New Drugs 2017: Central Nervous System

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Goal. The goal of this lesson is to provide a broad overview of central nervous system drugs approved by the Food and Drug Administration (FDA) in 2017, including indications, mechanisms of action, adverse events, warnings/contraindications, drug/food interactions, counseling information, and availability.

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

1. recognize the targeted pathologies for the new CNS drugs discussed in this lesson;
2. select the indication(s), pharmacologic action(s), clinical applications, dosing regimens, mode of administration, and availability for each drug;
3. list the most relevant adverse effects, warnings, precautions, contraindications, and significant drug-drug or drug-food interactions reported with these medications; and
4. list important patient counseling information to convey to patients and/or caregivers.

Valbenazine (Ingrezza®, IN-GRAY-zah) Neurocrine Biosciences) was approved by FDA on April 11, 2017 for the treatment of tardive dyskinesia. Tardive dyskinesia is a very difficult disorder to treat and very few therapy modalities are effective in controlling the tremors. Tardive dyskinesia is characterized by involuntary and/or restless rolling of the tongue or twitching of the face, trunk, or limbs. Antipsychotic medications are a known cause of tardive dyskinesia, with some drugs being worse than others.

Valbenazine is a highly-selective vesicular monoamine transporter 2 (VMAT2) inhibitor. The exact mechanism of action of valbenazine in the treatment of tardive dyskinesia is not known. Valbenazine has little to no binding affinity for VMAT1 or dopaminergic, serotonergic, adrenergic, histaminergic or muscarinic receptors.

FDA granted breakthrough status for valbenazine due to the novel mechanism of action. The Kinect 3 clinical trial compared a once-daily dose of 40 mg or 80 mg valbenazine to placebo over a six-week period in patients with schizophrenia, schizoaffective disorder, or mood disorders. After the initial six-week run-in period, all patients were placed on either 40 mg or 80 mg capsules once daily for 48 weeks. The clinical trial found this therapy to be effective in managing the symptoms of tardive dyskinesia with a tolerable side effect profile.

The most common adverse effect was somnolence at about two times the rate seen with the placebo. Potential side effects like inducing depression, suicidality, and QT prolongation have not been shown in clinical trials to-date. However, the studies have been limited in the number of patients included and long-term data are not yet known. Due to the VMAT2 mechanism, caution should be taken with patients with a history of depression or QT prolongation. Valbenazine has vasoconstriction properties and a clinical monograph services caution about the concomitant use with vasoconstrictor drugs such as epinephrine.

It should be noted that this drug has some significant drug-drug interactions with the other medications that inhibit or induce the CYP3A4 and/or the CYP2D6 pathways. The parent drug, valbenazine, is metabolized to an active metabolite by the CYP3A4 enzyme system and that active metabolite is then metabolized by the CYP2D6 enzyme system. Strong CYP3A4 inhibitors like carbamazepine, rifampin, and St. John’s wort are not recommended to be used concomitantly with valbenazine. Strong CYP3A4 inhibitors like clarithromycin, ketoconazole, and itraconazole can be used concurrently with valbenazine, but at a 40 mg daily dose. The manufacturer does not give specific labeling information for changes in dose when valbenazine is combined with strong CYP2D6 inhibitors like fluoxetine and paroxetine. Patients may require a dosage adjustment based on tolerability when combined with these drugs. Valbenazine is not recommended for use in patients with severe renal impairment defined as a creatinine clearance of less than 30 mL/minute, but no other dosing adjustments are necessary if the patient’s renal function exceeds the 30 mL/minute threshold. Dosing adjustment to
40 mg once daily is necessary in patients with moderate to severe liver impairment. Valbenazine has a bioavailability of less than 50 percent, but it has a fairly long half-life between 15 to 22 hours that allows for the once daily dosing. High-fat meals can decrease the overall absorption of the product and patients should be counseled to take on an empty stomach and be consistent in the time of the day that they take the medication.

Package labeling suggests starting patients on 40 mg once daily for one week, and then increase to 80 mg once daily thereafter. Some patients may be maintained on 40 mg daily if they are achieving an adequate response and are tolerating the medication with minimal side effects. Ingrezza® is available in 40 mg and 80 mg capsules.

