Major depressive disorder: mechanism-based prescribing for personalized medicine

Abstract: Individual patients with depression present with unique symptom clusters – before, during, and even after treatment. The prevalence of persistent, unresolved symptoms and their contribution to patient functioning and disease progression emphasize the importance of finding the right treatment choice at the onset and the utility of switching medications based on suboptimal responses. Our primary goal as clinicians is to improve patient function and quality of life. In fact, feelings of well-being and the return to premorbid levels of functioning are frequently rated by patients as being more important than symptom relief. However, functional improvements often lag behind resolution of mood, attributed in large part to persistent and functionally impairing symptoms – namely, fatigue, sleep/wake disturbance, and cognitive dysfunction. Thus, patient outcomes can be optimized by deconstructing each patient’s depressive profile to its component symptoms and specifically targeting those domains that differentially limit patient function. This article will provide an evidence-based framework within which clinicians may tailor pharmacotherapy to patient symptomatology for improved treatment outcomes.

Keywords: MDD, tailored pharmacotherapy, patient-specific profile, individualized pharmacotherapy

Defining depression

Depression is the most common psychiatric disorder and the leading cause of disability worldwide.1,2 In the US, about 7%–9% of the adult population experiences a major depressive episode (MDE) each year and an estimated 8 million (3.4%) meet criteria for major depressive disorder (MDD).3–5 The cognitive, emotional, and physical symptoms of depression translate to considerable impairments in psychosocial functioning across physical, social, and educational/occupational domains.6,7 Indirect workplace costs alone, characterized by low productivity (presenteeism) and days missed (absenteeism), account for over 60% of the total economic burden of depression and twice as much as that attributed to direct medical costs.8

The likelihood of long-term treatment success is improved with early and accurate diagnosis, continual multidimensional assessment, and rational pharmacotherapy tailored to the patient’s symptomatology, coexisting disorders, and treatment needs.9 Yet achieving these outcomes is confounded by the personal and multidimensional nature of the disease itself. There are no validated biological tests that can be used to diagnose depression. Further, without objective outcomes measures, clinicians must gauge treatment response and make clinical decisions over time based on subjective impressions of patient-reported symptoms.9–11

Validated assessment tools (eg, Montgomery–Åsberg Depression Rating Scale, Hamilton Rating Scale for Depression [HAM-D21]) based on core criteria (Table 1)12 can facilitate the categorical diagnosis of depression and help track the presence and...
Diagnosis of recurrent MDD requires that at least one of the symptoms is 1) depressed mood or 2) loss of interest or pleasure during a 3-year prospective study of at least 2 weeks and symptoms must be present almost every day for at least 2 weeks. In fact, patients with unresolved depressive symptoms are three times as likely to relapse as patients with asymptomatic recovery. Moreover, feelings of well-being and the return to premorbid levels of functioning are frequently rated by patients as more important than symptom relief, yet functional improvements often lag behind resolution of mood. Reasons for delayed functional recovery are only partly characterized; however, the symptoms that most impair function are the same symptoms that often show greater depressive illness burden as symptoms persist. The Sequenced Treatment Alternatives to Relieve Depression (STAR*D) study of nearly 4,000 ‘real-world’ outpatients reported a cumulative remission rate of 67% after four treatment steps; however, about 70% relapsed within 1 year. Figure 1 depicts a schematic representation of the progressive nature of depression, and illustrates the need for achieving and sustaining full symptom recovery early in disease pathogenesis.

Symptoms that persist during remission are associated with relapse, recurrence, and ultimately, treatment resistance. During a 3-year prospective study of 267 depressed patients, Conradi et al assessed the weekly presence of individual symptoms during each phase of depression (Figure 2). Study participants who relapsed within 8 weeks reported a greater overall symptom severity during the remission period than those who remained in remission for greater than 8 weeks (ie, in recovery). Gradual accumulation of subthreshold symptoms over time appeared to trigger the relapse, suggesting that the initial MDE had not resolved and remained subsyndromal only temporarily. In fact, patients with unresolved depressive symptoms are three times as likely to relapse as patients with asymptomatic recovery.

The prevalence of unresolved symptoms and their contribution to disease progression emphasize the importance of finding the right treatment choice at the onset and switching medications if necessary based on suboptimal responses. Moreover, feelings of well-being and the return to premorbid levels of functioning are frequently rated by patients as more important than symptom relief, yet functional improvements often lag behind resolution of mood. Reasons for delayed functional recovery are only partly characterized; however, the symptoms that most impair function are the same symptoms.

