Continuing Education for Pharmacists

New Drugs: Corlanor, Entresto, Vraylar, Rexulti

Mona T. Thompson, R.Ph., PharmD

Dr. Mona T. Thompson has no relevant financial relationships to disclose.

Goal. The goal of this lesson is to provide information on two new atypical antipsychotics for the treatment of mental illness: cariprazine (Vraylar™), and brexpiprazole (Rexulti®); as well as two agents approved for the treatment of heart failure: ivabradine (Corlanor®) and sacubitril/valsartan (Entresto™).

Objectives. At the completion of this activity, the participant will be able to:

1. recognize signs and symptoms, and key features of targeted pathologies for these new drugs, including information on their prevalence in the population;
2. select the indication(s), pharmacologic action(s), clinical applications, dosing regimens, mode of administration, and availability for each drug;
3. recognize adverse effects and toxicity, warnings, precautions, contraindications, and significant drug-drug or drug-food interactions; and
4. list important patient counseling information to convey to patients and/or caregivers.

The atypical antipsychotics discussed in this lesson are approved for the treatment of mental illness. The new-molecular drug entities indicated for heart failure relate to various stages of disease. This lesson provides a brief introduction to the new agents, along with a basic overview of the diseases for which they are intended to treat. The reader is, therefore, encouraged to refer to the products’ full prescribing information (i.e., package insert), FDA-approved Medication Guide when available, and other references.

Bipolar Disorder

Bipolar disorder is a mental illness characterized by an oscillation between periods of depression and low energy levels, and episodes of high energy or mania (e.g., extreme happiness, irritability), exaggerated self-confidence (e.g., feelings of invincibility), and hyperactivity, which may include dangerously impulsive behavior (e.g., excessive gambling). Because of this dual characteristic of the disease, it is also known as manic-depressive disorder.

Bipolar disorder is generally classified as either bipolar I disorder or bipolar II disorder as defined by a pattern of symptoms. While bipolar disorder is difficult to diagnose and not fully understood, it is hypothesized that excessive dopaminergic and serotonergic activity in the prefrontal cortex, nucleus accumbens, and the limbic system results in manic symptoms.

Schizophrenia

A less common, but serious mental disorder is schizophrenia, with a 0.5 to 1 percent prevalence worldwide. Schizophrenia is a debilitating mental disorder in which patients perceive false external signals. Patients may hear voices or see themselves in an alternate world (hallucinations) and try to interact with it, making little to no sense in reality. Many patients become paranoid and insist that those near them are dangerous or intend to harm them; this distrust only makes caring and treating a patient with schizophrenia even more difficult. Nearly one-third of all patients with schizophrenia attempt suicide, and about one in 10 are successful.

Similar to bipolar disorder, excessive dopamine is theorized to be the major driving pathogenic factor. Moreover, excess glutamate is thought to be a determinant of disease development and progression.

Genetics also play a large role in the risk factors for developing schizophrenia, particularly with genes responsible for regulating the dopaminergic and neurotransmitter signaling pathways and brain growth/development.

Cariprazine (Vraylar)

Vraylar (VRAY-lar) is an atypical antipsychotic indicated for the treatment of schizophrenia and the acute treatment of manic or mixed episodes associated with bipolar I
Mechanism of Action. The exact mechanism of action is unknown. It is theorized that cariprazine acts as a partial agonist at receptors for central dopamine 2 (D<sub>2</sub>) and serotonin 1A (5-HT<sub>1A</sub>), and as an antagonist at 5-HT<sub>2A</sub> receptors. This helps to better modulate the synaptic levels of these neurotransmitters and restore normal balance.

Efficacy and Safety. Schizophrenia. Three six-week, randomized, double-blinded, placebo-controlled trials were conducted, each using the Positive and Negative Syndrome Scale (PANSS) as the primary indicator. PANSS is a 30-item scale that measures positive and negative symptoms associated with schizophrenia and general psychopathology with a higher score reflecting greater disease severity. An active control arm, either risperidone or aripiprazole, was included in two of the three trials to assess assay sensitivity. In all three trials, Vraylar was superior to placebo in PANSS score reduction (change from baseline).

