Major Depressive Disorder: Understanding Unmet Needs, Treatment Challenges, and Potential Implications of Pathways Beyond the Monoamine System

INTRODUCTION

Major depressive disorder (MDD) is a common mental health condition that affects more than 16% of adults in the United States. The incidence of MDD is highest in adults aged 18 to 25 years; an estimated 10.9% of American adults in this age group (3.7 million adults) had at least 1 major depressive episode (MDE) within the past year compared with 4.8% of adults aged 50 years or older.

MDD poses the most substantial disability burden among the mental or behavioral disorders, accounting for 3.7% of all disability-adjusted life years and 8.3% of all years lived with disability in the United States. In 1 survey-based interview study, 59.3% of patients reported severe (40.2%) or very severe (19.1%) impairment, as measured by the Sheehan Disability Scale for home, work, relationships, and social domains. MDD also causes a substantial economic burden that is increasing over time; in 2010, the incremental economic burden of individuals with MDD was $210.5 billion compared with $173.2 billion in 2005, representing a greater than 20% increase.

There are several treatment challenges in MDD. MDD is a heterogeneous mental disorder and despite the availability of pharmacologic treatments for MDD, treatment to complete remission is often a challenge. Many patients with MDD fail to achieve a complete response with antidepressant medications and experience periods with residual symptom burdens.7,8 Because a substantial number of patients with MDD achieve only a partial response to treatment with current medications, there remains an unmet need to manage residual symptoms for better long-term outcomes. Current antidepressant medications target the monoamine pathways; however, there is evidence supporting the involvement of multiple biologic pathways in MDD pathogenesis. Investigation into other potential pathways and signaling factors which may be implicated in MDD, including acetylcholine, dopamine, gamma-aminobutyric acid (GABA), glutamate, opioid, norepinephrine, and vasoactive intestinal peptide, may offer insight regarding the complexity of MDD.

DIAGNOSTIC CRITERIA OF MDD

MDD is defined and diagnosed using the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5) developed by the American Psychiatric Association (APA), which classifies symptom and severity criteria of MDD.

MDD is characterized by discrete episodes lasting at least 2 consecutive weeks where patients experience depressive symptoms that are not attributed to the physiological effects of a substance or symptoms from another comorbid medical condition. Most MDEs exceed 2 weeks and involve marked changes in affect and cognition.

Depressive Symptoms

The diagnosis of MDD is considered in patients who experience at least 5 of the 9 following depressive symptoms for the majority of the day and nearly every day for at least 2 consecutive weeks: depressed mood most of the day; loss of interest or pleasure in nearly all activities; weight loss or gain (clinically significant weight loss or weight gain of more than 5% of body weight in a month);
insomnia or hypersomnia; psychomotor agitation or retardation; fatigue and loss of energy; excessive feelings of worthlessness or guilt; indecisiveness, decision making, problem solving, inability to think clearly or concentrate; deficits in attention, or struggle with memory retention; or suicidal ideations or attempts. Of the 9 DSM-5 criterion depressive symptoms, at least 1 core symptom of depressed mood or loss of interest or pleasure must be present nearly every day for the majority of the day for a diagnosis of MDD.14

**Functional Impairment**
For the diagnosis of MDD, DSM-5 depressive symptoms must cause clinically significant distress, where patients experience a range of occupational, social, and other functional impairments.14 Depending on the severity, symptoms of MDD functional impairments may limit an individual’s capability to complete ordinary tasks (eg, perform self-care or basic needs) and some patients may even become mute.14

The severity of MDEs, which are classified as mild, moderate, or severe, are defined by the number of DSM-5 criterion symptoms, the severity of symptoms, and the degree of functional disability.14 Patients with MDD with mild severity MDEs have a greater number of symptoms than necessary for diagnosis, but these symptoms are considered manageable and only create minor impairments in social or occupational roles. Severe MDEs are characterized by having a substantial excess of diagnostic DSM-5 criterion symptoms that are unmanageable and distressing; these symptoms markedly impair patients’ social and occupational functioning.14