**Deutetrabenazine (Austedo®, [aw-STED-oh] Teva Pharmaceuticals) is a VMAT2 inhibitor approved in April 2017 for the treatment of chorea associated with Huntington’s disease. Huntington’s disease is an inherited disease that results in a progressive degeneration of brain nerve cells. The disease causes a series of functional abnormalities such as movement disorders (chorea), changes in cognition, and psychiatric disorders. Signs and symptoms often become apparent when patients are in their 30s or 40s, but it can appear earlier or later in some cases. There is no cure for Huntington’s disease at this time; therapy is based on managing the symptoms and improving quality of life.

Deutetrabenazine was evaluated in a clinical trial of 90 patients and showed a statistically significant improvement in Total Maximal Chorea Scores over the 12-week study. At 12 weeks, the medication was stopped and patients returned to their baseline chorea score within one week of discontinuation.

Patients should be counseled to take this medication with food and to swallow the tablet whole without chewing or crushing. The warnings for this drug are similar to the other VMAT2 inhibitor, valbenazine, and include depression, QT prolongation, and suicidal ideation. This drug has a Boxed Warning for depression and it should not be started in a patient with untreated depression or suicidal ideation. Patients should be monitored closely for signs of worsening depression. Patients may also experience akathisia, which is a movement disorder characterized by a feeling of inner restlessness and a compelling need to be in constant motion. If this occurs, consideration should be given for reducing the dose or discontinuing the medication.

Deutetrabenazine has significant drug-drug interactions related to CYP2D6. Therefore, caution needs to be taken when combined with antidepressants such as paroxetine and fluoxetine.

Deutetrabenazine is structurally related to tetrabenazine (Xenazine®) which was FDA-approved in August 2008 for tardive dyskinesia. On August 30, 2017, FDA approved deutetrabenazine for the treatment of tardive dyskinesia making it the second FDA-approved drug for this condition. The indication for tardive dyskinesia resulted from two phase III clinical trials that showed a significant reduction in the severity of abnormal involuntary movements and

<table>
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<th>Table 1</th>
<th>Selected CNS drugs approved in 2017</th>
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<tr>
<td><strong>Generic (Trade Name)</strong></td>
<td><strong>Indication</strong></td>
</tr>
<tr>
<td>Valbenazine (Ingrezza®)</td>
<td>tardive dyskinesia</td>
</tr>
<tr>
<td>Deutetrabenazine (Austedo®)</td>
<td>Huntington’s chorea; tardive dyskinesia</td>
</tr>
<tr>
<td>Ocrelizumab (Ocrevus™)</td>
<td>primary progressive and relapsing MS</td>
</tr>
<tr>
<td>Edaravone (Radicava®)</td>
<td>amyotrophic lateral sclerosis</td>
</tr>
<tr>
<td>Desmopressin (Noctiva™)</td>
<td>nocturia due to nocturnal polyuria</td>
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an improvement in quality of life metrics as measured by the modified 24-item Craniocervical Dysarthria Questionnaire. These were short-term 12 week trials.

Dosing is similar for both indications; however, the starting dose for tardive dyskinesia is higher. The starting dose for Huntington’s disease is 6 mg once daily for one week. The dose may then be increased by 6 mg per day per week based on response and tolerability. For tardive dyskinesia, the starting dose is 6 mg twice daily, followed by 6 mg per day per week increases as necessary. When the total daily dose is 12 mg or above per day, the dose should be split into a twice daily regimen. The maximum daily dose should not exceed 48 mg. It is important to inform patients that dosing disruptions longer than seven days will necessitate restarting the titration process with 6 mg once or twice daily, depending on the condition being treated. Package labeling includes a chart for converting patients from tetrabenazine to deutetabenazine.

Austedo® is available in 6 mg, 9 mg, and 12 mg tablets.

Ocrelizumab (Ocrevus® [OAK-rev-us], Genentech), the first drug with an indication for both primary progressive (PPMS) and relapsing forms (RMS) of multiple sclerosis (MS), was approved by FDA on March 28, 2017. Ocrelizumab is a humanized monoclonal antibody that selectively targets CD20-positive B cells. These cells play a key role in the damage that MS causes to both myelin and axonal nerve cells.

Ocrelizumab had two published phase III trials in RMS called OPERA I and OPERA II, and one published phase III study in PPMS called ORATORIO. The OPERA studies showed a significant decrease in the rate of relapse in RMS within the first eight weeks of treatment and was shown to be superior to interferon therapies. The ORATORIO study showed a significant decrease in fatigue and disability in PPMS. The studies also demonstrated a reduction in brain lesions on MRI evaluation.