Bipolar I Disorder. The efficacy of Vraylar in the acute treatment of bipolar mania was established in three, three-week, placebo-controlled trials in patients who met criteria for bipolar I disorder with manic or mixed episodes with or without psychotic features. The Young Mania Rating Scale (YMRS), an 11-item clinician-rated scale used to assess the degree of manic symptomology, was used to assess the primary outcome measure for assessing psychiatric signs and symptoms. In each study, the decrease from baseline in YMRS total score at the end of week three was superior for Vraylar versus placebo.

Contraindications, Warnings, and Precautions. Vraylar is contraindicated in patients with a history of a hypersensitivity reaction to cariprazine. Hypersensitivity reactions, including angioedema, have been reported. As with other atypical antipsychotics, the product insert for Vraylar carries a boxed warning against the use in elderly patients with dementia-related psychosis due to an increased risk of mortality. Additionally, previous placebo-controlled studies in elderly patients with dementia resulted in an increased incidence of cerebrovascular adverse reactions, such as stroke and ischemic attack, in the group receiving a select atypical antipsychotic. Other listed warnings and precautions include: neuroleptic malignant syndrome, tardive dyskinesia, metabolic changes (i.e., hyperglycemia/diabetes mellitus, dyslipidemias, and weight gain), orthostatic hypotension, leukopenia, neutropenia, agranulocytosis, seizure, potential for cognitive and motor impairment, body temperature dysregulation, and dysphagia. Late-occurring adverse reactions may also occur as cariprazine and its active metabolites possess a long half-life and changes in dose will not be fully reflected in plasma levels for several weeks. Therefore, monitoring for several weeks following dosing adjustments is recommended for both adverse reactions and treatment response.

Adverse Reactions. The most common adverse reactions defined as >5 percent and at least twice the rate of placebo during clinical trials were, for schizophre- nia, extrapyramidal symptoms and akathisia and for bipolar mania: extrapyramidal symptoms, akathisia, dyspepsia, vomiting, somnolence, and restlessness. It is important to note that due to the short-term clinical trial length and the long half-life exhibited by cariprazine, the reported incidence of adverse reactions and significance of metabolic changes may not accurately reflect the rates following longer term exposures.

Drug Interactions. CYP3A4 is responsible for the formation and elimination of the major active metabolites of cariprazine. Dosing adjustments are recommended for patients initiating or discontinuing a strong CYP3A4 inhibitor while on a stable dose of Vraylar. Table 1 lists the dosing recommendations. Concomitant use of Vraylar and a CYP3A4 inducer is not recommended as this relationship has not been evaluated.

Administration, Dosing, and Availability. Vraylar is administered once daily, with or without food, and is available in 1.5 mg, 3 mg, 4.5 mg, and 6 mg capsules. When prescribed for either indication, the starting dose is 1.5 mg per day. The recommended dosing range for schizophrenia is 1.5 mg to 6 mg per day. The recommended dosing range for bipolar mania is 3 mg to 6 mg per day. Patient counseling information for cariprazine is summarized in Table 2.

Brexpiprazole (Rexulti) Rexulti (REX-ul-TEE) is an atypical antipsychotic indicated for use as an adjunctive therapy to antidepressants for the treatment of major depressive disorder (MDD) and for the treatment of schizophrenia.

Major Depressive Disorder (MDD). Major depression is one of
the most common mental disorders in the United States and, according to the World Health Organization (WHO), carries the heaviest burden of disability among mental and behavior disorders. In 2013, an estimated 15.7 million adults aged 18 years or older in the U.S. had at least one depressive episode. Depression is characterized by mood changes or other symptoms that may interfere with a person’s ability to live a normal life, such as loss of interest in pleasurable activities, loss of appetite, pessimism, and suicidal thoughts.

A selective serotonin reuptake inhibitor (SSRI) or serotonin-norepinephrine reuptake inhibitor (SNRI) is generally used for first-line treatment of major depression. If little to no response is observed, another SSRI or SNRI may be tried or an antidepressant from a different class may be attempted. Augmentation with antipsychotic drugs may be helpful when the response to antidepressant agents is inadequate after two or more trials. Prior to the approval of Rexulti, only three other atypical antipsychotic agents were approved as an adjunct to MDD treatment.

**Mechanism of Action.** Brexpiprazole is a second-generation atypical antipsychotic which is structurally similar to aripiprazole (Abilify). It is a dopamine D₃ and seroton 5-HT₁A partial agonist and 5-HT₂₅ antagonist.

