Depression: Overview and Treatment Options

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EDUCATIONAL OBJECTIVES

After the completion of this activity pharmacists will be able to:

• Describe two popular hypotheses used to explain the physiologic cause of depression.
• List criteria used to diagnose depression or MDD.
• Discuss pharmacologic treatment options for depression.

INTRODUCTION

Depression is a chronic illness that is common among all ethnicities. The typical onset of depression occurs in the late 20s and the estimated lifetime prevalence is 5-12% in men and 9-26% in women. Depression appears to be more common in lower socioeconomic classes and genetic factors may also contribute. Patients are 2.7 times more likely to develop depression if one parent has been diagnosed and 3 times more likely if both parents have been diagnosed with depression. Other factors that increase the likelihood of becoming depressed include a difficult childhood, abuse, chronic illnesses such as rheumatoid arthritis and AIDS, self-esteem issues, the death of a loved one, the ending of a serious relationship, and unemployment. Although most people experience depressive symptoms at some time during their lives, depressive disorders involve clinically-relevant symptoms that can have devastating consequences if left untreated. The American Psychiatric Association recently published the fifth edition of the Diagnostic and Statistical Manual of Mental Disorders (DSM-V). This manual provides the diagnostic criteria for major depressive disorder (MDD) which is based mainly on subjective symptoms.

Clinical depression is a medical condition classified in DSM-V as either 1) a single episode of major depressive disorder, 2) recurrent major depressive disorder or 3) depressive disorder not otherwise specified. People usually experience recurrent symptoms of major depression. The overall prevalence of MDD in the United States is 7%. Females are 1.5 to 3 times more likely to experience depression compared to males. The risk of recurrent depressive episodes increases with each episode (50% risk after the first episode, 70% after the second, etc.). Furthermore, risk factors for recurrent episodes include severe preceding episodes and young age at onset of initial episode. The risk of recurrent episodes decreases as the duration of remission increases. Significant functional disability, morbidity and mortality are all associated with depression. Treatment with antidepressants improves the symptoms of depression, increases the level of functioning and helps to prevent further episodes of depression. Response to treatment varies with 20% of patients experiencing improvement within 3 months and 80% experiencing improvement within 1 year.

PATHOPHYSIOLOGY

Two popular hypotheses have been generated to explain the physiologic cause of depression. The oldest is the monoamine hypothesis which links depression to decreases in levels of the neurotransmitters norepinephrine (NE), dopamine (DA), and serotonin (5-HT) in the brain. This hypothesis does not adequately explain depression for several reasons. The most common medications used for depression block the reuptake of these neurotransmitters which causes an almost immediate response in the neurotransmitter levels; however, full clinical effect does not occur for several weeks. In addition, not all patients with depression have decreased levels of NE, DA, and 5-HT, and some may even have higher levels than normal. The mechanism of efficacy in depression is thought to be through alterations in the balance of DA, 5-HT, and NE receptors, most importantly the down-regulation of 5-HT_{1A} presynaptic receptors that provide negative feedback.

A second hypothesis is the dysregulation hypothesis. Instead of having decreases in the levels of neurotransmitters, this hypothesis simply states that the neurotransmitter system is out of balance. The dysregulation can be due to problems such as impaired homeostasis or regulatory mechanisms, changes in basal rate of release of neurotransmitters, or disruption in normal rhythms such as the circadian rhythm.

SYMPTOMS OF DEPRESSION

There are classes of depression symptoms that can be used to help guide in diagnosis. Emotional symptoms of depression include a diminished ability to experience pleasure and loss of interest in activities, hobbies, or work. A depressed patient will appear sad and often have a pessimistic attitude. Feelings of worthlessness or guilt may prompt thoughts of suicide. The guilt may be unrealistic, inappropriate, or misplaced and can extend to delusional thoughts as well. Anxiety is present in almost 90% of depressed patients. The emotional symptoms can progress to psychotic features such as auditory hallucinations encouraging suicide.

Physical symptoms of depression are chronic fatigue, appetite disturbances, sleep disturbances, and sexual dysfunction. The fatigue is often worse in the morning and does not improve with rest. Accompanying it can be pain and headaches. The fatigue can impair the ability to perform normal daily tasks. Appetite disturbances can result in substantial weight loss from decreased appetite or weight gain from food cravings.

Intellectual or cognitive symptoms include impaired concentration, slowed thinking, poor short term memory of recent events, confusion, or indecision. When elderly patients display cognitive symptoms, depression should be considered. Psychomotor disturbance symptoms can manifest as slowed speech or movements or even as psychomotor agitation resulting in restless motion such as fidgeting or pacing.

DIAGNOSTIC CRITERIA

The standard for diagnosing depression or MDD has been set by the Diagnostic and Statistical Manual of Mental Disorders,
The important feature of a major depressive episode is presence of symptoms throughout most of the day, nearly every day, for two consecutive weeks. The practitioner must be able to probe beneath surface level questions and responses (to minimize under-diagnosis), and differentiate between grief and depression (to minimize over-diagnosis). The following are the criteria taken directly from the DSM-V.