**Heterogeneity of MDD Symptoms and Association With Functional Impairments**
The symptomatic profiles of individual patients with MDD are highly heterogeneous; different patients diagnosed with MDD may share no common symptomatology.15 The combinations of the 9 DSM-5 criterion symptoms can produce 227 unique symptom profiles, each of which can qualify for a diagnosis of MDD. With the inclusion of sub-symptom variations, the number of unique profiles may increase to as many as 16,400 different profiles that could be diagnosed as MDD.15

Due to the heterogeneous nature of depression, patients with the same quantity of depressive symptoms may present with different impairments in functioning.16 Several studies have investigated the relationship between individual DSM-5 criterion symptoms of MDD and functional impairments in patients with MDD.16,17

In an analysis of self-reported impairments in functioning from 3703 patients with MDD from the STAR*D (Sequenced Treatment Alternatives to Relieve Depression) study, investigators evaluated the severity of 14 individual symptoms from the 9 DSM-5 criterion depressive symptoms.16 The results demonstrated that individual DSM-5 MDD symptoms varied in their influence of impairment of normal functioning graded across 5 functional domains, including work, home management, close relationships, and social and private activities.16

The heterogeneity of symptom profiles and severity of MDD presents a substantial treatment challenge as patients may have varying responses to management approaches.11,14 The burden of individual MDD symptoms on multiple functional domains adds to the complexity of treatment selection and an effective MDD pharmacotherapy requires trying various medications.9,11 Increasing the difficulty in treating patients with MDD are those individuals who have treatment-resistant depression (TRD), or patients with MDD that fail to achieve remission after treatment with at least 2 different antidepressant medications.6,18,19 There is an unmet need for multiple approaches to be available for the management of MDD to address the burden of symptom variations and its impact on response and function.

**ECONOMIC BURDEN**
MDD is associated with substantial economic burden, with total costs estimated at $210.5 billion in 2010.6 Of those, 47% ($98.9 billion) were attributable to direct costs (hospitalizations, emergency department visits, and prescription medications) and 48% ($102 billion) to the indirect costs of absenteeism and presenteeism.6 Co-occurring disorders such as anxiety disorders, adjustment disorders, post-traumatic stress disorder, and nonpsychiatric medical conditions, such as chronic pain and insomnia, add to this financial burden.6

Presenteeism, or the reduced productivity from patients with depressive symptoms in the workplace, poses a large financial burden. In an analysis of commercial healthcare claims from nearly 375,000 employees over 3 years (1997 to 1999), presenteeism accounted for 71% of the economic burden of physical and mental illnesses for employers.20 Together, mental health disorders of depression, sadness, and mental illness were the third largest contributors to costs incurred from workplace presenteeism, behind the costs from hypertension and heart disease.20 The total economic burden from aggregate medical costs and productivity losses associated with depression, sadness, or mental illness was $348 per eligible employee per year, slightly less than hypertension and heart disease ($392 and $368, respectively).20

TRD contributes to the highest direct and indirect medical costs among those with MDD and these costs increase with the degree of TRD.21,22 Treatment-resistant patients are twice as likely to be hospitalized, and their cost of hospitalization is more than 6 times the mean total cost for patients with depression who are not treatment resistant.23 Compared with patients with non-TRD, TRD can nearly double direct and indirect 2-year employer medical expenditures.24

**PATHOPHYSIOLOGY**
Biological and environmental factors may contribute to a patient’s susceptibility for depression. Patients’ MDD may be impacted by varying genetic, epigenetic, endocrine, and environmental factors, such as traumatic or stressful life events, all of which could contribute to the heterogeneity of MDD.25

While the exact biological pathophysiology behind MDD is unknown, the major focus of treatment to date has been targeting monoamine pathways.10 The monoamine hypothesis proposes that depression is the result of deficiency in 1 or more monoamines (serotonin, norepinephrine, dopamine).10 However, monoamine pathways may be a
component of a much more intricate system of neural pathways that could form the basis of MDD. Numerous pathways and biological processes may have a role in the disease of MDD, including pathways which regulate serotonin, acetylcholine, dopamine, GABA, glutamate, opioid, norepinephrine, and vasoactive intestinal peptide, and have implications for patients with MDD. The endogenous opioid system is also thought to play an integral role in mood regulation, and previous studies have found that endogenous opioid systems differ between healthy patients and those diagnosed with MDD.