**Efficacy and Safety.** Adjunct therapy to Antidepressants for MDD. The efficacy of Rexulti in the adjunctive treatment of MDD was evaluated in two six-week, double-blind, placebo-controlled, fixed-dose trials of adult patients meeting DSM-IV-TR criteria for MDD who had not responded adequately to prior antidepressant therapy. Patients were randomized to receive brexpiprazole or placebo as an adjunct to an SSRI or SNRI. The primary endpoint was change from baseline to week 6 in the Montgomery-Asberg Depression Rating Scale (MADRS), a 10-item clinician-related scale used to assess the degree of depressive symptomatology. In one study, mean improvements in MADRS score were significantly greater with brexpiprazole 2 mg per day than with placebo. In the other study, improvement was numerically greater with brexpiprazole versus placebo but not statistically significant.

**Schizophrenia.** The efficacy of Rexulti in the treatment of adults with schizophrenia was demonstrated in two six-week, randomized, double-blind, placebo-controlled, fixed-dose clinical trials in patients who met DSM-IV-TR criteria for schizophrenia. The primary endpoint of both trials was the change in baseline to week 6 in the PANSS total score. In both studies, Rexulti was superior to placebo in reducing the PANSS total score.

**Contraindications, Warnings, and Precautions.** Rexulti is contraindicated in patients with a known hypersensitivity to Rexulti or any of its components. Reactions have included rash, facial swelling, urticaria, and anaphylaxis. As with cariprazine and other atypical antipsychotics, Rexulti carries multiple warnings cautioning against the use in elderly patients with dementia-related psychosis due to increased mortality and increased incidence of cerebrovascular adverse reactions. Additionally, a cautionary statement regarding the use of antidepressants in patients aged 24 years and younger is included in the boxed warning, as antidepressant use in this age group can increase the risk of suicidal thoughts and behaviors. All antidepressant-treated patients should be monitored for clinical worsening and emergence of suicidal thoughts and behaviors, especially in the first few months of drug therapy. Safety and effectiveness in pediatric patients have not been established. Other warnings and precautions include neuroleptic malignant syndrome, tardive dyskinesia, metabolic changes, leukopenia, neutropenia, agranulocytosis, orthostatic hypotension, syncope, and seizures.

---

**Table 2**

**Patient counseling information for Vraylar and Rexulti**

Inform patients:
- to take without regard to food.
- about the importance of following dose escalation instructions.
- that neuroleptic malignant syndrome (NMS) can occur and is potentially fatal. Contact a health care provider or report to an emergency room if symptoms occur (hyperpyrexia, muscle rigidity, altered mental status, and evidence of autonomic instability such as irregular pulse or blood pressure, tachycardia, or diaphoresis);
- that tardive dyskinesia, a syndrome of potentially irreversible, involuntary, and dyskinetic movements, can occur;
- about the risk of metabolic changes and how to recognize signs of hyperglycemia and diabetes mellitus, and of the need to monitor blood glucose, lipids, and weight changes;
- that patients with a pre-existing low WBC or a history of drug-induced leukopenia/neutropenia should have CBC monitoring;
- that orthostatic hypotension and syncope, especially early in treatment and also at times of re-initiating treatment or dose increases, may occur;
- that caution should be exercised when performing activities that require mental alertness;
- to avoid overheating and dehydration;
- to notify their physician of all prescription and over-the-counter (OTC) medications they currently take or plan to take;
- that females of reproductive capacity notify their physician of known or suspected pregnancy. During the third trimester Vraylar or Rexulti may cause extrapyramidal side effects (EPS) or withdrawal in neonates.

A complete list of counseling information is available in each of the product’s Prescribing Information leaflet.

**Adverse Reactions.** The most common adverse reactions when treating MDD were weight increase and akathisia (≥5 percent and at least twice the rate
Dosage adjustments of Rexulti for CYP2D6 poor metabolizers and for concomitant use with CYP3A4 and CYP2D6 inhibitors and/or CYP3A4 inducers