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.

1. Depressed mood most of the day, nearly every day, as indicated by either subjective report (e.g., feels sad, empty, hopeless) or observation made by others (e.g., 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 (e.g., a change of more than 5% of body weight in a month), or decrease or increase in appetite nearly every day. (Note: In children, consider failure to make expected weight gain.)

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.

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

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

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.

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

GRIEF VERSUS MDD

The DSM-V has made a point to distinguish between MDD and depressive symptoms caused by grief or response to a significant loss. There are distinguishable characteristics that separate a diagnosable condition from a transient state of mind. Grief symptoms may include sadness, insomnia, change in appetite or weight loss, which resemble Criterion A of the diagnostic criteria listed above. Assigning these symptoms to either MDD or grief requires careful consideration and extensive clinical judgment. The predominant symptoms of grief are feelings of emptiness and loss contrasted to the inability to experience happiness or pleasure in MDD. During the grieving process, these feelings tend to decrease in intensity over a period of time depending on the cause and occur in waves while the mood changes in MDD are persistent and are not tied to any specific thought or idea. Grief can be accompanied with thoughts and memories of the deceased rather than pessimistic or self-loathing thoughts seen in MDD.

PHARMACOLOGIC TREATMENT

Classes of antidepressants include monoamine oxidase inhibitors (MAOs), tricyclic antidepressants (TCAs), selective serotonin reuptake inhibitors (SSRIs), selective norepinephrine reuptake inhibitors (SNRIs), serotonin antagonists and reuptake inhibitors (SARIs) and other neurotransmitter-altering medications. Medications recently approved for depression include vilazodone (Viibryd) in 2011 as well as levomilnacipran (Fetzima) and vortioxetine (Brintellix) in 2013. Almost all antidepressants carry the following Black Box Warning (BBW): Antidepressants increased the risk compared to placebo of suicidal thinking and behavior (suicidality) in children, adolescents, and young adults in short-term studies of major depressive disorder (MDD) and other psychiatric disorders. The recommended stepwise pharmacologic approach to treating depression is outlined in Table 1.

SELECTIVE SEROTONIN REUPTAKE INHIBITORS (SSRIS)

SSRIs work by inhibiting the reuptake of serotonin into the presynaptic neuron. This causes an increase in the level of serotonin available in the synaptic cleft allowing for increased binding of postsynaptic serotonin receptors. SSRIs are frequently used to treat depression with approximately 65-75% of patients seeing improvement in their symptoms after initiation of an SSRI. These agents are considered first line therapy due to their increased safety and tolerability compared to other classes of antidepressants. SSRIs have very little affinity for muscarinic, GABA, benzodiazepine, alpha, beta, dopaminergic, and histamine receptors; therefore, they demonstrate less cardiovascular, anticholinergic, and sedative side effects seen with other antidepressants. Dosing recommendations for the SSRIs are outlined in Table 2.
### Table 1.

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Step 1</td>
<td>Assumption that there are no contraindications</td>
</tr>
<tr>
<td>Continue treatment with SSRI used in step 1 for at least 4 to 9 months</td>
<td>Appropriate for all patients who experience an adequate response or complete remission</td>
</tr>
<tr>
<td>Changing antidepressant to a different SSRI or to a Non-SSRI</td>
<td>Appropriate for patients who have no or partial response to treatment in step 1 or significant adverse effects</td>
</tr>
<tr>
<td>Adjunctive therapy or augmentation</td>
<td>Appropriate for patients who experience a partial response after optimizing the dose of the treatment started in step 1</td>
</tr>
<tr>
<td>Step 3</td>
<td>Appropriate for all patients who experience an adequate response or complete remission</td>
</tr>
<tr>
<td>Continue treatment started in step 2 for at least 4 to 9 months</td>
<td>Appropriate for all patients who have failed to achieve an adequate response from treatment started in step 2</td>
</tr>
<tr>
<td>Switch to a non-SSRI antidepressant</td>
<td>Appropriate for patients who experience a partial response after optimizing the dose of the treatment started in step 2</td>
</tr>
</tbody>
</table>