Ocrelizumab can increase the risk of infection. If patients present with signs and symptoms of infection, they should be referred to the appropriate healthcare provider for treatment.

Ocrelizumab is administered as an intravenous infusion, 300 mg on Day 1, followed by 300 mg two weeks later. Subsequent doses of 600 mg are administered once every six months, beginning six months after the first 300 mg dose. Patients may require pre-medication with corticosteroids and antihistamines to reduce infusion reactions.

Pharmacists can play a role encouraging patients to be compliant with their clinic visits, as well as direct them to available patient assistance programs.

Edaravone (Radicava®, Mitsubishi Tanabe Pharma) received FDA approval on May 5, 2017 as the first drug approved in 20 years for the treatment of amyotrophic lateral sclerosis (ALS), also referred to as Lou Gehrig’s disease. FDA gave orphan drug status to edaravone, which is a free radical scavenger that relieves the effects of oxidative stress which is considered a likely factor in the onset and progression of ALS.

Edaravone was evaluated in a six-month clinical trial. At 24 weeks, patients showed a slower decline in daily functioning compared to the placebo group.

The most common side effects include gait disturbances and bruising. Pharmacists can counsel patients on complying with clinic visits and help monitor for side effects.

Edaravone is administered as an intravenous infusion on a 14-day cycle. For the first cycle, patients receive 60 mg, infused over 60 minutes, daily for 14 days, followed by 14 days off. Then 60 mg infusions are administered daily for 10 days followed by 14 days off. This cycle is then repeated with active infusions starting every 24 days. The intravenous solutions are available as 30 mg/100 mL.

Desmopressin Acetate Nasal Spray (Noctiva™ [nok-TEE-va], Serenity Pharmaceuticals). On March 3, 2017, FDA approved desmopressin acetate, a vasopressin analog, nasal spray for the treatment of nocturnal polyuria. Other desmopressin products are currently on the market indicated for the management of diabetes insipidus, hemophilia A, and von Willebrand disease. FDA defined nocturnal polyuria as having to get up at least twice during sleep to urinate. Noctiva™ has not been studied for any other indications at the time of writing, and has not been studied in patients less than 50 years of age.

Pharmacists should counsel patients on minimizing fluid intake near bedtime, both to help reduce nocturnal polyuria and also to reduce the risk of hyponatremia (low serum sodium levels). This product includes a Boxed Warning for drug-induced hyponatremia that can be life-threatening. Many medications (e.g., thiazide diuretics, loop diuretics, tricyclic antidepressants, selective serotonin re-uptake inhibitors, nonsteroidal anti-inflammatory drugs, glucocorticoids, opioids, lamotrigine, and carbamazepine) can increase the risk of developing hyponatremia and pharmacists should review the patient’s medication profile prior to dispensing Noctiva™. Serum sodium levels should be measured within seven days of initiating therapy, and then at one month with periodic measurements thereafter. Sodium levels should also be repeated if the dosage is increased and consideration should be given to monitoring more often in patients over the age of 65 years. Pharmacists can help patients understand the need for this monitoring, making sure patients are getting blood levels drawn when appropriate.

Noctiva™ should be avoided in patients with congestive heart failure, fluid overload, uncontrolled hypertension, electrolyte distur-
bances, syndrome of inappropriate antidiuretic hormone secretion (SIADH) or poor renal function. Besides hyponatremia, common adverse events for Noctiva™ noted in the clinical trials were mostly related to local reactions in the nasal cavity such as irritation, congestion, sneezing, and bleeding. This drug may increase the patient’s blood pressure and pharmacists can help monitor patients to make sure they are meeting their blood pressure goals.

Pharmacists should store Noctiva™ in the refrigerator prior to dispensing. Patients should be counseled that the spray may remain at room temperature for up to 60 days after opening and then discarded. The product should not be exposed to extreme temperatures. It is important to store Noctiva™ in an upright position after opening, and not in purses, glove boxes, or suitcases where the product can be tipped over.

Patients should be counseled not to shake the product before delivery into the nostrils. The spray needs to be primed before the first-time use by pumping the actuator five times into the air and away from the body or face. The product does not need to be re-primed unless it has not been used for more than three days. If this occurs, the patient should be counseled to re-prime the pump with two actuations in the air.

Dosing of Noctiva™ is based on patient age. For those under 65 years of age without an increased risk of hyponatremia, 1.66 mcg/0.1 mL spray should be used in one nostril nightly, 30 minutes prior to going to bed. The dose for patients 65 years or older, or those at risk for hyponatremia, is 0.83 mcg/0.1 mL nightly. This dose can be increased if necessary if the serum sodium remains normal. Note that dosing is only in one nostril (either left or right) each night.