**TREATMENT OF MDD AND ASSESSING TREATMENT RESPONSE**

**Phases of MDD Treatment and Goals**

The current pharmacological treatment options recommended by the APA are antidepressant medications, which are primarily monoamine-based. These include tricyclic antidepressants (TCAs), monoamine oxidase inhibitors (MAOIs), selective serotonin reuptake inhibitors (SSRIs), serotonin-norepinephrine reuptake inhibitors (SNRIs), and norepinephrine-dopamine reuptake inhibitors (NDRIs). Depending on patient response or severity of MDD, antidepressant medications can be augmented with adjunctive treatment (ie, atypical antipsychotics). Additionally, the APA guidelines recommend that clinicians consider the efficacy, side effects, and adherence when selecting an antidepressant medication for each patient. Undertreatment of patients with MDD is common; currently, an estimated 37% of adults who experienced an MDE did not receive treatment.

The APA practice guideline for the treatment of patients with MDD divides treatment into 3 phases: acute, continuation, and maintenance.
- Antidepressant agents are recommended as the initial treatment for patients with mild, moderate, or severe MDD during the acute phase of treatment. The goals of the acute phase of MDD treatment are to allow patients to achieve remission and return to their normal daily functional capacity. The acute phase of MDD treatment typically lasts an average of 6 to 12 weeks.
- Patients who have successfully completed the acute phase of therapy with antidepressant medications continue treatment with the same agent, dose, intensity, and frequency that were effective during the acute phase to reduce the risk of relapse during continuation. The continuation phase typically lasts 4 to 9 months. The aim of treatment is to preserve remission and prevent relapse, which is the reemergence of MDD symptoms or functional impairments following remission where patients are most vulnerable to developing an MDE.
- After the continuation phase, patients who do not relapse can proceed to the maintenance phase of treatment. Maintenance treatment should be considered in patients with 3 or more prior MDEs, or those with additional risk factors for a recurrent MDE (eg, residual symptoms, early age of onset, family history of mood disorders). The goal of maintenance treatment is to reduce the risk of recurrent MDEs, given that 20% of patients will experience a recurrence within the first 6 months following recovery from an MDE.

**MDD Treatment Response**

Patient response to treatment may be variable; approximately 10% to 30% of patients with MDD who take antidepressants experience a poor response with residual symptoms and need to attempt a variety of treatment alternatives. As the disease course of MDD is variable, different patients may experience MDEs of varying severity, frequency, and characteristics of symptom onset which may affect treatment response. For example, after a period of recovery, some patients with MDD may experience years without symptoms or they may have periods with few residual symptoms.

According to the American College of Neuropsychopharmacology (ACNP), response to therapy can be defined as a clinically meaningful change in MDD symptoms such that a patient experiences an improvement in mood, function, or pain. The determination of a clinically meaningful benefit of treatment depends on the initial severity of MDD, degree of resistance to the antidepressant medication, and the rating scale used to assess benefit in symptom improvements. The ACNP defines a typical meaningful response as a greater than 50% reduction in pretreatment severity using the Hamilton Rating Scale for Depression (17 items) or the Inventory of Depressive Symptomatology.

Some patients may respond only partially to treatment, particularly those with personality disorders and those undergoing psychosocial stress; in these cases, extending the duration of treatment by 4 to 8 weeks may improve response in up to an additional one-third of patients. For patients who have undergone 4 to 8 weeks of treatment but have not achieved a complete response to therapy, adjusting the intensity of psychotherapy or increasing the dose of medication are potential strategies.

Even with multiple antidepressant medications, patients with MDD do not always achieve remission and often experience residual symptom burdens. Despite substantial improvements in somatic burden, residual symptoms of an MDE are associated with a more than 3 times faster rate of relapse to the next MDE compared with asymptomatic recovery.