### Table 2.

<table>
<thead>
<tr>
<th>SSRI:</th>
<th>Initial Dose:</th>
<th>Max Dose:</th>
<th>Special Populations:</th>
</tr>
</thead>
<tbody>
<tr>
<td>Citalopram (Celexa)</td>
<td>20 mg daily</td>
<td>40 mg/day</td>
<td>Geriatric (&gt;60 years): 20 mg daily (initial and max) Children (&gt;9 years): 10-40 mg Hepatic impairment: 20 mg daily is max dose Renal impairment: no adjustment</td>
</tr>
<tr>
<td>Escitalopram (Lexapro)</td>
<td>10 mg daily</td>
<td>20 mg/day</td>
<td>Geriatric: 10 mg daily Children (&gt;12 years): 10 mg daily Hepatic impairment: 10 mg daily is max dose Renal impairment: no adjustment</td>
</tr>
<tr>
<td>Fluoxetine (Prozac)</td>
<td>20 mg daily or 90 mg once weekly</td>
<td>80 mg/day</td>
<td>Children (&gt;8 years): 10-20 mg daily Hepatic impairment: no adjustment Renal impairment: no adjustment</td>
</tr>
<tr>
<td>Fluvoxamine (Luvox)</td>
<td>50 mg QHS 100 mg (CR) QHS</td>
<td>300 mg/day</td>
<td>Children 8-11 years: Initially 25 mg QHS, max dose is 200 mg/day 12-17 years: Initially 25 mg QHS, max dose is 300 mg/day Hepatic impairment: no adjustment Renal impairment: no adjustment</td>
</tr>
<tr>
<td>Paroxetine (Paxil)</td>
<td>20 mg daily 25 mg (ER) daily</td>
<td>50 mg/day</td>
<td>Geriatric: 10 mg daily, max dose is 40 mg/day Children: safety has not been established Hepatic impairment: max dose is 40 mg/day Renal impairment: No adjustment</td>
</tr>
<tr>
<td>Sertraline (Zoloft)</td>
<td>25 mg daily</td>
<td>200 mg/day</td>
<td>Children: same as adult Hepatic impairment: no adjustment Renal impairment: no adjustment</td>
</tr>
</tbody>
</table>
All of the SSRIs undergo hepatic cytochrome (CYP) metabolism.\textsuperscript{6,7,8} Citalopram, escitalopram, and fluvoxamine are specifically metabolized by CYP 3A4 so drug-drug interactions are highly likely with these three agents. Patients starting fluoxetine should wait at least 2 weeks after discontinuing an MAOI before initiating fluoxetine. If initiating an MAOI in a patient previously taking fluoxetine, wait at least 5 weeks following discontinuation of fluoxetine before starting the MAOI. All of the SSRIs are Food and Drug Administration (FDA) pregnancy risk category C, except paroxetine which is category D. Abrupt discontinuation of an SSRI may result in symptoms including: agitation, anxiety, confusion, dizziness, headache, insomnia, or irritability. SSRIs are highly plasma protein bound so caution should be used when they are administered with other highly plasma protein bound drugs such as warfarin or digoxin. Drugs that interfere with the reuptake of serotonin when combined with drugs interfering with blood clotting (NSAIDs, aspirin, warfarin) can increase the risk of gastrointestinal bleeds. The risk of occurrence of some specific side effects of the SSRIs are ranked in Table 3.\textsuperscript{2} Paroxetine causes the most weight gain compared to all other SSRIs. The SSRIs that are least likely to cause sexual dysfunction are citalopram, fluoxetine, and fluvoxamine. Patients being treated with an SSRI should see relief of symptoms within 4-6 weeks and should be re-evaluated at this time for efficacy.

### Table 3.

<table>
<thead>
<tr>
<th>SSRI:</th>
<th>Anticholinergic Effects</th>
<th>Sedation</th>
<th>Orthostatic Hypotension</th>
<th>Seizures</th>
<th>Conduction Abnormalities</th>
</tr>
</thead>
<tbody>
<tr>
<td>Citalopram</td>
<td>None</td>
<td>Very little</td>
<td>None</td>
<td>Little</td>
<td>None</td>
</tr>
<tr>
<td>Escitalopram</td>
<td>None</td>
<td>None</td>
<td>None</td>
<td>None</td>
<td>None</td>
</tr>
<tr>
<td>Fluoxetine</td>
<td>None</td>
<td>None</td>
<td>None</td>
<td>Low</td>
<td>None</td>
</tr>
<tr>
<td>Fluvoxamine</td>
<td>None</td>
<td>None</td>
<td>None</td>
<td>Low</td>
<td>None</td>
</tr>
<tr>
<td>Paroxetine</td>
<td>Very little</td>
<td>Very little</td>
<td>None</td>
<td>Low</td>
<td>None</td>
</tr>
<tr>
<td>Sertraline</td>
<td>None</td>
<td>None</td>
<td>None</td>
<td>Low</td>
<td>None</td>
</tr>
</tbody>
</table>