It is also important that pharmacists counsel patients that the two dosage forms (1.66 mcg/0.1 mL and 0.83 mcg/0.1mL) are not interchangeable. If a patient is taking 0.83 mcg/0.1 mL and the prescriber would like to switch to 1.66 mcg/0.1 mL, the patient should discontinue the 0.83 mcg/0.1 mL spray and start on 1.66 mcg/0.1 mL spray. If a patient is taking 1.66 mcg/0.1 mL and the prescriber would like to switch to 0.83 mcg/0.1 mL, the patient should discontinue the 1.66 mcg/0.1 mL spray and start on 0.83 mcg/0.1 mL spray.

**Table 2: Selected CNS drugs approved in 2017**

<table>
<thead>
<tr>
<th>Generic (Trade Name)</th>
<th>Indication</th>
<th>Dose</th>
<th>Dosage Form</th>
<th>Side Effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Amphetamine (Mydayis®)</td>
<td>ADHD</td>
<td>12.5 mg to 25 mg daily, increased by 12.5 mg; 50 mg maximum dose</td>
<td>12.5 mg, 25 mg, 37.5 mg, 50 mg capsules</td>
<td>decreased appetite, weight loss, dry mouth, anxiety, increased heart rate; <em>Boxed Warning: abuse potential and dependence</em></td>
</tr>
<tr>
<td>Methylphenidate (Cotempa XR-ODT™)</td>
<td>ADHD for 6-17 year-olds</td>
<td>17.3 mg daily, titrated to not exceed 51.8 mg</td>
<td>8.6 mg, 17.3 mg, 25.9 mg orally disintegrating extended-release tablets</td>
<td>decreased appetite, weight loss, dry mouth, increased heart rate, anxiety; <em>Boxed Warning: abuse potential and dependence</em></td>
</tr>
<tr>
<td>Amphetamine (Adzenys ER™)</td>
<td>ADHD ≥6 years</td>
<td>6.3 mg daily, increasing by 3.1 mg or 6.3 mg at weekly intervals to not exceed 12.5 mg or 18.8 mg based on patient age</td>
<td>1.25 mg/mL 450 mL suspension</td>
<td>decreased appetite, weight loss, dry mouth, anxiety, increased heart rate; <em>Boxed Warning: abuse potential and dependence</em></td>
</tr>
<tr>
<td>Oxycodone (RoxyBond™)</td>
<td>severe pain</td>
<td>5 mg to 15 mg every 4-6 hours as needed for pain</td>
<td>5 mg, 15 mg, 30 mg tablets</td>
<td>drowsiness, itching, nausea, constipation, abnormal dreams, euphoria, withdrawal</td>
</tr>
<tr>
<td>Naldemedine (Symproic®)</td>
<td>opioid-induced constipation</td>
<td>0.2 mg daily</td>
<td>0.2 mg tablets</td>
<td>gastrointestinal perforation possible, but rare</td>
</tr>
<tr>
<td>Safinamide (Xadago®)</td>
<td>Parkinson’s disease “off” episodes</td>
<td>50 mg daily, increased after two weeks to 100 mg daily</td>
<td>50 mg, 100 mg tablets</td>
<td>dyskinesia, hypertension, impulse control disorder, serotonin syndrome</td>
</tr>
<tr>
<td>Amantadine (Gocovri™)</td>
<td>levodopa-induced dyskinesia</td>
<td>137 mg nightly, increased after one week to 274 mg</td>
<td>68.5 mg, 137 mg extended-release capsules</td>
<td>dizziness, hallucinations, dry mouth, constipation, falls, swelling of hands and feet</td>
</tr>
</tbody>
</table>
Amphetamine Mixed Salt (Mydayis®) [my-DAY-is], Shire U.S.) received FDA approval on June 20, 2017 for the treatment of attention deficit hyperactivity disorder (ADHD). Mydayis® is approved for ages 13 years and older as a CNS stimulant for once-daily administration. The extended-release capsule is effective for 16 hours and contains one immediate-release set of beads and two sustained-release sets of beads formulated to release at different times during the day.

Mydayis® was evaluated for efficacy and safety in over 1600 patients in 16 clinical studies. The studies were placebo-controlled and showed statistically significant improvements in several ADHD scales. Improvements were seen as early as two hours after the dose.