<table>
<thead>
<tr>
<th>Factors</th>
<th>Adjusted Rexulti Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Known CYP2D6 poor metabolizers</td>
<td>Administer half of the usual dose</td>
</tr>
<tr>
<td>Known CYP2D6 poor metabolizers + taking strong/moderate CYP3A4 inhibitors</td>
<td>Administer a quarter of the usual dose</td>
</tr>
<tr>
<td>Strong CYP2D6 inhibitors*</td>
<td>Administer half of the usual dose</td>
</tr>
<tr>
<td>Strong CYP3A4 inhibitors</td>
<td>Administer half of the usual dose</td>
</tr>
<tr>
<td>Strong/moderate CYP2D6 inhibitors with strong/moderate CYP3A4 inhibitors</td>
<td>Administer a quarter of the usual dose</td>
</tr>
<tr>
<td>Strong CYP3A4 inducers</td>
<td>Double usual dose over 1 to 2 weeks</td>
</tr>
</tbody>
</table>

*In clinical trials examining adjunctive use of Rexulti in the treatment of MDD, dosage was not adjusted for strong CYP2D6 inhibitors. CYP considerations are already factored into general dosing recommendations for MDD, and Rexulti may be administered without dosage adjustment in patients with MDD.

Heart Failure

Heart failure (HF) is a complex and progressive clinical syndrome caused by inability of the heart to pump sufficient blood to meet the body’s metabolic need. HF can result from any disorder that reduces ventricular filling and/or myocardial contractility. Primary symptoms of HF include dyspnea (particularly on exertion) and fatigue, which may limit exercise tolerance. Fluid overload can result in pulmonary congestion and peripheral edema. The lifetime risk of developing HF is 20 percent in Americans >40 years of age, and is associated with an increased risk of incidence with age. Approximately 6.6 million persons in the U.S. have HF, with an estimated 670,000 new diagnoses each year.

The American College of Cardiology Foundation/American Heart Association (ACCF/AHA) staging system and the New York Heart Association (NYHA) functional classification system are the two methods used to classify and treat heart failure. The ACCF/AHA stages emphasize disease development and progression, whereas the NYHA system focuses on capacity of physical activity and symptom severity. The combination of the two systems provides complementary information about the presence and severity of HF; however, the ACCF/AHA system is utilized increasingly more often to direct the treatment of HF.

The newer staging system allows for an objective approach to classification with an opportunity to identify patients at high risk for HF. Early intervention has been proven to reduce long-term morbidity and mortality. The four stages to this system include stage...
A, B, C, and D which progress from patients at high risk with no structural disease to refractory HF requiring special intervention. The stages are progressive and irreversible which means once patients advance to stage C they can never return to stage A or B.

The NYHA functional classification system allows physicians to classify HF based exclusively on limitations to physical activity. This is a subjective approach to classification which largely describes the severity of symptoms in stages C and D. It may be used less frequently for treatment of HF than ACCF/AHA stages.

In the upcoming sections of this lesson, two new novel agents for the treatment of HF will be discussed. Neither of these agents were available for evaluation or inclusion when the 2013 guidelines were released by ACCF/AHA.

Ivabradine (Corlanor)
Corlanor (CORE-lan-ore) is a hyperpolarization-activated cyclic nucleotide-gated channel blocker that reduces the spontaneous pacemaker activity of the cardiac sinus node by selectively inhibiting the I current, resulting in heart rate reduction with no effect on ventricular depolarization or myocardial contractility. It is indicated to reduce the risk of hospitalization for worsening heart failure in patients with stable, symptomatic chronic heart failure with left ventricular ejection fraction ≤35 percent, who are in sinus rhythm with resting heart rate ≥70 beats per minute, and either are on maximally tolerated doses of beta-blockers or have a contraindication to beta-blocker use.

Efficacy of Ivabradine and Place in HF Therapy. Beta-blocker treatment is a staple of heart failure therapy as clinical data indicate that heart rate reduction is beneficial at any stage of heart failure. Additionally, elevated heart rate is a recognized risk factor in HF, independent of other measures of disease severity. Beta-blockers are thought to improve left ventricular remodeling, at least in part due to their heart rate lowering properties. However, beta-blocker use is often limited in the most severely ill patients because of hypotension and other tolerability barriers.