Adapted from Dipro’s Chapter 77: Major Depressive Disorder

### Table 4.

<table>
<thead>
<tr>
<th>SNRI:</th>
<th>Initial Dose:</th>
<th>Max Dose:</th>
<th>Special Populations:</th>
</tr>
</thead>
</table>
| Duloxetine (Cymbalta) | 40-60 mg/day | 60 mg/day | Geriatric: May initiate at lower dose  
Hepatic Impairment: Contraindicated  
Renal Impairment: Do not use in CrCl < 30 mL/min or end stage renal disease |
| Venlafaxine (Effexor) | IR: 75 mg/day, ER: 37.5-75 mg/day | IR: 225-375 mg/day, ER: 225 mg/day | Geriatric: May initiate at lower dose  
Hepatic Impairment: Reduce total daily dose by 50%  
Renal Impairment:  
GFR: 10-70 mL/min: Reduce total daily dose by 25% to 50%  
Hemodialysis: Reduce total daily dose by 50% |
| Desvenlafaxine (Pristiq) | 50 mg/day | 50 mg/day | Geriatric: Same as adult dosing  
Hepatic Impairment:  
Moderate to severe impairment: 50 mg/day  
Renal Impairment:  
CrCl 30-50 mL/min: Max of 50 mg/day  
CrCl <30 mL/min: Max of 50 mg every other day  
Hemodialysis: Max of 50 mg every other day |
| Milnacipran (Savella) | 50 mg BID | 200 mg/day | Geriatric: Same as adult dosing  
Hepatic Impairment: No adjustment  
Renal Impairment:  
CrCl ≤29 mL/min: 25 mg BID  
Do not use in end stage renal disease |
SEROTONIN/NOREPINEPHRINE REUPTAKE INHIBITORS (SNRIS)

The SNRIs include duloxetine (Cymbalta), venlafaxine (Effexor), desvenlafaxine (Pristiq), and milnacipran (Savella). The SNRIs work by inhibiting the reuptake of both serotonin and norepinephrine into the presynaptic neuron. Dosing recommendations for the SNRIs are outlined in Table 4. All SNRIs are hepatically metabolized. These agents are contraindicated in patients with uncontrolled closed angle glaucoma. The SNRIs are FDA pregnancy category C. Possible side effects of the SNRIs include hypertension, tachycardia, sweating, increased risk of bleeding, and insomnia. Antidepressant results should be seen by 2-3 weeks after starting an SNRI. The use of an SNRI is as an alternative in patients with MDD who have responded poorly to SSRIs.

SEROTONIN ANTAGONISTS AND REUPTAKE INHIBITORS (SARI)

The SARI includes trazodone (Oleptro) and nefazodone (Serzone). The SARI have been shown to inhibit the reuptake of serotonin and antagonize 5HT2A/2C serotonin receptors. Dosing recommendations for trazodone and nefazodone are outlined in Table 5. Trazodone and nefazodone both undergo hepatic metabolism to active metabolites. Nefazodone has a BBW for hepatic failure. Common side effects of the SARI includes constipation, nausea, dizziness, and headache. The SARI are FDA pregnancy category C. It may take 2-4 weeks for the SARI’s antidepressant effect to be seen. These drugs are considered 3rd line agents if the use of SSRIs, SNRIs, and TCAs has failed. Trazodone can also be used as adjunctive treatment to help patients fall asleep.

Bupropion (Wellbutrin) works by inhibiting the neuronal reuptake of norepinephrine and dopamine. There are various dosage forms of bupropion available including immediate release (IR), sustained release (SR), and extended release (ER). The dosing recommendations for the various dosage forms are outlined in Table 6. In geriatric patients, dosing should start at 37.5 mg IR BID up to 300 mg/day. In pediatric patients, bupropion should be dosed at 1.4-6 mg/kg/day. A reduction in dose or frequency should be considered in patients with renal or hepatic impairment. The maximum dose is reduced to 75 mg IR daily in patients with severe hepatic impairment. Common side effects of bupropion are tachycardia, headache, insomnia, dizziness, xerostomia, weight loss, and anxiety. Contraindications include seizure disorder, history of anorexia or bulimia, and use in patients undergoing abrupt discontinuation of ethanol or sedatives. Bupropion is hepatically metabolized by CYP2B6 and is FDA pregnancy category C. Bupropion may be chosen over other antidepressants because of its reduced risk of anticholinergic side effects, cardiovascular side effects, antihistaminic side effects, weight gain, and sexual dysfunction. Bupropion may have benefit in patients with refractory depression, and it is commonly used as adjunct rather than as monotherapy.

MIRTAZAPINE (REMERON)

Mirtazapine acts as a central α-2 adrenergic receptor antagonist that increases the release of norepinephrine and serotonin. It is also a potent 5-HT2 and 5-HT3 receptor antagonist which decreases the incidence of adverse effects like insomnia and nausea seen with SSRIs. It is also a significant H1 antagonist which is why it can cause some sedation. It is

| Table 5. |
|---|---|---|
| **SARI:** | | **Special Populations:** |
| **Initial Dose:** | **Max Dose:** | |
| **Trazodone (Oleptro)** | 150 mg/day in three divided doses | 600 mg/day; ER: 375 mg/day |
| | ER: 150 mg QHS | |
| **Geriatric:** | IR: 25-50 mg QHS with 25-50 mg/day increase weekly |
| | ER: Same as adult dosing |
| **Children:** | 6-12 years old: Initial: 1.5-2 mg/kg/day in divided doses; max: 6 mg/kg/day in 3 divided doses |
| | Adolescents: Initial: 25-50 mg/day; increase to 100-150 mg/day in divided doses |
| | Hepatic Impairment: No adjustment |
| | Renal Impairment: No adjustment |
| **Nefazodone (Serzone)** | 200 mg/day in two divided doses | 600 mg/day in two divided doses |
| | Geriatric: Initial: 50 mg BID; usual maintenance dose: 200-400 mg/day |
| | Hepatic Impairment: No adjustment |
| | Renal Impairment: No adjustment |