The most common adverse events were decreased appetite, decreased weight, dry mouth, increased heart rate, and anxiety. The drug is not approved in younger pediatric patients at this time due to an increase in irritability that was shown in the clinical trials, as well as higher blood levels of the drug.

Mydayis® carries a warning for cardiovascular events and a Boxed Warning for abuse potential. Patients at risk for cardiovascular events should be screened for abnormalities which can be detected with an electrocardiogram (EKG).

Mydayis® is available in 12.5 mg, 25 mg, 37.5 mg, and 50 mg capsules. The salt mixture for the 12.5 mg capsule includes dextroamphetamine sulfate 3.125 mg, dextroamphetamine saccharate 3.125 mg, amphetamine aspartate monohydrate 3.125 mg, and amphetamine sulfate 3.125 mg.

Mydayis® is dosed initially at 12.5 mg to 25 mg once daily in the morning, then increased by 12.5 mg per day no sooner than once weekly with a maximum dose of 50 mg/day for adults and 25 mg/day in pediatric patients.

It is important for practitioners to note that Mydayis® is not interchangeable with other amphetamine mixed salt forms. These products are not equivalent on a milligram to milligram basis. If a patient is to be switched from another product, the package labeling specifically indicates that the other product should be discontinued before the initial doses of Mydayis® are started and the patient then titrated up to the appropriate dose. Clinical studies did not show any additional benefit with doses over 50 mg for adults and 25 mg for pediatrics.

Patient counseling is similar to other amphetamine-based ADHD products on the market. The capsule can be swallowed whole or opened and sprinkled on applesauce; the beads should not be chewed.

Methylphenidate (Cotempla XR-ODTM, Neos Therapeutics) is an extended-release orally disintegrating tablet approved on June 19, 2017 for ADHD in pediatric patients six to 17 years of age. It is an innovative formulation designed for oral disintegration without losing the extended-release properties.

The recommended starting dose is 17.3 mg per day taken in the morning. Based on response, doses may be increased once weekly in increments of 8.6 mg to 17.3 mg per day. Doses exceeding 51.8 mg per day are not recommended.

This medication can be taken with or without food. However, patients should take it consistently with either food or without food. For example, if the patient takes the medication with breakfast, then it should never be taken on an empty stomach.

Pharmacists should counsel patients on the proper way to handle the drug. Cotempla XR-ODTM should not be removed from the blister package until just prior to taking the dose. The tablet should be taken immediately and not stored for future use. It is important to have dry hands when handling the blister pack and the tablet. It is important to peel the foil from the blister pack rather than pushing the tablet through the foil. The tablet should be placed on the patient’s tongue and allowed to dissolve without chewing or crushing. The tablet will dissolve in the saliva and then be swallowed. No additional liquid should be taken with the tablet.

This product is a CII controlled substance and carries a Boxed Warning for abuse potential and dependence, and should be monitored as other methylphenidate medications.

It is important to note that altering gastric pH can affect the release of Cotempla XR-ODTM. Medications such as proton pump inhibitors (e.g., omeprazole) and histamine-2 antagonists (e.g., famotidine) can alter the release of Cotempla XR-ODTM and its pharmacodynamics. Pharmacists should counsel patients and caregivers to avoid these products, as well as antacids and over-the-counter sodium bicarbonate products.

Cotempla XR-ODTM is available in 8.6 mg, 17.3 mg and 25.9 mg tablets. Cotempla XR-ODTM comes with a reusable travel case that is ideal for storing and transporting medication to keep it protected from light, as well as to protect the integrity of the product.

Amphetamine (Adzenys ER™ [ad-ZEN-es] (Neos Therapeutics) is a once-daily extended-release suspension, approved September 15, 2017, for the treatment of ADHD in patients six years of age and older. It is a CII controlled substance.

Adzenys ER™ was designed with the same modified-release system as Adzenys XR-ODTM amphetamine orally disintegrating tablet. Thus, the two formulations are interchangeable. Both Adzenys ER™ and Adzenys XR-ODTM are bioequivalent to Adderall XR®. The patient package insert for Adzenys ER™ contains a chart with equivalent doses. Any other amphetamine formulations are not interchangeable.
able on a milligram per milligram basis, and patients should be counseled to discontinue the other product before starting the new one.

Adzenys ER™ carries the same warnings and patient counseling advice as other amphetamine ADHD medications.