The Systolic Heart failure treatment with the I inhibitor Ivabradine Trial (SHIFT) was a randomized, double-blind trial comparing Corlanor and placebo in 6,558 patients with stable NYHA class II to IV heart failure, left ventricular ejection fraction ≤35 percent, and resting heart rate ≥70 bpm. In addition to other criteria, patients were on a stable and optimized heart failure regimen, which included maximally tolerated doses of beta-blockers. All of the patients had been hospitalized for heart failure within 12 months prior to study entry. The primary endpoint was a composite of the first occurrence of either hospitalization for worsening heart failure or cardiovascular death. Most patients (89 percent) were taking beta-blockers, with 26 percent on a guideline-defined target daily dose. The main reasons for not receiving the target beta-blocker doses at baseline were hypotension, fatigue, dyspnea, dizziness, history of cardiac decompensation, and bradycardia. For the 11 percent not receiving any beta-blocker at baseline, the main reasons were chronic obstructive pulmonary disease, hypotension, and asthma. Mean follow-up was at 22.9 months (range 18-29 months). SHIFT demonstrated that Corlanor reduced the risk for hospitalization for worsening heart failure. While SHIFT demonstrated that heart rate reduction with ivabradine significantly improved clinical outcomes, there was no favorable effect on cardiovascular death.

Contraindications, Warnings, and Precautions. Corlanor is contraindicated in patients with acute decompensated heart failure, blood pressure <90/50 mmHg, sick sinus syndrome, sinoatrial block or 3rd degree AV bock, unless a functional demand pacemaker is present; resting heart rate <60 bpm prior to treatment; severe hepatic impairment; pacemaker dependence (i.e., heart rate maintained exclusively by the pacemaker); and in combination with a strong CYP3A4 inhibitor. Concurrent use of verapamil and diltiazem will increase ivabradine exposure and may themselves contribute to heart rate lowering. Product insert warnings include a provision to monitor patients for atrial fibrillation, heart rate decreases, and bradycardia during treatment as these events have occurred during clinical trials. Risk factors for bradycardia include the use of other negative chronotropes such as digoxin, diltiazem, verapamil, and amiodarone. Corlanor may cause fetal toxicity when administered to a pregnant woman based on findings in animal studies.

Adverse Reactions. The most common adverse reactions occurring in >1 percent of patients are bradycardia, hypertension, atrial fibrillation, and luminous

<table>
<thead>
<tr>
<th>Table 4</th>
<th>Patient counseling information for Corlanor</th>
</tr>
</thead>
<tbody>
<tr>
<td>Inform patients:</td>
<td>• that females of reproductive potential are advised to use effective contraception and to notify their healthcare provider with a known or suspected pregnancy;</td>
</tr>
<tr>
<td></td>
<td>• to report significant decreases in heart rate or symptoms such as dizziness, fatigue, or hypotension;</td>
</tr>
<tr>
<td></td>
<td>• to report symptoms of atrial fibrillation, such as heart palpitations or racing, chest pressure, or worsened shortness of breath;</td>
</tr>
</tbody>
</table>
| | • about the possible occurrence of luminous phenomena (phosphenes). 
Advise patients to use caution if they are driving or using machines where sudden changes in light intensity may occur, especially when driving at night. Advise patients that phosphenes may subside spontaneously during continued treatment with Corlanor; |
| | • to avoid ingestion of grapefruit juice and St. John’s wort; |
| | • to take Corlanor twice daily with meals. |

Note: Table 4 contains information about patient counseling. Detailed instructions and warnings are provided for patients using Corlanor.
phenomena (phosphenes). Phosphenes are phenomena described as a transiently enhanced brightness in a limited area of the visual field, halos, image distortion, colored bright lights, or multiple images. The adverse event is thought to be due to ivabradine’s effect on retinal photoreceptors. Onset is generally within the first two months of treatment. Phosphenes are generally reported as mild to moderate and most often recur during or after treatment (although they can recur during treatment).

**Drug Interactions.** Ivabradine is primarily metabolized by CYP3A4. Therefore, concomitant use with CYP3A4 inhibitors increases ivabradine plasma concentrations and the use of CYP3A4 inducers decreases them. Increased plasma concentrations of ivabradine may exacerbate bradycardia and conduction disturbances. Use with CYP3A4 inducers and moderate CYP3A4 inhibitors should be avoided with ivabradine. The concomitant use of a strong CYP3A4 is contraindicated.