**Table 1 DSM-5 criteria for MDE**

- At least five of the following symptoms that cause clinically significant distress or impairment in social, occupational, or other important areas of functioning
- At least one of the symptoms is 1) depressed mood or 2) loss of interest or pleasure
- Symptoms must be present almost every day for at least 2 weeks
  - Depressed mood most of the day
  - Diminished interest or pleasure in all or most activities
  - Significant unintentional weight loss or gain
  - Insomnia or sleeping too much
  - Agitation or psychomotor retardation noticed by others
  - Fatigue or loss of energy
  - Feelings of worthlessness or excessive guilt
  - Diminished ability to think or concentrate, or indecisiveness
  - Recurrent thoughts of death
- Diagnosis of recurrent MDD requires ≥2 MDEs separated by at least 2 months in which criteria are not met for an MDE

**Abbreviations:** DSM-5, Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition; MDD, major depressive disorder; MDE, major depressive episode.

Severity of symptoms at each visit. However, clinicians may find it more practical to ask about symptoms directly through the course of the patient interview. Direct questioning combined with a clinical impression formed by the patient’s speech, affect, and appearance can help define how individual symptoms adversely affect patient-specific functioning and quality of life (QoL). If the symptom profile of an MDE is not properly assessed before and during a well-orchestrated antidepressant trial, ongoing symptoms may not be easily distinguished from treatment-related side effects or from those due to comorbid psychiatric or medical conditions. About half of patients who report normal functioning consider themselves to be in remission from depression despite persistent depressive symptoms. Therefore, understanding the relationship between the symptoms of depression and how they adversely affect patient functioning is essential for optimized clinical decision making.

**Defining recovery**

The gold standard for treatment is the full resolution of symptoms and associated improvements in function and QoL. While response to treatment implies a clinically meaningful degree of symptom reduction (typically defined as ≥50% reduction in pretreatment symptom severity), remission and recovery require that the symptoms of depression be absent or close to it (Figure 1). Many clinical studies define remission as low scores on rating scales, which is not equivalent to an asymptomatic state. Further, as depressed mood and loss of interest generally overshadow other symptoms of depression, when mood improves, patients may misguidedly be considered in remission. In fact, most patients considered ‘in remission’ do not actually achieve complete resolution from all symptoms, even after multiple treatment steps, and often show greater depressive illness burden as symptoms persist.
that commonly persist despite treatment, namely fatigue, sleep/wake disturbance, and cognitive dysfunction.6,18,29,31–33 For example, patient self-reports frequently identify fatigue and low energy, insomnia, and concentration and memory problems as especially disruptive to occupational and global functioning.6,32 In the seminal study by Conradi et al (Figure 2), patients exhibited problems with cognition 60% of the time during periods of remission compared with 41% during periods of recovery.29 Similarly, a lack of energy was reported nearly half of the time during remission but only...
one-third of the time during recovery. These data suggest that antidepressant selection based, in part, on the most disabling patient-reported symptoms may help optimize treatment outcomes and add to a growing body of evidence on the importance of initial and ongoing individualized assessment. Table 2 highlights the MDD-associated symptoms that may co-occur during depressive episodes or persist during remission. While additional studies are needed to gauge the most effective treatments for these symptoms, Table 2 includes select approaches with demonstrated efficacy.