**Achieving Remission**

The criteria and definition of remission with treatment for MDD differs across the available guidelines.
- The APA practice guidelines and ACNP Taskforce indicate remission is achieved during the acute phase when patients experience at least 3 weeks without the core depressive symptoms of sad mood and reduced interest, and when patients present 3 or fewer symptoms meeting criteria for an MDE.
- According to the DSM-5 manual, remission may be defined as a period of 2 or more months without symptoms, or with 1 to 2 symptoms of MDD of mild severity. Patients who achieve partial remission present with a low number of residual symptoms from the previous MDE, but no longer meet diagnostic criteria, or experience a period of less than 2 months without any clinically significant depressive symptoms at the end of the index MDE. Full remission is characterized by a period of 2 months at the end of the index MDE without clinically depressive significant signs or symptoms.
The course of MDD remission may widely vary between patients. As the duration of remission increases, the risk of recurrence decreases gradually over time.14 Although some patients with MDD may experience remission that lasts years, many patients with MDD will not achieve remission.14,15 Approximately 50% to 85% of patients with MDD will have at least 1 recurrence within their lifetime, usually within 2 or 3 years; however, the time to recurrence varies.13 A chronic presentation of depressive symptoms lowers the probability that the patient will successfully achieve full symptom resolution. For patients who have experienced multiple episodes during their lifetime, the risk of recurrence increases by 16% with each successive episode.11 Additionally, the severity of symptoms during remission is associated with lower recovery rates, and recurrence rates are higher for patients with severe episodes or multiple episodes.13,14

Recurrence is especially high among patients with persistent mild depressive symptoms during remission.11 Mild depressive symptoms during remission, or residual symptoms, strongly predict the likelihood of a recurrent MDE.14 In addition to the presence of residual symptoms, the risk of recurrence is also higher for patients who have risk factors such as psychosocial stress, family history of mood disorders, and severe prior episodes.11

**Evidence of Inability to Achieve Remission With First-Line Treatment**

Results of the STAR*D study indicated that patients with difficult-to-treat depression can improve as a result of trying different courses of treatment, although the chance of resolving the symptoms of depression diminished with each additional treatment.3,27 The STAR*D trial also highlighted the unmet need of additional therapy options for patients who do not respond to first-line treatment. It is not uncommon for patients to fail to achieve remission or a response to therapy. Of the patients who completed step 1 treatment with a first-line antidepressant, 325 patients failed to achieve remission (63.3%) and 1895 patients failed to respond to therapy (51.6%).3

**Increased Risk of Relapse With Residual Symptom Burdens**

Studies suggest that the presence of residual symptoms is associated with an increased risk of relapse, and that patients with a greater number of residual symptoms have a higher risk of relapse.26 An analysis of STAR*D study data explored the residual symptomatic burdens of MDD in patients receiving antidepressant therapy and identified the most common and persistent symptoms over the course of treatment.27 Response to treatment was defined in patients who achieved a 50% or greater reduction in the 16-item Quick Inventory of Depressive Symptomatology (Self-Report) (QIDS-SR16) score from baseline at the end of the 12-week treatment course.

Of the 4041 patients, 71% (n = 2876) achieved a response to antidepressant treatment. Among those who responded, 428 patients (15%) did not achieve remission, defined as patients who achieved a total QIDS-SR16 score of 5 or less in symptomatic burden at the conclusion of treatment.27 Approximately 75% of patients who did not achieve remission reported 5 or more residual DSM-5 depressive symptoms of at least mild severity. Most common mild severity symptoms in these patients included insomnia (94.6%), sad mood (70.8%), decreased concentration (69.6%), and psychomotor disturbances (67.3%).27