IR: immediate release; ER: extended release
also a moderate α-1 antagonist which is why it may cause some orthostatic hypotension. Mirtazapine is considered a second line treatment for MDD behind the SSRIs. When initiating treatment with mirtazapine, it should be started at 15 mg QHS and titrated up every 2 weeks if needed to a maximum dose of 45 mg QHS. Mirtazapine is heptatically metabolized by CYPs 2D6, 1A2, and 3A4. Mirtazapine has not been proven safe for use in children. Common side effects of mirtazapine include increased appetite, weight gain, increased triglycerides, constipation, dry mouth, and somnolence. Mirtazapine is FDA pregnancy category C. It will take 1-2 weeks to begin seeing the effects of mirtazapine and 2-4 weeks to see its full effect.

**TRICYCLIC ANTIDEPRESSANTS (TCAS)**

The TCAs include amitriptyline (Elavil), imipramine (Tofranil), nortriptyline (Pamelor), desipramine (Norpramin), doxepin (Silenor), and Clomipramine (Anafranil). The TCAs work by decreasing the reuptake of norepinephrine and serotonin within the CNS. Dosing recommendations for the TCAs are listed in Table 7.

The TCAs are metabolized in the liver. Contraindications to the TCAs include recent heart attack and narrow angle glaucoma. The list of side effects of the TCAs is extensive. Common side effects include orthostatic hypotension, weight gain, sedation, and anticholinergic effects (urinary retention, blurred vision, memory impairment). Nortriptyline causes the least anticholinergic effects and sedation and is the preferred choice when choosing a TCA. It will take 2 weeks or more to see the full anti-depressant effect of these drugs. The TCAs are effective at treating depression, but they are not the drugs of choice due to the large number of side effects associated with them.

**MONOAMINE OXIDASE INHIBITORS (MAOIs)**

MAOIs work by binding to and inhibiting the activity of the monoamine oxidase (MAO) enzyme. Reduction of MAO activity causes an increased concentration of neurotransmitters, such as epinephrine, norepinephrine, and dopamine, at various storage sites in the CNS and sympathetic nervous system. While MAOIs have been proven effective in treating depression, they are no longer considered first line agents due to the numerous side effects and interactions associated with this class of drugs. The MAOIs have been replaced by other drugs (SSRIs) that are safer and effective at relieving the symptoms of depression. Dosing recommendations for the MAOIs are listed in Table 8.

All MAOIs except phenelzine undergo hepatic metabolism. Contraindications to MAOIs include pheochromocytoma, abnormal liver function tests or history of hepatic disease, and renal disease or impairment. In general, one should wait at least 2 weeks after discontinuing an MAOI before initiating therapy with another antidepressant. One should also wait 2 weeks after discontinuing therapy with another antidepressant before initiating MAOI therapy. MAOIs should never be administered in combination with another antidepressant. Side effects of MAOIs include orthostatic hypotension, anxiety, dizziness, fatigue, insomnia, seizure, tremor, weight gain, constipation, sexual dysfunction, blurred vision, and jaundice.

All MAOIs are FDA pregnancy category C. Patient counseling is of utmost importance with the MAOIs. Information provided should include that 2-3 weeks may be needed to see a decrease in symptoms. Patients should avoid alcohol, caffeine, and tyramine-containing foods (cheese, yogurt, beer, sardines, processed meats, liver, chocolate, soy sauce, sauerkraut, and licorice).