| Table 2 Possible pharmacotherapeutic approaches for the treatment of select symptoms in MDD |
|-------------------------------------|-------------------------------------|
| **Symptom**                        | **Pharmacotherapy**                |
| Anxiety                             | • Buspirone                        |
|                                     | • Citalopram                       |
|                                     | • Escitalopram                      |
|                                     | • Fluoxetine                        |
|                                     | • Fluvoxamine                       |
|                                     | • Lorazepam                         |
|                                     | • Mirtazapine                       |
|                                     | • Sertraline                        |
|                                     | • Venlafaxine                       |
|                                     | • Vilazodone                        |
|                                     | • Vortioxetine                      |
|                                     | • Doxepin                           |
|                                     | • Donepezil                         |
|                                     | • Duloxetine                        |
|                                     | • Galantamine                       |
|                                     | • Methylphenidate                   |
|                                     | • Modafin                           |
|                                     | • Vortioxetine                      |
| Cognitive problems                  | • Amantadine                        |
|                                     | • Amoxapine                         |
|                                     | • Clonazepam                        |
|                                     | • Esmolol                            |
|                                     | • Galantamine                       |
|                                     | • Methylphenidate                   |
|                                     | • Modafin                           |
|                                     | • Paroxetine                        |
|                                     | • Ramelteon                         |
|                                     | • Trazodone                         |
|                                     | • Zaleplon                          |
|                                     | • Zolpidem                          |
| Insomnia                            | • Atomoxetine                       |
|                                     | • Bupropion                         |
|                                     | • Claritine                         |
|                                     | • Duloxetine                        |
|                                     | • Fluoxetine                        |
|                                     | • Modafin                           |
|                                     | • Sertraline                        |
|                                     | • Venlafaxine                       |
| Lack of energy/fatigue              | • Atomoxetine                       |
|                                     | • Bupropion                         |
|                                     | • Desvenlafaxine                    |
|                                     | • Duloxetine                        |
|                                     | • Esmolol                            |
|                                     | • Milnacipran                       |
|                                     | • Nortriptyline                     |
|                                     | • Paroxetine                        |
|                                     | • Ramelteon                         |
|                                     | • Trazodone                         |
|                                     | • Zaleplon                          |
|                                     | • Zolpidem                          |
|                                     | • Ziprasidone                       |
|                                     | • Venlafaxine                       |
|                                     | • Mirtazapine                       |
|                                     | • Vortioxetine                      |
|                                     | • Doxepin                           |
|                                     | • Desvenlafaxine                    |
|                                     | • Sertraline                        |
|                                     | • Venlafaxine                       |
|                                     | • Zaleplon                          |
|                                     | • Zolpidem                          |
|                                     | • Ziprasidone                       |
|                                     | • Venlafaxine                       |
|                                     | • Mirtazapine                       |
|                                     | • Atomoxetine                       |
|                                     | • Bupropion                         |
|                                     | • Modafin                           |

Notably, reduced hippocampal volume is common among depressed patients and directly correlates with frequency and length of depressive episodes. The hippocampus plays a salient role in explicit memory formation, homeostatic adaptation to stressful stimuli, and emotion processing. Hippocampal volume reductions were found to occur after disease onset, emphasizing the importance of early treatment to minimize disease progression. Further, discrete brain regions of depressed patients – including the prefrontal and limbic areas – demonstrate differential metabolic rates, reflecting aberrant neural activity thought to contribute to depressive symptomatology. In addition to structural changes, alterations in neural function in the brain are also implicated in the neurobiology of MDD. A recent neuroimaging study that investigated reduced gray matter volume in the parietal–temporal regions and functional alterations in the temporal regions and cerebellum in patients with MDD suggested that structural and functional deficits contributed independently to the neurobiology of the disease. While the relationship between altered brain structure and function and MDD symptoms remains an active area of research, the data increasingly suggest that core criterion symptoms of depression can be mapped to these and other regions of the brain (Figure 3).

**Note:** Most SSRIs are also approved by the US Food and Drug Administration to treat generalized anxiety disorder.

**Abbreviations:** MDD, major depressive disorder; SSRI, selective serotonin reuptake inhibitor.
Individualized pharmacotherapy for major depressive disorder

Figure 3 Neurotransmitters and their hypothetically malfunctioning brain circuits in regions associated with the diagnostic symptoms for depression.

Notes: Depression diagnosis requires at least one of these *symptoms and †4 of these ‡symptoms. From Lum CT, Stahl SM. Opportunities for reversible inhibitors of monoamine oxidase-A (RIMAs) in the treatment of depression. CNS Spectrums. 2012;17(3):107–120, reproduced with permission.

Abbreviations: A, amygdala; BF, basal forebrain; C, cerebellum; H, hypothalamus; NA, nucleus accumbens; NT, neurotransmitter centers; PFC, prefrontal cortex; S, striatum; SC, spinal cord; T, thalamus.

- Appetite and weight changes
- Guilt and feelings of worthlessness
- Suicidal ideation
- Depressed mood
- Sleep disturbances
- Psychomotor disturbances
- Apathy
- Executive dysfunction
- Fatigue

Serotonin
Norepinephrine
Dopamine
The structure and function of these brain regions are modulated by monoaminergic neurotransmission. The serotonin (5-hydroxytryptamine, 5HT), norepinephrine (NE), and dopamine (DA) systems originate from the brainstem and each project to select brain regions (Figure 3). The interdependent biological actions of 5HT, NE, and DA are mediated by their cognate transporters and receptors. For example, the serotonin 5HT1A and 5HT2C receptor subtypes inhibit postsynaptic connections on the NE and DA systems, respectively. D2-like receptor subtypes and alpha-1 adrenoceptors can positively influence 5HT neurotransmission while presynaptic alpha-2 adrenoceptors are thought to dampen 5HT signaling (Figure 4). Further, in addition to directly influencing extracellular monoamine levels, postsynaptic 5HT receptors (eg, 5HT1A, 5HT2A, 5HT3) modulate inhibitory gamma-aminobutyric acid (GABA) interneurons, which in turn affect the release of 5HT itself, acetylcholine (ACh), NE, DA, and glutamate (Glu) (Figure 4). 