Another investigation highlighted the prevalent and persistent symptom burdens throughout the course of MDD, despite treatment.29 In a prospective study, 267 patients with depression were evaluated over 3 years to assess the presence of DSM-IV criterion MDD symptoms during periods of an MDE and a non-MDE.29 Patients in this study experienced the core symptoms of sad mood and loss of interest 100% of the time during an MDE and 21% of the time during non-MDE periods. The 3 most prevalent symptoms were poor concentration and indecisiveness, lack of energy, and difficulty with sleeping, which occurred 85% to 94% of the time during an MDE and 35% to 44% of the time during non-MDE periods.29 Additional symptoms such as worthlessness or guilt, eating problems, suicidal ideation, and psychomotor impairment also remained prevalent during both states of an MDE and a non-MDE.29

Patients with MDD who experience complete symptom resolution have been observed to be more likely to remain symptom-free compared with patients who have experienced symptom improvement.11 Among 237 patients with MDD, those without residual symptoms did not experience an MDE recurrence until a median 4.4 years, compared with just over 1 year in those with residual symptoms.30 A more recent analysis led by the same group found that 61.2% of patients recovered asymptomatically from their index MDE,31 and that these patients remained free of a depressive episode relapse or recurrence 4.2 times longer than those with residual symptoms (135 vs 32 weeks; P < .0001).31 The consequences of a patient failing to achieve remission may include recurrent episodes of MDD, significant psychosocial disability, faster relapse rate, a potentially chronic future disease course, and work impairment.11

**Treatment-Resistant Depression**

TRD is a common clinical occurrence that affects up to 30% of patients with MDD. Patients who do not respond to treatment exhibit treatment-resistant symptoms and difficulties in social and occupational function, deterioration of physical health, suicidal ideation, and increased healthcare utilization. Currently, no clear consensus exists for TRD criteria and more than 15 different definitions may exist; this inconsistency may interfere with research regarding TRD treatment options.39,42 However, an emerging consensus is that major depression is usually considered resistant when at least 2 appropriate trials of antidepressants from different pharmacological classes have failed to produce clinical remission.19

**UNDERSTANDING CHALLENGES IN ANTIDEPRESSANT TREATMENT RESPONSE: POTENTIAL IMPLICATIONS OF ADDITIONAL PATHWAYS**

Due to the diverse array of symptom profiles and underlying pathology, patients’ response to antidepressant treatment widely varies. Rather than being one single disorder, depression results from varying pathophysiology, and thus patients may respond best to personalized treatment.35
Agents currently approved for the treatment of MDD primarily target the monoamine pathway and fall into several categories: SSRIs; SNRIs; TCAs; MAOIs, and NDRIs. The monoamine hypothesis suggests that MDD is associated with reduced monoamine function and has been the prevailing hypothesis of depression pathophysiology for several decades. Current pharmacologic treatment options for MDD therefore target the monoamine system; however, other pathways may be involved, and the heterogeneity of symptoms in patients with MDD warrants the investigation of the potential role of other pathways in MDD.

The SSRIs and SNRIs, which came on the market over 30 years ago, have been recommended as the first-line treatment for MDD and are among the most widely used pharmacologic psychiatric medications. As both SSRIs and SNRIs affect monoamines, attempts have been made to better understand the monoaminergic mechanisms by targeting additional monoamine receptors or transporters and enhancing the effects of SSRIs and SNRIs with adjunctive treatment. The main objectives of this approach have been to increase the medication's efficacy or reduce the time to therapeutic benefit of SSRIs and SNRIs.

As discussed previously, depending on patient response or severity of MDD, antidepressant medications can be augmented with adjunctive treatment (ie, atypical antipsychotics). Other antidepressants have been used as alternative monotherapy or adjunctive treatment in the event that the patient experiences an inadequate response to SSRIs or intolerable side effects associated with SSRIs, such as sexual dysfunction and weight gain.

**Implications of Additional Pathways in MDD**

Pathways possibly involved in MDD include: glutamate, cholinergic, and GABA. Changes in stress hormones and neuronal plasticity are also involved.

**Glutamate System**

The glutamate system may be involved in MDD. In healthy patients, normal glutamatergic activity is thought to be involved in maintaining normal neuroplasticity. Under conditions of stress or depression, glutamate signaling is impaired and leads to a reduction in neuroplasticity.