**HYPERICUM PERFORATUM (ST. JOHN’S WORT)**

Meta-analyses of quality clinical trials support the role of St. John’s Wort in the treatment of depression. Effectiveness is comparable with standard antidepressants, while adverse events are lower than with conventional antidepressants; however, interactions with other drugs and quality control issues may limit its use. Research has shown that St. John’s Wort extracts are more effective than placebo, likely as effective as low dose TCAs, and likely as effective as the SSRIs fluoxetine, sertraline, and paroxetine. Short-term response rates to St. John’s Wort appear to be between 65% and 100%; however, long-term, the response rates appear to be lower, 60% to 69%. Hyperforin is one of the main components of St. John’s Wort. It is thought to be responsible for the antidepressant effects by causing inhibition of the reuptake of serotonin, dopamine, and norepinephrine. Hyperforin is a CYP3A4 inducer which leads to numerous drug interactions. St. John’s Wort capsules or tablets should be dosed at 300 mg TID with a maximum dose of 1200 mg/day. Liquid extracts should be dosed at 2-4 mL TID, and St. John’s Wort tea should be consumed as a single dose of 2-3 g. Contraindications to St. John’s Wort include pregnancy, HIV/AIDS, MAOI therapy, and severe depression with suicidal ideation. There is a lack of clinical data for the safety and efficacy of St. John’s Wort in children. Common side effects of St. John’s Wort include nausea, vomiting, constipation, diarrhea, itching, fatigue, headache, dizziness, and
<table>
<thead>
<tr>
<th>TCA:</th>
<th>Initial Dose:</th>
<th>Max Dose:</th>
<th>Special Populations:</th>
</tr>
</thead>
</table>
| **Amitriptyline**    | 50-150 mg/day in a single dose at bedtime or in divided doses | 300 mg/day | Geriatric: 10-25 mg QHS  
Children:  
Do not use if < 12 years old  
9-12 years: 1 mg/kg/day in 3 divided doses  
Max dose: 3 mg/kg/day  
Adolescent: Initial 25-50 mg/day  
Max dose: 100 mg/day  
Hepatic Impairment: No adjustment  
Renal Impairment: No adjustment |
| **Imipramine**       | 75 mg/day     | 200 mg/day | Geriatric: Initial: 25-50 mg QHS  
Max Dose: 100 mg/day  
Children:  
Initial: 1.5 mg/kg/day  
Increase by 1 mg/kg/day every 3-4 days  
Max Dose: 5 mg/kg/day  
Hepatic Impairment: No adjustment  
Renal Impairment: No adjustment |
| **Nortriptyline**    | 25 mg 3-4 times a day | 150 mg/day | Geriatric: Initial: 30-50 mg QHS  
Children:  
1.5 mg/kg/day  
Increase in 1-3 mg/kg/day increments  
Hepatic Impairment: Use lower doses and slower titration  
Renal Impairment: No adjustment |
| **Desipramine**      | 100-200 mg/day | 300 mg/day | Geriatric:  
Initial: Start at lower dose  
Maintenance dose: 25-100 mg/day  
Max Dose: 150 mg/day  
Children:  
Do not use if < 6 years old  
6-12 years: 1-3 mg/kg/day  
Max Dose: 5 mg/kg/day  
Adolescents:  
Initial dose: Start at lower dose  
Maintenance Dose: 25-100 mg/day  
Max Dose: 150 mg/day  
Hepatic Impairment: No adjustment  
Renal Impairment: No adjustment |
| **Doxepin**          | 25-150 mg QHS or in 2-3 divided doses | 300 mg/day | Geriatric:  
Initial: 10-25 mg QHS  
Increase by 10-25 mg weekly  
Max Dose: 75 mg/day  
Children:  
Children < 12 years: 1-3 mg/kg/day  
Children >/= 12 years and Adolescents:  
Initial: 25-50 mg /day  
Max Dose: 100 mg/day  
Hepatic Impairment:  
Use lower doses and slower titration  
Initiate Silenor at 3 mg once daily  
Renal Impairment: No adjustment |
Vilazodone (Viibryd) is an SSRI and a partial agonist of 5HT1A receptors that was approved in January 2011.\(^2\) The recommended dosing technique is 10 mg daily for 7 days, then 20 mg daily for 7 days, then 40 mg daily. Titration of the dose in this manner helps decrease the occurrence of GI-related adverse effects when vilazodone is first initiated as well as aid the physician in deciding upon the lowest effective dose for the patient. The maximum dose is 40 mg/day or 20 mg/day if the patient is also taking a strong CYP3A4 inhibitor or has intolerable side effects with a moderate CYP3A4 inhibitor. CYP3A4 is a major metabolizer of vilazodone. This drug has not been studied in children, and there is no dosage adjustments needed for renal impairment, hepatic impairment, or in the elderly. Vilazodone has a BBW regarding its ability to increase the risk of suicide in young adults. Contraindications include concomitant use of an MAOI, use of vilazodone within 14 days of discontinuing an MAOI, and use of an MAOI within 14 days of discontinuing vilazodone. Vilazodone is FDA pregnancy category C. Side effects are similar to those of the other SSRIs with sexual dysfunction being reported less with vilazodone. Patients should begin to see an antidepressant effect within 2-3 weeks of starting vilazodone. Vilazodone appears to have similar efficacy and tolerability to the other SSRIs. Two randomized, double-blind, placebo-controlled trials showed that vilazodone is effective in adult patients with MDD with tolerable side effects.\(^29,30\) Tests used to compare vilazodone to placebo included Montgomery-Asberg Depression Rating Scale (MADRS), the 17-item Hamilton Depression Rating Scale (HDRS-17), the 21-item Hamilton Depression Rating Scale, Hamilton Anxiety Rating Scale (HARS), Clinical Global Impressions-Severity of Illness (CGI-S), and Clinical Global Impressions-Improvement (CGI-I). Vilazodone treatment groups consistently had improved symptoms from baseline based on each test compared to placebo. Vilazodone did not achieve higher remission rates compared to placebo; however, this was most likely due to the short duration of 8 weeks in each study. Although clinical data is lacking, monotherapy with vilazodone may be a viable option to combination therapy of buspirone and SSRIs for the treatment of MDD. A randomized clinical trial is currently under development comparing vilazodone to citalopram.\(^31\) The usefulness of vilazodone may be further defined when clinical data from this trial becomes available.