Interconnected monoaminergic neurotransmission provides a neural basis for mood, reward, pleasure, motivation, and related cognitive and executive functions. Critically, disturbances in the functional connectivity in these and related neural networks appear to be integrally involved in the onset and progression of major depression. Aberrant DA and NE signaling is thought to adversely influence motivation, an essential driver of goal-directed behaviors and related executive functions. Impaired 5HT neurotransmission forms, at least in part, the pathophysiologic basis for anhedonia, guilt, and similar ‘negative affects’ of depression. Further, 5HT and NE have descending spinal pathways that mediate physical fatigue and related somatic symptoms. Of note, numerous studies have demonstrated

**Figure 4** The serotonergic synapse.

**Notes:** Serotonin (5HT) is produced from tryptophan and packaged into storage vesicles until its release into the synapse. Multiple postsynaptic 5HT receptors interact with SHT to mediate its signaling and modulate diverse systems such as NE, 5HT, ACh, GABA, and Glu. Excess 5HT is removed from the synaptic cleft by SERT or degraded to an inactive metabolite 5HIAA by MAO. Presynaptic 5HT1A and 5HT2C autoreceptors detect the presence of 5HT in the synapse and shut down further 5HT release, while D2-like dopamine receptors and α1- and α2-adrenoceptors positively (+) or negatively (−) influence 5HT transmissions.

**Abbreviations:** 5HIAA, 5-hydroxyindoleacetic acid; 5HT, 5-hydroxytryptamine or serotonin; ACh, acetylcholine; DA, dopamine; GABA, gamma-aminobutyric acid; Glu, glutamate; MAO, monoamine oxidase; NE, norepinephrine; SERT, serotonin transporter.
an increased risk for depression linked to genetic polymorphisms of 5HT, NE, or DA receptor subtypes and transporters.\textsuperscript{48}

While the particulars are extraordinarily complex and still only partly understood, monoamine signaling clearly exerts profound ‘downstream’ effects – both inhibitory and stimulatory – on interconnected neural networks, disturbances of which can manifest as depressive symptoms and contribute to disease progression.\textsuperscript{32} Importantly, these and related biochemical lesions provide a mechanistic rationale for antidepressant therapy. Emerging data now support the very real prospect of individualized pharmacotherapy. For example, neuroimaging studies have shown that antidepressants can reverse functional changes observed in depressed patients.\textsuperscript{58} These and related advances in translational research are beginning to characterize the neurobiological correlates of antidepressant treatment responses.\textsuperscript{54} While we are not yet at a stage to characterize lesions on a patient-by-patient basis, we can nevertheless build a conceptual framework within which clinicians can compare individual antidepressant medications and, based on empirical observations of treatment response, adjust therapeutic strategies accordingly.

### Monoaminergic pathways as drug targets

Current first-line treatment options include selective serotonin reuptake inhibitors (SSRIs), serotonin–norepinephrine reuptake inhibitors (SNRIs), and norepinephrine–dopamine reuptake inhibitors (NDRIs).\textsuperscript{9,14} While the precise mechanisms by which these agents achieve their antidepressant effects are only partly characterized, subtle changes in monoaminergic neural systems clearly play an important role. More precisely, these drugs selectively inhibit the serotonin transporter (SERT), the NE transporters (NET), and/or the DA transporters (DAT), and thereby increase synaptic concentrations of their respective monoamines, which in turn affect the activity of interconnected neurotransmitter systems. However, there may be some mechanistic overlap between classes of antidepressants, and individual agents demonstrate subtle yet clinically relevant pharmacologic differences (Table 3 and Figure 5).\textsuperscript{63,72–74} And while all SSRIs chiefly inhibit SERT, select agents also influence NE and DA neuronal activity – for example, paroxetine weakly inhibits NET and sertraline weakly inhibits DAT.\textsuperscript{72,75} Further, although paroxetine and fluvoxamine have similar half-lives, paroxetine, which also binds to cholinergic receptors and