**Administration, Dosing, and Availability.** The starting dose of Corlanor is 5 mg by mouth twice daily with meals. After two weeks of treatment, the dose is adjusted to achieve a resting heart rate between 50 to 60 bpm. The maximum dose is 7.5 mg twice daily. In patients with conduction defects or in whom bradycardia could lead to hemodynamic compromise, Corlanor should be initiated at 2.5 mg twice daily. No dosing adjustments are required for patients with mild to moderate hepatic impairment or for patients with a creatinine clearance 15 to 60 mL/min. It is available as 5 mg and 7.5 mg tablets. Table 4 summarizes patient counseling information.

**Sacubitril/Valsartan (Entresto)**

Entresto (en-TRESS-toe) is a combination of sacubitril, a nephrilysin inhibitor, and valsartan, an angiotensin II receptor blocker. It is indicated to reduce the risk of cardiovascular death and hospitalization for heart failure in patients with chronic heart failure (NYHA Class II-IV) and reduced ejection fraction. Entresto is usually administered in conjunction with other heart failure therapies, in place of an angiotensin converting enzyme inhibitor (ACEI) or other angiotensin receptor blocker (ARB).

**Efficacy of Sacubitril/Valsartan (Entresto) and Place in HF Therapy.** A primary target in the treatment of HF is the renin-angiotensin-aldosterone system (RAAS). The RAAS pathway is a compensatory mechanism in the body, and one factor responsible for the process of cardiac remodeling and progressive decline in cardiac function when the system is chronically activated. The RAAS is currently targeted by ACEIs and ARBs in the first steps of treatment. The active metabolite of sacubitril inhibits nephrilysin and the degradation of peptides such as natriuretic peptides. The beneficial cardiovascular and renal effects of Entresto in heart failure are attributed to increased levels of such peptides. The new drug, sacubitril/valsartan, will hence target natriuretic peptide and angiotensin II.

FDA approval of Entresto was based on results from the PARADIGM-HF clinical trial involving 8,442 patients with symptomatic chronic heart failure (NYHA Class II-IV) and systolic dysfunction. The study was halted early after a median of 27 months, when the results for sacubitril/valsartan crossed the pre-specified margin for a significant reduction in the risk of cardiovascular death and hospitalizations in patients with heart failure in comparison to enalapril.

**Contraindications, Warnings, and Precautions.** Entresto is contraindicated in patients with hypersensitivity to any component; patients with a history of angioedema related to previous ACE inhibitor or ARB therapy; with concomitant use of ACEIs (increased risk of angioedema); or with concomitant use of aliskiren in patients with diabetes. Angioedema can occur with Entresto. In PARADIGM-HF, 0.5 percent of patients treated with Entresto experienced angioedema in comparison to 0.2 percent in the enalapril group. In the event of angioedema, Entresto should be discontinued immediately. Treatment for angioedema may include antihistamines and subcutaneous epinephrine based on the severity and extent of edema. Entresto is associated with a higher incidence rate of angioedema in Black than in non-Black patients.

Entresto can cause fetal harm when administered to a pregnant woman as with all drugs that act on the renin-angiotensin system. Use of these agents during the second or third trimester of pregnancy reduces fetal renal function and increases fetal and neonatal morbidity and death.

**Adverse Reactions.** Adverse reactions occurring in >5 percent of patients are hypotension, hyperkalemia, cough, dizziness, and renal failure. Patients who are volume and/or salt-depleted (those treated with high doses of diuretics) are at greater risk of hypotension. Patients with risk factors for hyperkalemia include those with severe renal impairment, diabetes, hypoaldosteronism, or a high potassium diet.

**Drug Interactions.** Dual blockade of the renin-angiotensin system is not recommended. Do not use with aliskiren in patients with diabetes, and avoid use with an additional ARB or ACEI. Use with other drugs that block angiotensin II or its effects, concomitant use of potassium-sparing diuretics, potassium supplements, or salt substitutes containing potassium may lead to hyperkalemia.

**Administration, Dosing, and Availability.** The recommended starting dose of Entresto is 49/51 mg (sacubitril/valsartan) twice daily. If switching from an ACE inhibitor to Entresto, a 36-hour washout period should be allowed between administration of the two drugs. The dose should be doubled after two to four weeks to the target maintenance dose of 97/103 mg twice daily as tolerated by the
patient. A reduced starting dose of 24/26 mg twice daily is indicated for patients not currently taking an ACEI or an ARB, or previously taking a low dose of these agents; patients with severe renal impairment; and patients with moderate hepatic impairment. Film-coated tablets of Entresto are available in the following fixed combinations: 24/26 mg, 49/51 mg, and 97/103 mg. Refer to Table 5 for patient counseling information for Entresto.

