient's chronobiological cycle, which induces antidepressant effects both in those with[101] and those without seasonal-onset variants of major depressive disorder.[102] Bright light therapy has also been shown to be effective in bipolar disorder[103] and was more effective than medications as usual for patients with bipolar disorder when used in combination with sleep phase advancement and sleep deprivation.[104] Light boxes and transcranial direct current stimulators can both be purchased by patients via the Internet, and both can potentially induce mania/hypomania in patients with bipolar disorder.

CONCLUSION

Major depressive disorder and bipolar disorder are common mood disorders that are highly comorbid among patients with neurologic illnesses. The symptoms of both conditions are functionally impairing, can greatly increase a patient's mortality and morbidity, and create challenges with adherence. In some patients, the neurologic disorder can induce mood symptoms, while in other patients, genetic risks exist for both a mood disorder and neurologic disorder to emerge at some point independently of the other illness. Some medications used to treat common neurologic disorders may induce depressive or manic/hypomanic symptoms, and, conversely, some medications used to treat major depressive disorder or bipolar disorder may cause neurologic side effects. It is not surprising that somatic treatments developed to treat neurologic illnesses are now being applied to the treatment of mood disorders. This convergence represents the future of treatment for many patients whose underlying brain dysfunction may

manifest itself with a myriad of different symptoms and require a more integrated approach to their care. This suggests that neurologists would be wise to commonly screen for mood disorders with a valid tool, such as the Patient Health Questionnaire-9 or Mood Disorders Questionnaire, and, likewise, psychiatrists must be more aware of the possibility of underlying neurologic disorders. Fortunately, a wide array of treatment options is available for patients with major depressive disorder or bipolar disorder.

KEY POINT

- **Bright light therapy is expected to modulate the patient's chronobiological cycle, which induces antidepressant effects both in those with and those without seasonal-onset variants of major depressive disorder.**

REFERENCES

1 Kessler RC, Berglund P, Demler O, et al. The epidemiology of major depressive disorder: results from the National Comorbidity Survey Replication (NCS-R). JAMA 2003;289(23):3095–3105. doi:10.1001/jama.289.23.3095.

2 Merikangas KR, Akiskal HS, Angst J, et al. Lifetime and 12-month prevalence of bipolar spectrum disorder in the National Comorbidity Survey replication. Arch Gen Psychiatry 2007;64(5):543–552. doi:10.1001/archpsyc.64.5.543.

3 Papakostas GI, Petersen T, Mahal Y, et al. Quality of life assessments in major depressive disorder: a review of the literature. Gen Hosp Psychiatry 2004;26(1):13–17. doi:10.1016/j.genhosppsych.2003.07.004.

4 Michalak EE, Yatham LN, Lam RW. Quality of life in bipolar disorder: a review of the literature. Health Qual Life Outcomes 2005;3:72. doi:10.1186/1477-7525-3-72.

5 Cuijpers P, Smit F. Excess mortality in depression: a meta-analysis of community studies. J Affect Disord 2002;72(3):227–236. doi:10.1016/S0165-0327(01)00413-X.

6 Crump C, Sundquist K, Winkleby MA, Sundquist J. Comorbidities and mortality in bipolar disorder: a Swedish national cohort study. JAMA Psychiatry 2013;70(9):931–939. doi:10.1001/jamapsychiatry.2013.1394.

7 Ferrari AJ, Charlson FJ, Norman RE, et al. Burden of depressive disorders by country, sex, age, and year: findings from the global burden of disease study 2010. PLoS Med 2013;10(11):e1001547. doi:10.1371/journal.pmed.1001547.

8 Williams LS, Jones WJ, Shen J, et al. Prevalence and impact of depression and pain in neurology outpatients. J Neurol Neurosurg Psychiatry 2003;74(11):1587–1589. doi:10.1136/jnnp.74.11.1587.

9 Kessler RC, Berglund P, Demler O, et al. Lifetime prevalence and age-of-onset distributions of DSM-IV disorders in the National Comorbidity Survey Replication. Arch Gen Psychiatry 2005;62(6):593–602. doi:10.1001/archpsyc.62.6.593.

10 Solomon DA, Keller MB, Leon AC, et al. Recovery from major depression. A 10-year prospective follow-up across multiple episodes. Arch Gen Psychiatry 1997;54(11):1001–1006. doi:10.1001/archpsyc.1997.01830230033005.