### photosensitivity.

It is important to remember that St. John’s Wort is not FDA approved, and it interacts with many other medications; however, St. John’s Wort is a natural alternative for patients with MDD who want a cheaper option and want to avoid prescription medications.\(^2\)

## DRUGS RECENTLY APPROVED

Vilazodone is an SSRI and a partial agonist of 5HT1A receptors that was approved in January 2011.\(^2\) The recommended dosing technique is 10 mg daily for 7 days, then 20 mg daily for 7 days, then 40 mg daily. Titration of the dose in this manner helps decrease the occurrence of GI-related adverse effects when vilazodone is first initiated as well as aid the physician in deciding upon the lowest effective dose for the patient. The maximum dose is 40 mg/day or 20 mg/day if the patient is also taking a strong CYP3A4 inhibitor or has intolerable side effects with a moderate CYP3A4 inhibitor. CYP3A4 is a major metabolizer of vilazodone. This drug has not been studied in children, and there is no dosage adjustments needed for renal impairment, hepatic impairment, or in the elderly. Vilazodone has a BBW regarding its ability to increase the risk of suicide in young adults. Contraindications include concomitant use of an MAOI, use of vilazodone within 14 days of discontinuing an MAOI, and use of an MAOI within 14 days of discontinuing vilazodone. Vilazodone is FDA pregnancy category C. Side effects are similar to those of the other SSRIs with sexual dysfunction being reported less with vilazodone. Patients should begin to see an antidepressant effect within 2-3 weeks of starting vilazodone. Vilazodone appears to have similar efficacy and tolerability to the other SSRIs. Two randomized, double-blind, placebo-controlled trials showed that vilazodone is effective in adult patients with MDD with tolerable side effects.\(^29,30\) Tests used to compare vilazodone to placebo included Montgomery-Asberg Depression Rating Scale (MADRS), the 17-item Hamilton Depression Rating Scale (HDRS-17), the 21-item Hamilton Depression Rating Scale, Hamilton Anxiety Rating Scale (HARS), Clinical Global Impressions-Severity of Illness (CGI-S), and Clinical Global Impressions-Improvement (CGI-I). Vilazodone treatment groups consistently had improved symptoms from baseline based on each test compared to placebo. Vilazodone did not achieve higher remission rates compared to placebo; however, this was most likely due to the short duration of 8 weeks in each study. Although clinical data is lacking, monotherapy with vilazodone may be a viable option to combination therapy of buspirone and SSRIs for the treatment of MDD. A randomized clinical trial is currently under development comparing vilazodone to citalopram.\(^31\) The usefulness of vilazodone may be further defined when clinical data from this trial becomes available.

### Vilazodone

<table>
<thead>
<tr>
<th>Drug</th>
<th>Initial Dose</th>
<th>Max Dose</th>
<th>Special Populations</th>
</tr>
</thead>
</table>
| Clomipramine (Anafranil) | 25 mg/day | 250 mg/day | Geriatric: Same as adult dosing  
Children:  
Initial Dose: 25 mg/day  
Max Dose: 3 mg/kg/day or 200 mg/day, whichever is smaller  
Hepatic Impairment: No adjustment  
Renal Impairment: No adjustment |
| Phenelzine (Nardil) | 15 mg TID | 90 mg/day | Geriatric: begin with 15 mg QAM with gradual titration to 60 mg/day  
Children: contraindicated  
Hepatic Impairment: contraindicated  
Renal Impairment: contraindicated |
| Selegiline (Emsam)  | Transdermal Patch:  
6 mg/24 hours applied once daily | 12 mg/day | Geriatrics (>/= 65 years): 6 mg/24 hour patch  
Children < 12 years: do not use  
Hepatic Impairment: no dosage adjustment  
Renal Impairment: no dosage adjustment |
| Tranylcypromine (Parnate) | 30 mg/day in divided doses | 60 mg/day | Geriatric: low initial doses with gradual increases  
Children < 16 years: do not use  
Hepatic Impairment: contraindicated  
Renal Impairment: contraindicated |
| Isocarboxazid (Marplan) | 10 mg 2-4 times/day | 60 mg/day | Geriatric: low initial doses with gradual increases  
Hepatic Impairment: contraindicated  
Renal Impairment: contraindicated |