### Table 3 Potential targets of first-line and emerging antidepressants

<table>
<thead>
<tr>
<th>Transporters</th>
<th>SERT</th>
<th>NET</th>
<th>DAT</th>
<th>5HT\textsubscript{1A}</th>
<th>5HT\textsubscript{1B/D}</th>
<th>5HT\textsubscript{1A}</th>
<th>5HT\textsubscript{1C}</th>
<th>5HT\textsubscript{3}</th>
<th>5HT\textsubscript{7}</th>
</tr>
</thead>
<tbody>
<tr>
<td>SSRIs</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Citalopram</td>
<td>✓</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Escitalopram</td>
<td>✓</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fluoxetine</td>
<td>✓</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fluvoxamine</td>
<td>✓</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Paroxetine</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sertraline</td>
<td>✓</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>SNRIs</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Duloxetine</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Venlafaxine</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>NDRIs</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bupropion</td>
<td>✓</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Common TCAs</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Amitriptyline</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Desipramine</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Imipramine</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Multimodal (novel agents)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Trazodone\textsuperscript{*}</td>
<td>✓</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Vilazodone\textsuperscript{†}</td>
<td>✓</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Vortioxetine</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Triple reuptake inhibitor</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Amitifadine</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Notes:** *Trazodone is a serotonin antagonist reuptake inhibitor; Vilazodone is a serotonin partial agonist reuptake inhibitor; † indicate the potential targets (ie, transporters and/or 5HT receptor subtypes) for each antidepressant. Data from.\textsuperscript{62,71,76}**

**Abbreviations:** 5HT, 5-hydroxytryptamine or serotonin; DAT, dopamine transporter; NDRi, norepinephrine–dopamine reuptake inhibitor; NET, norepinephrine transporter; SERT, serotonin transporter; SNRI, serotonin–norepinephrine reuptake inhibitor; SSR1, selective serotonin reuptake inhibitor; TCAs, tricyclic antidepressants.
The clinical manifestation of these pharmacologic differences was recently illustrated in a meta-analysis of 117 randomized controlled trials (25,928 participants) comparing clinical response and discontinuation rates of antidepressants. Using citalopram as the reference compound, the odds ratio (OR) for an SSRI initiating a treatment response ranged from a lower likelihood with escitalopram (OR: 0.68) to a higher likelihood with reboxetine (OR: 1.72); while tolerability ranged from a lower likelihood of tolerance with mirtazapine (OR: 0.42) to a higher likelihood of tolerance with escitalopram (OR: 1.17). Differences were also observed between the two SNRIs – duloxetine and venlafaxine – included in the study (Figure 5). These data highlight the importance of balancing the known efficacy of a drug with its side effect profile, and the potential benefits gained from switching to another antidepressant, even within the same class.

In fact, recent studies have demonstrated that the initial choice of antidepressant medication and self-reported symptomatic improvement over 2 weeks are predictive of treatment outcomes. Yet the criteria by which to select the initial antidepressant have not been well-defined. This does not translate, however, into a strictly arbitrary choice. Careful alignment of patient symptomatology with the biochemical pharmacology of antidepressants can help clinicians tailor therapy. While symptom resolution is the primary driver, the efficacy of a chosen antidepressant should be weighed against other patient-specific factors such as functional goals and expectations, comorbid conditions, and concerns about side effects (eg, weight gain, sedation) and treatment costs.

Mechanism-based prescribing
Interrelationships between clinical symptoms, affected neural systems, and antidepressant mechanisms of action may help clinicians customize pharmacotherapy to a patient’s unique clinical profile. As noted, fatigue, sleep/wake disturbances, and cognitive dysfunction are among the most troublesome symptoms, as they commonly persist after antidepressant therapy and have a disparate impact on patient functioning. Clinicians may wish to identify and specifically target these and other baseline symptoms to facilitate asymptomatic remission and thereby minimize the associated risk of relapse and recurrence.

Results from STAR*D and other studies underscore the importance of therapeutic adjustments tailored to initial and ongoing monitoring. Most patients do not respond to the initial antidepressant regimen or are nonadherent because of side effects. Nonadherence with antidepressant medications is as high as 52% in patients with MDD, with inefficacy, sexual dysfunction, and weight gain the most cited reasons for discontinuation. Physicians may wish to adjust the dose of the initial antidepressant, switch to an alternative medication, or consider adjunctive treatment. Nearly one-third of patients who fail an initial SSRI treatment may benefit from augmenting the dose of the initial antidepressant, switching to an alternative antidepressant, or considering adjunctive treatment. A second antidepressant with a different mechanism of action or an atypical antipsychotic can be added to the treatment plan. Evidence-based adjunctive treatment strategies have been reviewed elsewhere. As treatment options continue to evolve, many primary care providers prefer to consult psychiatrists for guidance on switch and augmentation treatment strategies.