11 Solomon DA, Keller MB, Leon AC, et al. Multiple recurrences of major depressive disorder. Am J Psychiatry 2000;157(2):229–233. doi:10.1176/appi.ajp.157.2.229.

12 American Psychiatric Association. Diagnostic and statistical manual of mental disorders, 4th ed, text revision (DSM-IV-TR). Washington, DC: American Psychiatric Association, 2000.

13 Albert PR. Why is depression more prevalent in women? J Psychiatry Neurosci 2015;40(4):219–221. doi:10.1503/jpn.150205.

14 Sullivan PF, Neale MC, Kendler KS. Genetic epidemiology of major depression: review and meta-analysis. Am J Psychiatry 2000;157(10):1552–1562. doi:10.1176/appi.ajp.157.10.1552.

15 Stroud CB, Davila J, Moyer A. The relationship between stress and depression in first onsets versus recurrences: a meta-analytic review. J Abnorm Psychol 2008;117(1):206–213. doi:10.1037/0021-843X.117.1.206.

16 American Psychiatric Association. Diagnostic and statistical manual of mental disorders, 5th ed (DSM-5). Washington, DC: American Psychiatric Association, 2013.

17 Solomon DA, Leon AC, Coryell WH, et al. Longitudinal course of bipolar I disorder: duration of mood episodes. Arch Gen Psychiatry 2010;67(4):339–347. doi:10.1001/archgenpsychiatry.2010.15.

18 Judd LL, Akiskal HS, Schettler PJ, et al. A prospective investigation of the natural history of the long-term weekly symptomatic status of bipolar II disorder. Arch Gen Psychiatry 2003;60(3):261–269. doi:10.1001/archpsyc.60.3.261.

19 Judd LL, Akiskal HS, Schettler PJ, et al. The long-term natural history of the weekly symptomatic status of bipolar I disorder. Arch Gen Psychiatry 2002;59(6):530–537. doi:10.1001/archpsyc.59.6.530.

20 Tohen M, Zarate CA Jr, Hennen J, et al. The McLean-Harvard First-Episode Mania Study: prediction of recovery and first recurrence. Am J Psychiatry 2003;160(12):2099–2107. doi:10.1176/appi.ajp.160.12.2099.

21 Diflorio A, Jones I. Is sex important? Gender differences in bipolar disorder. Int Rev Psychiatry 2010;22(5):437–452. doi:10.3109/09540261.2010.514601.

22 McGuffin P, Rijsdijk F, Andrew M, et al. The heritability of bipolar affective disorder and the genetic relationship to unipolar depression. Arch Gen Psychiatry 2003;60(5):497–502. doi:10.1001/archpsyc.60.5.497.

23 Smoller JW, Finn CT. Family, twin, and adoption studies of bipolar disorder. Am J Med Genet C Semin Med Genet 2003;123C(1):48–58. doi:10.1002/ajmg.c.20013.

24 Proudfoot J, Whitton A, Parker G, et al. Triggers of mania and depression in young adults with bipolar disorder. J Affect Disord 2012;143(1–3):196–202. doi:10.1016/j.jad.2012.05.052.

25 Fiedorowicz JG, He J, Merikangas KR. The association between mood and anxiety disorders with vascular diseases and risk factors in a nationally representative sample. J Psychosom Res 2011;70(2):145–154. doi:10.1016/j.jpsychores.2010.07.010.

26 Raskind MA. Diagnosis and treatment of depression comorbid with neurologic disorders. Am J Med 2008;121(11 suppl 2):S28–S37. doi:10.1016/j.amjmed.2008.09.011.

27 Saunamäki T, Jehkonen M. Depression and anxiety in obstructive sleep apnea syndrome: a review. Acta Neurol Scand 2007;116(5):277–288. doi:10.1111/j.1600-0404.2007.00901.x.

28 McDermid J, Sareen J, El-Gabalawy R, et al. Co-morbidity of bipolar disorder and borderline personality disorder: findings from the National Epidemiologic Survey on Alcohol and Related Conditions. Compr Psychiatry 2015;58:18–28. doi:10.1016/j.comppsych.2015.01.004.

29 Forty L, Ulanova A, Jones L, et al. Comorbid medical illness in bipolar disorder. Br J Psychiatry 2014;205(6):465–472. doi:10.1192/bjp.bp.114.152249.

30 Hirschfeld RM. History and evolution of the monoamine hypothesis of depression. J Clin Psychiatry 2000;61(suppl 6):4–6.