**Cholinergic Hypothesis**

Pharmacologic and molecular decreases in hippocampal acetylcholinesterase activity have been associated with an increase in depression-like behaviors. In addition, patients who are actively depressed have substantially higher levels of extracellular acetylcholine than their healthy counterparts, further supporting the potential role of the cholinergic system in MDD. While the inhibition of cholinesterase has been shown to exacerbate depression, muscarinic antagonists (eg, TCAs) have antidepressant activity. Current data on the role of the cholinergic/adrenergic system in precipitating MDD is limited.

Acetylcholinesterase inhibitors include donepezil, rivastigmine, and galantamine, and have been evaluated in patients with depression as adjunctive therapy for enhancing cognition and decreasing the symptoms of depression.

**GABA**

Reduced levels of the inhibitory amino acid neurotransmitter GABA may be involved in the etiology of MDD. GABA deficiency has been consistently documented in adults and teenagers with depression, including those with treatment-resistant depression. Further research with respect to this pathway may be informative.

**Inflammation**

Acute traumatic or chronic stress is the most significant factor that influences a patient's susceptibility for depression. Inflammation triggered by stress is also thought to be involved in the pathobiology of depression. Specifically, stress causes the hypothalamus to secrete corticotropin-releasing hormone. The sympathetic nervous system stimulates the adrenal medulla to release epinephrine and norepinephrine in response to stress. Epinephrine and norepinephrine modulate cytokine release through alpha- and beta-adrenoceptors of immune cells and increase pro-inflammatory cytokines such as interleukin-6 and tumor necrosis factor alpha. Therefore, in MDD, continuous sympathetic activity may increase pro-inflammatory cytokine levels. The effect of stress on inflammatory hormones and the beneficial effect of anti-inflammatory drugs on depression suggests that pathways mediating stress response may be informative.

**Neuroplasticity**

Neuroplasticity has been defined as the ability of the central nervous system to respond to changes in the environment. This adaptation may involve modifications in overall cognitive strategies to successfully cope with new challenges, recruit new or different neural networks, or change the strength of connections or specific brain areas (eg, areas involved in movement, language, vision, and hearing). Brain scans in patients with MDD showed reduced gray matter compared with that in healthy controls, and this reduction correlated with the duration and severity of depression. Additionally, patients with MDD had a reduced number of synapse-related genes in the prefrontal cortex compared with healthy controls. Of note, enhanced neurogenesis and synaptogenesis appear to represent a common mechanism across antidepressants.

**Exploring the Potential Role of the Endogenous Opioid Pathway in Mood Regulation**

From analyses of functional magnetic resonance imaging and positron emission tomography (PET) scans, studies have demonstrated that there may be overlap between the brain's opioidergic system and emotional circuits. During periods of different emotions, opioid release may occur through emotion-motivational circuits.
animal models and human studies have found evidence that these regions can be modulated by behaviors and experiences and may play an integral role in mood regulation. One study found that meditation may modulate pain response and that this effect was reversed by the administration of an opioid antagonist; this finding may suggest the involvement of the endogenous opioid system. Likewise, the act of laughing appears to stimulate endorphin release and produces a subsequent opiate effect that is demonstrated by an increased pain threshold. In animal studies, acute and chronic exercise were shown to modulate opioid receptor binding in various areas of the brain. These studies further suggest that the opioid system plays a role in mood regulation in response to environmental stimuli.

The endogenous opioid system is widely, but selectively, distributed throughout the central and peripheral nervous systems. The endogenous opioid system is involved in pain modulation, autonomic control, and stress and reward responses. The complex neuromodulatory system consists of the 3 receptors (mu, delta, and kappa) which interact with a family of endogenous opioid peptides known as beta-endorphin, enkephalins, and dynorphins. Beta-endorphin exert biological effects primarily through activation of mu opioid receptors (MOR). MORs regulate reward processes, analgesia, and mood. Enkephalin-mediated activation of delta opioid receptors (DOR) regulates analgesia and emotional states, but activation of DORs act in opposition to MORs. Dynorphins interact with kappa opioid receptors (KOR) and stimulate KOR activity. KOR activation is associated with an anti-reward system that involves dysphoria and limits the motivational properties associated with drugs of abuse. In addition, KORs are also recruited and activated during stressful experiences, thereby contributing to the emergence of depressive states.