The simplicity and safety of monotherapy are frequently cited by patients and clinicians who prefer to avoid combination therapy or adjunctive treatment with atypical antipsychotics. Novel monotherapeutic agents that engage multiple targets may therefore provide an attractive option with the...
potential to ameliorate functionally impairing symptoms and reduce side effects. Interestingly, genetic variations explain an estimated 50% of an antidepressant’s efficacy. These and related data support the development of multimodal agents that target multiple gene products, each a validated target for therapeutic intervention that may maximize the likelihood of eliciting a response.

Triple reuptake inhibitors block SERT, NET, and DAT (Table 3), and may address potential disturbances across three neurotransmitter circuits and their associated depressive symptoms simultaneously (Figure 3). However, the degree of activity at each transporter needs to be considered – too much DAT inhibition may render the drug potentially abusable, whereas too little SERT inhibition may provide insufficient antidepressant action. Amitifadine inhibits SERT, NET, and DAT with a potency ratio of 1:2:8, respectively, and is currently in clinical trials.

Multimodal drugs interact with both transporters and membrane-bound receptors, employing two distinct modes of neural signaling that may improve symptomatic resolution and reduce treatment-related side effects. The recently approved drugs vilazodone and vortioxetine exhibit SERT inhibition and 5HT1A agonism (Table 3). 5HT1A receptors play a critical autoregulatory role in the synthesis and release of serotonin. Continuous treatment with SSRIs desensitizes 5HT1A autoreceptors, leading to enhanced serotonergic neurotransmission. However, 5HT1A desensitization generally requires 2 weeks, which may account for the delayed onset of traditional SSRIs. Multimodal agents with 5HT1A agonist activity should therefore accelerate treatment response. Preclinical studies support this model: vortioxetine treatment desensitizes 5HT neuronal firing after only 1 day (vs 14 days with fluoxetine). In one clinical trial, reduction in depressive symptoms was observed after 1 week of treatment with vilazodone, although the findings were not replicated in a second study. Vortioxetine is also a 5HT1D, 5HT3, and 5HT3 receptor antagonist and 5HT1B receptor partial agonist. Interestingly, current and emerging research suggests that 5HT1 receptors play an important if partly characterized role in cognition and sleep, and are thought to reflect their effects on Glu and serotonin signaling in cortical and subcortical circuits, among other areas of the brain. Through these multimodal mechanisms, vilazodone and vortioxetine can modulate downstream effects of 5HT on interconnected neurotransmitter systems. Further, clinical studies with vilazodone and vortioxetine have demonstrated favorable side effect profiles with minimal reports of sexual dysfunction and weight gain. Additional long-term studies are required to further evaluate the clinical relevance of these pharmacologic properties.

Cognition

The diminished ability to think or concentrate, or indecisiveness is one of the core diagnostic features of depression (Table 1) and among the most frequently persisting and functionally debilitating symptoms following treatment. All domains of cognition are worse in patients with depression than in healthy controls, and many – including immediate memory, attention, ideation fluency, and visuospatial function and learning – continue to adversely affect life functioning despite improvement of depressive symptoms. In a recent systematic review, nine of eleven studies reported that patients with remitted unipolar depression had decreased performance on neuropsychological tests compared with never depressed controls. Sustained cognitive impairments following an MDE frequently lead to frustration, low self-esteem, and impaired interpersonal relationships in the family, workplace, and social network. Further, cognitive dysfunction is associated with the cumulative duration of depressive episodes, emphasizing the need for early detection and targeted treatment.