31 Delgado PL. Depression: the case for a monoamine deficiency. J Clin Psychiatry 2000;61(suppl 6):7–11.

32 Kaufman J, DeLorenzo C, Choudhury S, Parsey RV. The 5-HT1A receptor in major depressive disorder. Eur Neuropsychopharmacol 2016;26(3):397–410. doi:10.1016/j.euroneuro.2015.12.039.

33 Duman RS, Li N. A neurotrophic hypothesis of depression: role of synaptogenesis in the actions of NMDA receptor antagonists. Philos Trans R Soc Lond B Biol Sci 2012;367(1601):2475–2484. doi:10.1098/rstb.2011.0357.

34 Wohleb ES, Gerhard D, Thomas A, Duman RS. Molecular and cellular mechanisms of rapid-acting antidepressants ketamine and scopolamine. Curr Neuropharmacol 2017;15(1):11–20. doi:10.2174/1570159X14666160309114549.

35 Kim YK, Na KS, Myint AM, Leonard BE. The role of pro-inflammatory cytokines in neuroinflammation, neurogenesis and the neuroendocrine system in major depression. Prog Neuropsychopharmacol Biol Psychiatry 2016;64:277–284. doi:10.1016/j.pnpbp.2015.06.008.

36 Leonard B, Maes M. Mechanistic explanations how cell-mediated immune activation, inflammation and oxidative and nitrosative stress pathways and their sequels and concomitants play a role in the pathophysiology of unipolar depression. Neurosci Biobehav Rev 2012;36(2):764–785. doi:10.1016/j.neubiorev.2011.12.005.

37 Muneer A. Bipolar disorder: role of inflammation and the development of disease biomarkers. Psychiatry Investig 2016;13(1):18–33. doi:10.4306/pi.2016.13.1.18.

38 Andreazza AC, Kauer-Sant'anna M, Frey BN, et al. Oxidative stress markers in bipolar disorder: a meta-analysis. J Affect Disord 2008;111(2–3):135–144. doi:10.1016/j.jad.2008.04.013.

39 Fernandes BS, Molendijk ML, Köhler CA, et al. Peripheral brain-derived neurotrophic factor (BDNF) as a biomarker in bipolar disorder: a meta-analysis of 52 studies. BMC Med 2015;13:289. doi:10.1186/s12916-015-0529-7.

40 Gonzalez R. The relationship between bipolar disorder and biological rhythms. J Clin Psychiatry 2014;75(4):e323–e331. doi:10.4088/JCP.13r08507.

41 Pies RW. The bereavement exclusion and DSM-5: an update and commentary. Innov Clin Neurosci 2014;11(7–8):19–22.

42 Kroenke K, Spitzer RL, Williams JB. The Patient Health Questionnaire-2: validity of a two-item depression screener. Med Care 2003;41(11):1284–1292. doi:10.1097/01.MLR.0000093487.78664.3C.

43 Kroenke K, Spitzer RL, Williams JB. The PHQ-9: validity of a brief depression severity measure. J Gen Inter Med 2001;16(9):606–613. doi:10.1046/j1525-1497200101600960 6x.

44 Rush AJ, Trivedi MH, Ibrahim HM, et al. The 16-Item Quick Inventory of Depressive Symptomatology (QIDS), clinician-rating (QIDS-C), and self-report (QIDS-SR): a psychometric evaluation in patients with chronic major depression. Biol Psychiatry 2003;54(5):573–583. doi:10.1016/S0006-3223(02)01866-8.

45 Siu AL, US Preventive Services Task Force (USPSTF), Bibbins-Domingo K, et al. Screening for depression in adults: US preventive services task force recommendation statement. JAMA 2016;315(4):380–387. doi:10.1001/jama.2015.18392.

46 Zimmerman M, Galione JN. Screening for bipolar disorder with the Mood Disorders Questionnaire: a review. Harv Rev Psychiatry 2011;19(5):219–228. doi:10.3109/10673229.2011.614101.

47 Zimmerman M. Screening for bipolar disorder with self-administered questionnaires: a critique of the concept and a call to stop publishing studies of their performance in psychiatric samples. Depress Anxiety 2017;34(9):779–785. doi:10.1002/da.22644.

48 Sculthorpe LD, Douglass AB. Sleep pathologies in depression and the clinical utility of polysomnography. Can J Psychiatry 2010;55(7):413–421. doi:10.1177/070674371005500704.