Neurons containing beta-endorphin, a main opioid peptide, have widespread projections and are mostly localized in 2 areas, the arcuate nucleus of the hypothalamus and the nucleus tractus solitarius. Enkephalin and dynorphin, the other 2 main opioid peptides, are primarily located in local neurons and are spread heterogeneously throughout the central nervous system. For example, the precursor to enkephalin is abundantly expressed in the thalamus and the dynorphin precursor molecule is present in the hippocampus, hypothalamus, and nucleus accumbens. Opioids are also co-expressed in various regions with other neurotransmitters, such as GABA.

THE POTENTIAL LINK BETWEEN ENDOGENOUS OPIOIDS AND THEIR RECEPTORS: A POTENTIAL UNDERLYING ABNORMALITY IN MDD

Compared with healthy controls, altered MOR activity has been observed in the brains of patients with MDD. Specifically, in a study of 28 female participants, no evidence of mu-opioid system activation was documented in the healthy control group in response to the induction of a sustained sadness state. Patients with MDD demonstrated significant activation of mu-opioid neurotransmission in the left inferior temporal cortex (P < .01), represented as reduction in mu-opioid receptor availability from the neutral to the sadness state. The MOR system is hypothesized to dampen “social pain” because of the similar pathways shared by social rejection and physical pain. In a study comparing patients with MDD on antidepressants (n = 17) with healthy controls (n = 18), investigators used PET scanning with carfentanil to test the difference in MOR system activation in response to social rejection and acceptance. During rejection, patients in the healthy control group experienced MOR activation in multiple brain regions, while patients in the MDD group experienced MOR deactivation in the amygdala and slower emotional recovery. Patients with MDD also had reduced MOR activation and endogenous opioid release in the brain regions regulating stress, mood, and motivation. These observations regarding the potential role of the MOR system could help explain the observation that some patients with MDD experience slow recovery from rejection and poor engagement in positive social interactions.

Kappa-opioid ligands may also have a potential role in MDD. In vivo studies in rats have demonstrated the effects of systemic KOR drugs in depression. Norbinaltorphimine, an opioid antagonist highly selective to the kappa-opioid receptor, and 5′-guanidinonaltrindole, a dissimilar antagonist, produced antidepressant effects in forced swimming and learned helplessness, which suggest that these antidepressant-like effects may be due to KOR selectivity. Agonism of the KOR adversely affects mood in humans and may be reversed with receptor antagonism; in a study of male subjects, administration of a benzomorphan kappa agonist resulted in dose-dependent dysphoric and psychotomimetic effects that were antagonized by naltrexone.

Greater understanding of the role of the opioid system, as well as other systems beyond the monoamine system, may advance our understanding of MDD.

CONCLUSION

MDD poses a tremendous national healthcare burden. In the United States, the debilitating effects of MDD result in high direct and indirect costs due to treatment, hospitalizations, absenteeism, and presenteeism. Additionally, more than 90% of patients with MDD who achieve remission continue to experience at least 1 residual symptom. Patients with MDD who partially respond to treatment may continue to experience residual symptoms that impair role functioning at work and home, and in social activities and interpersonal relationships. Unlike patients whose symptoms resolve completely, continued residual symptoms are associated with a higher risk of relapse, highlighting the urgent unmet need to manage residual symptoms for better long-term outcomes in patients with MDD. Pathways in addition to the monoamine pathway, including the opioid, glutamate, cholinergic, and GABA pathways, may have implications for patients with MDD. Further investigation of these pathways may provide a deeper understanding of the complexities of MDD and help address some of the unmet needs of patients with MDD.

Acknowledgement

This article is sponsored by Alkermes, Inc.