While additional studies are required to elucidate the neurochemical basis of persistent cognitive deficits, recent imaging studies suggest that hypofunctional frontal and prefrontal cortices contribute to the diminished ability to think, concentrate, or make decisions. Numerous neurotransmitters – including 5HT, DA, NE, ACh, and Glu – shape the activity of procognitive circuits and provide insights into mechanism-based treatments that may be more likely to reduce cognitive impairment in depression. For example, the decreased dopaminergic activity associated with depressive symptoms suggests that increasing DA activity may reduce cognitive impairment in depression. Indeed, drug combinations with DA agonists like pramipexole as add-on treatments to antidepressants in patients with affective disorders have been shown to improve cognition in some studies. Glu, especially, is essential for cognitive processing, and therapeutic agents that modulate Glu transmission, such as the N-methyl-D-aspartate antagonists memantine and ketamine, have demonstrated antidepressant-like properties; follow-up studies in depressed patients have shown conflicting neurocognitive effects, however. 5HT action across discrete 5HT receptor subtypes is thought to modulate GABAergic interneurons that influence Glu circuits involved in cognitive functions. Vortioxetine, with known effects on 5HT1A, 5HT1B, 5HT1D, 5HT3, and 5HT7, has demonstrated...
neurotransmitters (eg, NE, DA, ACh, histamine). Fatigue is regulated at the cortical level by several key neurotransmitters. In addition, both 5HT and DA projections to the striatum and 5HT and NE projections to the cerebellum regulate psychomotor functioning (Figure 3). Inhibition of NET and/or DAT by vortioxetine, bupropion, and sertraline (Table 3) can modulate NE and/or DA neurotransmission; offering advantages over SERT inhibition alone. When patients present with fatigue at baseline, clinicians should select antidepressants less likely to have sedating effects (eg, venlafaxine, bupropion, sertraline). A pooled analysis showed that bupropion is associated with lower levels of residual fatigue compared with the SSRIs. An alternative treatment strategy is to use adjunctive therapy that targets fatigue directly with medications by increasing NE and/or DA neurotransmission; agents such as psychostimulants, the NE reuptake inhibitor atomoxetine, or lower doses of atypical antipsychotics may alleviate fatigue by promoting improved nighttime sleep quality and quantity. Clinical studies evaluating the effects of multimodal agents on fatigue and related outcomes have been encouraging, though additional longitudinal studies of agents with comparable antidepressant efficacy are needed with larger patient populations.

**Fatigue**

Fatigue or loss of energy is a defining criterion for depression (Table 1). The severity of fatigue reported by patients with MDD independently correlates with the severity of depression (P=0.028), which often persists following resolution of depressed mood, and markedly impairs psychosocial functioning and QoL.

The prevalence of fatigue and loss of energy despite antidepressant treatment highlights the need for additional treatment options targeting the diverse neurobiology underlying psychomotor retardation, painful somatic symptoms, and executive dysfunction. Treatment-related side effects can complicate treatment as well. Tricyclic antidepressants (TCAs) and some SSRIs and SNRIs demonstrate sedative effects and can induce or exacerbate symptoms of fatigue and related functional impairments.

Descending 5HT and NE fibers in the spinal cord may regulate the perception of physical tiredness, while mental fatigue is regulated at the cortical level by several key neurotransmitters (eg, NE, DA, ACh, histamine). In addition, both 5HT and DA projections to the striatum and 5HT and NE projections to the cerebellum regulate psychomotor functioning (Figure 3). Inhibition of NET and/or DAT by venlafaxine, bupropion, and sertraline (Table 3) can modulate NE and/or DA neurotransmission, offering advantages over SERT inhibition alone. When patients present with fatigue at baseline, clinicians should select antidepressants less likely to have sedating effects (eg, venlafaxine, bupropion, sertraline). A pooled analysis showed that bupropion is associated with lower levels of residual fatigue compared with the SSRIs. An alternative treatment strategy is to use adjunctive therapy that targets fatigue directly with medications by increasing NE and/or DA neurotransmission; agents such as psychostimulants, the NE reuptake inhibitor atomoxetine, or lower doses of atypical antipsychotics may alleviate fatigue by promoting improved nighttime sleep quality and quantity. Clinical studies evaluating the effects of multimodal agents on fatigue and related outcomes have been encouraging, though additional longitudinal studies of agents with comparable antidepressant efficacy are needed with larger patient populations.

**Sleep/wake**

Disruptions in circadian rhythms and the sleep/wake cycle are experienced in nearly all patients with depression. Even after treatment, sleep/wake problems – particularly insomnia or hypersomnia – commonly persist. Depression is associated with both long and short sleep durations, as well as over- or underestimation of sleep time. Compared with patients demonstrating good sleep/wake quality, those with sleep/wake problems and comorbid depression have significantly worse QoL, more functional impairments, and when accompanied by nightmares, increased risk for suicidal ideation and suicide attempts. Moreover, sleep/wake disturbances – including insomnia and sedation – have also been reported as side effects of common antidepressants (eg, paroxetine, venlafaxine). These data highlight the essential need to assess sleep/wake quality and quantity before, during, and even after treatment with antidepressants.