49 Plante DT, Winkelman JW. Sleep disturbance in bipolar disorder: therapeutic implications. Am J Psychiatry 2008;165(7):830–843. doi:10.1176/appi.ajp.2008.08010077.

50 McIntyre RS, Lee Y. Cognition in major depressive disorder: a 'Systemically Important Functional Index' (SIFI). Curr Opin Psychiatry 2016;29(1):48–55. doi:10.1097/YCO.0000000000000221.

51 Kessing LV. Cognitive impairment in the euthymic phase of affective disorder. Psychol Med 1998;28(5):1027–1038. doi:10.1017/S0033291798006862.

52 Small GW, Liston EH, Jarvik LF. Diagnosis and treatment of dementia in the aged. West J Med 1981;135(6):469–481.

53 Ownby RL, Crocco E, Acevedo A, et al. Depression and risk for Alzheimer disease: systematic review, meta-analysis, and metaregression analysis. Arch Gen Psychiatry 2006;63(5):530–538. doi:10.1001/archpsyc.63.5.530.

54 Alexopoulos GS, Meyers BS, Young RC, et al. The course of geriatric depression with "reversible dementia": a controlled study. Am J Psychiatry 1993;150(11):1693–1699. doi:10.1176/ajp.150.11.1693.

55 Vrabie M, Marinescu V, Talaşman A, et al. Cognitive impairment in manic bipolar patients: important, understated, significant aspects. Ann Gen Psychiatry 2015;14:41. doi:10.1186/s12991-015-0080-0.

56 Arnold LM. Understanding fatigue in major depressive disorder and other medical disorders. Psychosomatics 2008;49(3):185–190. doi:10.1176/appi.psy.49.3.185.

57 Khan AA, Gardner CO, Prescott CA, Kendler KS. Gender differences in the symptoms of major depression in opposite-sex dizygotic twin pairs. Am J Psychiatry 2002;159(8):1427–1429. doi:10.1176/appi.ajp.159.8.1427.

58 Fava GA, Grandi S, Canestrari R, Molnar G. Prodromal symptoms in primary major depressive disorder. J Affect Disord 1990;19(2):149–152. doi:10.1016/0165-0327(90)90020-9.

59 Gold PW, Gabry KE, Yasuda MR, Chrousos GP. Divergent endocrine abnormalities in melancholic and atypical depression: clinical and pathophysiologic implications. Endocrinol Metab Clin North Am 2002;31(1):37–62, vi. doi:10.1016/S0889-8529(01)00022-6.

60 Felger JC, Lotrich FE. Inflammatory cytokines in depression: neurobiological mechanisms and therapeutic implications. Neuroscience 2013;246:199–229. doi:10.1016/j.neuroscience.2013.04.060.

61 Felger JC, Li Z, Haroon E, et al. Inflammation is associated with decreased functional connectivity within corticostriatal reward circuitry in depression. Mol Psychiatry 2016;21(10):1358–1365. doi:10.1038/mp.2015.168.

62 Fava GA, Grandi S, Zielezny M, et al. Cognitive behavioral treatment of residual symptoms in primary major depressive disorder. Am J Psychiatry 1994;151(9):1295–1299. doi:10.1176/ajp.151.9.1295.

63 Isometsä E. Suicidal behaviour in mood disorders–who, when, and why? Can J Psychiatry 2014;59(3):120–130. doi:10.1177/070674371405900303.

64 Nordentoft M, Mortensen PB, Pedersen CB. Absolute risk of suicide after first hospital contact in mental disorder. Arch Gen Psychiatry 2011;68(10):1058–1064. doi:10.1001/archgenpsychiatry.2011.113.

65 Jamison KR. Suicide and bipolar disorder. J Clin Psychiatry 2000;61(suppl 9):47–51.

66 Baldessarini RJ, Pompili M, Tondo L. Suicide in bipolar disorder: risks and management. CNS Spectr 2006;11(6):465–471. doi:10.3109/9780203007051-43.

67 Arciniegas DB, Anderson CA. Suicide in neurologic illness. Curr Treat Options Neurol 2002;4(6):457–468. doi:10.1007/s11940-002-0013-5.

68 Zhang K, Zhu Y, Zhu Y, et al. Molecular, functional, and structural imaging of major depressive disorder. Neurosci Bull 2016;32(3):273–285. doi:10.1007/s12264-016-0030-0.