Overview and Summary
The medications discussed in this lesson represent new drug options for complex disease states where no one treatment strategy fits all. While incidence of bipolar disorder and schizophrenia may be relatively low, there is still demand for a therapeutic option that achieves maximum benefit with limited side effects. Medications such as Rexulti may even present an additional option as adjunct therapy for patients with uncontrolled major depressive disorder.

With significant elevated risk of negative outcomes associated with heart failure, Corlanor and Entresto exhibit potential benefit of lowering risk of hospitalization and cardiovascular death, respectively. Entresto even introduces a new class of medications in heart failure with its inclusion of the neprilysin inhibitor sacubitril.

It is important to address the potential risks and benefits with each of these new agents as they may provide additional support in managing the challenging disease states of heart failure and mental disorders.

The author, the Ohio Pharmacists Foundation and the Ohio Pharmacists Association disclaim any liability to you or your patients resulting from reliance solely upon the information contained herein. Bibliography for additional reading and inquiry is available upon request.

This lesson is a knowledge-based CPE activity and is targeted to pharmacists in all practice settings. Disclosure. The OPF trustees and other individuals responsible for planning OPF continuing pharmacy education activities have no relevant financial relationships to disclose.

Program 0129-0000-16-006-H01-P
Release date: 6-15-16
Expiration date: 6-15-19
CPE Hours: 1.5 (0.15 CEU)
New Drugs: Corlanor, Entresto, Vraylar, Rexulti

1. A mental disorder characterized by an oscillation between periods of depression and low energy levels and episodes of mania is:
   a. bipolar disorder.  c. major depressive disorder.
   b. schizophrenia.

2. Bipolar disorder and schizophrenia are thought to result from excessive dopaminergic activity in the brain.
   a. True  b. False

3. Vraylar carries a boxed warning against use in:
   a. patients ≤24 years because of increased risk of suicide.
   b. elderly patients with dementia-related psychosis.

4. All of the following are common adverse reactions with cariprazine EXCEPT:
   a. extrapyramidal symptoms.  c. akathisia.
   b. somnolence.  d. weight increase.

5. When prescribed for bipolar disorder or schizophrenia, the starting daily dose of Vraylar is:
   a. 1.5 mg.  c. 4.5 mg.
   b. 3 mg.  d. 6 mg.

6. Rexulti is indicated for all of the following EXCEPT:
   a. schizophrenia.  c. bipolar disorder.
   b. major depressive disorder.

7. First-line treatment of major depression is:
   a. brexpiprazole.
   b. cariprazine.
   c. SSRI.

8. In patients known to be CYP2D6 poor metabolizers, the dose of Rexulti should be:
   a. reduced by a quarter.  c. increased by a quarter.
   b. reduced by half.  d. increased by half.

9. Which of the following systems for heart failure classification is most often used to direct treatment?
   a. New York Heart Association (NYHA)
   b. American College of Cardiology Foundation/American Heart Association (ACCF/AHA)

10. When counseling patients on Corlanor, inform them that the phosphenes adverse reaction:
    a. is life-threatening.
    b. is non-reversible.
    c. is prevalent in >50 percent of patients.
    d. may subside spontaneously during treatment.

11. Ivabradine is primarily metabolized by:
    a. CYP2D6.  c. CYP3A4.
    b. CYP3A6.  d. CYP2D4.

12. Corlanor is taken:
    a. on an empty stomach.  c. without regard to meals.
    b. with meals.

13. Angioedema related to use of sacubitril/valsartan has a higher incidence rate in:
    a. Black patients.  b. non-Black patients.

14. Adverse reactions associated with sacubitril/valsartan include all of the following EXCEPT:
    a. cough.  c. hyperkalemia.
    b. renal failure.  d. hypertension.

15. After an ACE inhibitor is discontinued, how long should a patient wait before initiating Entresto therapy?
    a. 12 hours  c. 36 hours
    b. 24 hours  d. 48 hours

To receive CPE credit, your quiz must be received no later than June 15, 2019. A passing grade of 80% must be attained. CPE credit for successfully completed quizzes will be uploaded to the CPE Monitor. CPE statements of credit can be printed from the CPE Monitor website. Send inquiries to opa@ohiopharmacists.org.