Sleep/wake disturbance can be mapped to dysfunction in the hypothalamus (Figure 3). States of arousal are regulated by the hypothalamic sleep/wake switch and brainstem monoamine projections to the cortex. Serotonin, histamine, and GABA each play a role in regulating normal wakefulness and sleep and can be modulated with appropriate treatment. Specifically, serotonin 5HT, 5HT, and 5HT, receptors have been linked to sleep, circadian rhythm, and mood. The 5HT antagonist properties of trazodone (Table 3) likely contribute to its known sleep-promoting effects. Doxepin, a TCA approved for the treatment of depression, anxiety, and insomnia, antagonizes histamine H1 receptors and is...
beneficial as an add-on treatment with antidepressant therapy in depressed patients with comorbid insomnia or anxiety.\textsuperscript{128,129} Hypnotic medications (eg, zolpidem, zaleplon) are GABA\textsubscript{A} receptor allosteric modulators that potentiate GABA neurotransmission to promote sleep.\textsuperscript{128} When sleep problems emerge with treatment, switching to another antidepressant or adding a hypnotic medication may be beneficial.\textsuperscript{9} Further, sedating antidepressants should be avoided in patients with hypersomnia. Additional studies are needed – particularly well-designed head-to-head studies – to evaluate the differential effects of antidepressants on sleep/wake disturbances. Interestingly, the therapeutic effects of melatonin receptor agonists like agomelatine (not currently approved in the US), which have sleep-promoting, antidepressant, and anxiolytic properties, are currently an active area of research.\textsuperscript{129–134} However, the implications of melatonergic agents for clinical practice have yet to be fully realized.

**Conclusion**

A complete baseline assessment of depressive symptoms before initiating treatment provides a patient-specific profile from which the therapeutic plan may emerge. Clarifying the prior medication history is essential to differentiate between unresolved residual symptoms, comorbid conditions, and treatment-emergent side effects. By understanding the nature and magnitude of functional impairment, physicians can formulate treatment regimens based on realistic treatment goals. Further, the symptoms and symptom clusters can, with some degree of precision, be aligned with the pharmacologic actions of current and emerging antidepressants. An operational understanding of the neural systems and targets engaged by each agent at clinically relevant doses can help physicians customize pharmacotherapy to a patient’s unique constellation of symptoms. Such mechanism-based pharmacotherapy is the linchpin of personalized treatment, and provides a rational basis on which to make initial therapeutic choices for newly diagnosed patients, and those struggling with unremitting symptoms.

**Acknowledgment**

Medical writing assistance, supported financially by Takeda Pharmaceuticals, was provided by Bomina Yu, PhD, of inVentiv Medical Communications during the preparation of this manuscript.

**Disclosure**

Philip F Saltiel, MD, has received honoraria from AstraZeneca and Eli Lilly and Company for lectures and presentations. Daniel I Silvershein, MD, has received honoraria from King Pharmaceuticals, Inc. and Pfizer Inc. for lectures and presentations.

**References**


29. Lam RW, Michalak EE, Bond DJ, Tam EM, Axler A, Yatham LN. Which depressive symptoms and medication side effects are perceived by patients as interfering the most with occupational functioning? Depress Res Treat. 2012;2012:630206.


46. Jacobsen PL, Mahableshwarkar AR, Chen Y, Chrones L, Clayton AH. Randomized, double-blind, head-to-head, flexible-dose study of vortioxetine vs escitalopram in sexual functioning in adults with well-controlled major depressive disorder experiencing treatment-emergent sexual dysfunction. Poster presented at: 29th CINP World Congress of Neuropsychopharmacology; June 22–26, 2014; Vancouver, Canada.

47. Montgomery SA, Nielsen RZ, Poulsen LH, Häggsström L. A randomised, double-blind study in adults with major depressive disorder with an inadequate response to a single course of selective serotonin reuptake inhibitor or serotonin-noradrenaline reuptake inhibitor treatment switched to vortioxetine or agomelatine. Psychopharmacology. 2014;29(5):470–482.


60. Lum CT, Stahl SM. Opportunities for reversible inhibitors of monoamine oxidase A (RIMAs) in the treatment of depression. CNS Spectr. 2012;17(3):107–120.


66. Dunlop BW, Nemeroff CB. The role of dopamine in the pathophysiology of depression. Arch Gen Psychiatry. 2007;64(3):327–337.


70. Pehrson AL, Sanchez C. Serotonergic modulation of glutamate neurotransmission as a strategy for treating depression and cognitive dysfunction. CNS Spectr. 2014;19(2):121–133.


99. Citrome L. Vortioxetine for major depressive disorder: a systematic review of the efficacy and safety profile for this newly approved antidepressant – what is the number needed to treat, number needed to harm and likelihood to be helped or harmed? Int J Clin Pract. 2014;68(1):60–82.