69 Phillips ML, Swartz HA. A critical appraisal of neuroimaging studies of bipolar disorder: toward a new conceptualization of underlying neural circuitry and a road map for future research. Am J Psychiatry 2014;171(8):829–843. doi:10.1176/appi.ajp.2014.13081008.

70 Farah MJ, Gillihan SJ. The puzzle of neuroimaging and psychiatric diagnosis: technology and nosology in an evolving discipline. AJOB Neurosci 2012;3(4):31–41. doi:10.1080/21507740.2012.713072.

71 Masdeu JC. Neuroimaging in psychiatric disorders. Neurotherapeutics 2011;8(1):93–102. doi:10.1007/s13311-010-0006-0.

72 American Psychiatric Association. Practice guideline for the treatment of patients with major depressive disorder. 3rd ed. Arlington, VA: American Psychiatric Association, 2010.

73 DeRubeis RJ, Siegle GJ, Hollon SD. Cognitive therapy versus medication for depression: treatment outcomes and neural mechanisms. Nat Rev Neurosci 2008;9(10):788–796. doi:10.1038/nrn2345.

74 Schatzberg AF, Rush AJ, Arnow BA, et al. Chronic depression: medication (nefazodone) or psychotherapy (CBASP) is effective when the other is not. Arch Gen Psychiatry 2005;62(5):513–520. doi:10.1001/archpsyc.62.5.513.

75 Dunlop BW, Rajendra JK, Craighead WE, et al. Functional connectivity of the subcallosal cingulate cortex and differential outcomes to treatment with cognitive-behavioral therapy or antidepressant medication for major depressive disorder. Am J Psychiatry 2017;174(6):533–545. doi:10.1176/appi.ajp.2016.16050518.

76 Stern S, Santos R, Marchetto MC, et al. Neurons derived from patients with bipolar disorder divide into intrinsically different sub-populations of neurons, predicting the patients' responsiveness to lithium [published online ahead of print February 28, 2017]. Mol Psychiatry doi:10.1038/mp.2016.260.

77 Benedetti F, Poletti S, Hoogenboezem TA, et al. Higher baseline proinflammatory cytokines mark poor antidepressant response in bipolar disorder. J Clin Psychiatry 2017;78(8):e986–e993. doi:10.4088/JCP.16m11310.

78 Churchill R, Moore TH, Furukawa TA, et al. 'Third wave' cognitive and behavioural therapies versus treatment as usual for depression. Cochrane Database Syst Rev 2013;(10):CD008705. doi:10.1002/14651858.CD008705.pub2.

79 Miklowitz DJ, Otto MW, Frank E, et al. Psychosocial treatments for bipolar depression: a 1-year randomized trial from the Systematic Treatment Enhancement Program. Arch Gen Psychiatry 2007;64(4):419–426. doi:10.1001/archpsyc.64.4.419.

80 Miklowitz DJ. Adjunctive psychotherapy for bipolar disorder: state of the evidence. Am J Psychiatry 2008;165(11):1408–1419. doi:10.1176/appi.ajp.2008.08040488.

81 Divac N, Prostran M, Jakovcevski I, Cerovac N. Second-generation antipsychotics and extrapyramidal adverse effects. Biomed Res Int 2014;2014:656370. doi:10.1155/2014/656370.

82 Leo RJ. Movement disorders associated with the serotonin selective reuptake inhibitors. J Clin Psychiatry 1996;57(10):449–454. doi:10.4088/JCP.v57n1002.

83 Yatham LN, Kennedy SH, Parikh SV, et al. Canadian Network for Mood and Anxiety Treatments (CANMAT) and International Society for Bipolar Disorders (ISBD) collaborative update of CANMAT guidelines for the management of patients with bipolar disorder: update 2013. Bipolar Disord 2013;15(1):1–44. doi:10.1111/bdi.12025.

84 Raskin S, Durst R. Bupropion as the treatment of choice in depression associated with Parkinson's disease and its various treatments. Medical Hypotheses 2010;75(6):544–546. doi:10.1016/j.mehy.2010.07.024.

85 Zaluska M, Dyduch A. Bupropion in the treatment of depression in Parkinson's disease. Int Psychogeriatr 2011;23(2):325–327. doi:10.1017/S1041610210001687.

86 Tesei S, Antonini A, Canesi M, et al. Tolerability of paroxetine in Parkinson's disease: a prospective study. Mov Disord 2000;15(5):986–989. doi:10.1002/1531-8257(200009)15:5<986::AID-MDS1034>3.0.CO;2-I.