\(^2\) It is important to remember that St. John’s Wort is not FDA approved, and it interacts with many other medications; however, St. John’s Wort is a natural alternative for patients with MDD who want a cheaper option and want to avoid prescription medications.\(^2\)
Levomilnacipran (Fetzima) is a potent and selective inhibitor of norepinephrine and serotonin reuptake (SNRI) approved in July of 2013.42 Levomilnacipran predominately enhances the effect of norepinephrine. As with vilazodone, a specific dosing technique is recommended when levomilnacipran is initiated in order to decrease the occurrence of adverse effects, specifically orthostatic hypotension, and determine the lowest effective dose. The patient should start with 20 mg/day for 2 days then increase to 40 mg/day on day 3. This dose may then be increased in increments of 40 mg at intervals of 2 or more days. Maintenance dosing is 40-120 mg/day, and the maximum dose is 120 mg/day. No dosage adjustments are required for elderly patients or patients with hepatic impairment. Levomilnacipran is not approved for use in children, and the dose must be adjusted based on creatinine clearance in patients with renal impairment. Contraindications to levomilnacipran include hypersensitivity to milnacipram, uncontrolled narrow-angle glaucoma, and use of an MAOI concurrently, within 7 days of discontinuing levomilnacipran, or within 2 weeks of discontinuing an MAOI. Levomilnacipran has a BBW for its ability to increase risk of suicide in young adults. This drug is FDA pregnancy category C, and its most common side effects are orthostatic hypotension and nausea. Levomilnacipran is extensively metabolized by CYP3A4 in the liver. Two randomized, placebo controlled trials showed that sustained release levomilnacipran significantly improved depressive symptoms compared to placebo.35,36 Both trials showed that levomilnacipran was generally well tolerated. The levomilnacipran group did not achieve a higher remission rate compared to placebo; however, the study was limited due to its short duration. Due to the potent inhibition of norepinephrine reuptake, levomilnacipran may be useful in treating the depressive symptoms associated with the noradrenergic symptom cluster in depression. These symptoms include functional impairment, concentration problems, lassitude, psychomotor retardation, and reduced self-care.

Vortioxetine (Brintellix) is a serotonin reuptake inhibitor, 5-HT1A agonist, and 5-HT3 antagonist approved in September of 2013.37,38 It is dosed initially at 10 mg/day and can be increased to 20 mg/day as tolerated. A dose of 5 mg/day may be considered for patients who do not tolerate higher doses. The maintenance dose of vortioxetine is usually 5-20 mg/day. This drug is not approved for use in children, and there are no dosage adjustments required for elderly patients or patients with renal impairment. Vortioxetine is not recommended for use in patients with severe hepatic impairment. Contraindications to vortioxetine include use of an MAOI concurrently or within 21 days of discontinuing vortioxetine or within 14 days of discontinuing the MAOI. Vortioxetine has a BBW for its ability to increase risk of suicide in young adults. This drug is FDA pregnancy category C, and its most common side effects are nausea and sexual dysfunction. Vortioxetine is extensively metabolized by CYP3A4. Two clinical trials demonstrated that vortioxetine is well tolerated; however, both of these studies failed to demonstrate improvement of symptoms compared to placebo.37,38

Other drug therapies that are expected to reach the market in the future include a pipamperone/citalopram combination, a buprenorphine/samidorphan combination, amitifadine, liрафesine, and GLYX 13.43 Pipamperone, a dopamine receptor 4 (D4) and 5HT2A receptor antagonist, has been shown to enhance the antidepressant effect of citalopram. Buprenorphine, a partial agonist of the mu opioid receptor in combination with samidorphan, an antagonist of mu opioid receptors is thought to be a potential non-addictive treatment for depression. Amitifadine and liрафesine are both nonselective reuptake inhibitors of serotonin, dopamine and norepinephrine. Amitifadine failed to achieve a significant difference compared to placebo in the improvement of the MADRS score; however, the investigators believe that this was due to subtherapeutic dosing. GLYX 13 is a partial agonist of the N-Methyl-D-aspartate (NMDA) receptor. Results from phase II trials have suggested that GLYX 13 may be useful in treatment-resistant depression and may also offer a more rapid response to treatment compared to traditional antidepressants.

Clinical trials have demonstrated the efficacy of ketamine in treatment-resistant depression.44-46 Currently, an ongoing study suggests that the antidepressant effect seen with ketamine is due to the increased glutamate and gamma aminobutyric acid (GABA) levels seen in the brain after ketamine administration.47 The purpose of this trial is to determine how ketamine works in the treatment of depression. Evidence provided in this trial may aid in the development of future glutamate and GABA-enhancing drugs that are orally available.

CONCLUSION
Depression is most commonly a chronic condition requiring pharmacologic treatment. Antidepressants have various effects on the nervous system both centrally and peripherally. Response to therapy usually takes several weeks. Changes in therapy should be considered if patients fail to achieve adequate response to their initial treatment. Older medications, such as MAOIs and TCAs, should be reserved for patients who fail therapy with second generation antidepressants. Medications are currently under development that may be useful in treatment-resistant depression and may also offer a more rapid response to therapy.
REFERENCES