87 Rocha FL, Murad MG, Stumpf BP, et al. Antidepressants for depression in Parkinson's disease: systematic review and meta-analysis. J Psychopharmacol 2013;27(5):417–423. doi:10.1177/0269881113478282.

88 Rektorová I, Rektor I, Bares M, et al. Pramipexole and pergolide in the treatment of depression in Parkinson's disease: a national multicentre prospective randomized study. Eur J Neurol 2003;10(4):399–406. doi:10.1046/j.1468-1331.2003.00612.x.

89 Serafini G, Howland RH, Rovedi F, et al. The role of ketamine in treatment-resistant depression: a systematic review. Curr Neuropharmacol 2014;12(5):444–461. doi:10.2174/1570159X12666140619204251.

90 Zhang MW, Ho RC. Controversies of the effect of ketamine on cognition. Front Psychiatry 2016;7:47. doi:10.3389/fpsyt.2016.00047.

91 Dunlop BW. Pharmacogenetic decision support tools: a component of precision medicine for psychiatry? Focus 2017;15(4):3s–4s. doi:10.1176/appi.focus.154S03.

92 Winner JG, Carhart JM, Altar CA, et al. A prospective, randomized, double-blind study assessing the clinical impact of integrated pharmacogenomic testing for major depressive disorder. Discov Med 2013;16(89):219–227.

93 Singh AB. Improved antidepressant remission in major depression via a pharmacokinetic pathway polygene pharmacogenetic report. Clin Psychopharmacol Neurosci 2015;13(2):150–156. doi:10.9758/cpn.2015.13.2.150.

94 Greenberg RM, Kellner CH. Electroconvulsive therapy: a selected review. Am J Geriatr Psychiatry 2005;13(4):268–281. doi:10.1176/appi.ajgp.13.4.268.

95 Gaynes BN, Lloyd SW, Lux L, et al. Repetitive transcranial magnetic stimulation for treatment-resistant depression: a systematic review and meta-analysis. J Clin Psychiatry 2014;75(5):477–489; quiz 489. doi:10.4088/JCP.13r08815.

96 Howland RH. Vagus nerve stimulation. Curr Behav Neurosci Rep 2014;1(2):64–73. doi:10.1007/s40473-014-0010-5.

97 Delaloye S, Holtzheimer PE. Deep brain stimulation in the treatment of depression. Dialogues Clin Neurosci 2014;16(1):83–91.

98 Holtzheimer PE, Kelley ME, Gross RE, et al. Subcallosal cingulate deep brain stimulation for treatment-resistant unipolar and bipolar depression. Arch Gen Psychiatry 2012;69(2):150–158. doi:10.1001/archgenpsychiatry.2011.1456.

99 Meron D, Hedger N, Garner M, Baldwin DS. Transcranial direct current stimulation (tDCS) in the treatment of depression: systematic review and meta-analysis of efficacy and tolerability. Neurosci Biobehav Rev 2015;57:46–62. doi:10.1016/j.neubiorev.2015.07.012.

100 Dondé C, Amad A, Nieto I, et al. Transcranial direct-current stimulation (tDCS) for bipolar depression: a systematic review and meta-analysis. Prog Neuropsychopharmacol Biol Psychiatry 2017;78:123–131. doi:10.1016/j.pnpbp.2017.05.021.

101 Golden RN, Gaynes BN, Ekstrom RD, et al. The efficacy of light therapy in the treatment of mood disorders: a review and meta-analysis of the evidence. Am J Psychiatry 2005;162(4):656–662. doi:10.1176/appi.ajp.162.4.656.

102 Al-Karawi D, Jubair L. Bright light therapy for nonseasonal depression: meta-analysis of clinical trials. J Affect Disord 2016;198:64–71. doi:10.1016/j.jad.2016.03.016.

103 Tseng PT, Chen YW, Tu KY, et al. Light therapy in the treatment of patients with bipolar depression: a meta-analytic study. Eur Neuropsychopharmacol 2016;26(6):1037–1047. doi:10.1016/j.euroneuro.2016.03.001.

104 Wu JC, Kelsoe JR, Schachat C, et al. Rapid and sustained antidepressant response with sleep deprivation and chronotherapy in bipolar disorder. Biol Psychiatry 2009;66(3):298–301. doi:10.1016/j.biopsych.2009.02.018.