Adzenys ER™ should be stored at room temperature. Patients and caregivers should be counseled to shake the suspension prior to use, and administer with a clean oral syringe. Pharmacists are key in assuring patients and caregivers use an accurate oral syringe and administer the correct volume.

The recommended starting dose of Adzenys ER™ for patients six to 17 years of age is 6.3 mg (5 mL) once daily in the morning. Increases in dosing can be done in increments of 3.1 mg (2.5 mL) or 6.3 mg (5 mL) at weekly intervals. The maximum dose is 18.8 mg (15 mL) daily for patients six to 12 years, and 12.5 mg (10 mL) daily for patients 13 to 17 years.

Efficacy of Adzenys ER™ is also affected by changes in gastric pH, and pharmacists should provide similar counseling about GI products as recommended with Cotempra XR-ODT™.

Adzenys XR-ODT™ is available in 3.1 mg, 6.3 mg, 9.4 mg, 12.5 mg, 15.7 mg, and 18.8 mg strengths, while the ER suspension is 1.25 mg/mL. The orange-flavored suspension is available as a 450 mL bottle.

Oxycodeone Hydrochloride (RoxyBond™, Inspirion Delivery Sciences) received FDA approval April 20, 2017. This CII controlled substance is an immediate-release, abuse-deterrent formulation of oxycodone for the management of severe pain. RoxyBond™ uses physical and chemical barriers to deter abuse rather than aversive agents or opioid antagonists. It meets FDA’s 2015 Guidance for Industry standards for abuse deterrent opioids.

Initial dosing of RoxyBond™ is 5 mg to 15 mg every four to six hours as needed for pain. Product labeling specifies that this drug should be used for the management of pain severe enough to require an opioid analgesic and for which alternative treatments are inadequate. Pharmacists should counsel patients on the use and potential misuse of this product.

RoxyBond™ is available as 5 mg, 15 mg and 30 mg tablets.

Naldemedine (Symproic®, Shionogi Incorporated with partner Purdue Pharma) was approved March 23, 2017 for the treatment of opioid-induced constipation (OIC). It is a peripherally-acting mu-opioid receptor antagonist (PAMORA) specifically indicated for OIC.

Symproic® is classified as a CII controlled substance since it is structurally similar to naltrexone. At the time of writing, the manufacturer was petitioning the Drug Enforcement Administration (DEA) to overturn that ruling since it is a peripherally-acting drug and has not been shown to have abuse potential in clinical trials. It is estimated that 40-50 percent of patients on opioid medications suffer from OIC.

FDA approval was based on data from the COMPOSE program, a global comprehensive development program comprised of clinical studies conducted in adult patients with OIC and chronic non-cancer pain. COMPOSE I and II were 12-week, multicenter, randomized, double-blind, placebo-controlled, parallel-group studies, while COMPOSE III was a 52-week efficacy and long-term safety study.

Symproic® is available as a 0.2 mg tablet and is dosed as 0.2 mg daily. Pharmacists should counsel patients to discontinue Symproic® when the patient is no longer taking opioid medications.

Although rare, Symproic® can cause gastrointestinal perforation. Patients should be counseled to seek emergency treatment for severe GI pain and discomfort.

Symproic® has the potential to have significant drug-drug interactions with the CYP3A4 medications. Strong CYP3A4 inducers, such as rifampin, can decrease naldemedine concentrations, while moderate to strong CYP3A4 inhibitors, such as itraconazole, can increase naldemedine concentrations. Symproic® also interacts with drugs that affect P-glycoprotein inhibitors, such as cyclosporine. It crosses the placenta and can cause opioid withdrawal in a fetus exposed to opioid drugs. FDA requires a Medication Guide be dispensed with this product.

Safinamide (Xadago®, Newron Pharmaceuticals) is a new monoamine oxidase type B (MAO-B) inhibitor indicated as adjunctive treatment to levodopa/carbidopa in patients with Parkinson’s disease experiencing “off” episodes. It was approved in March of 2017. It joins other MAO-B inhibitors currently on the market for managing Parkinson’s disease. These products include rasagiline (Azilect®) and selegiline.

The clinical trials submitted for approval of the drug were all placebo-controlled and none were comparator studies to MAO-B inhibitors currently on the market.

Xadago® is labeled for use only in combination with levodopa/carbidopa. It is essential that patients continue on both medications. Xadago® is dosed at 50 mg once daily, and increased after two weeks to 100 mg once daily. The maximum dose for patients with liver dysfunction (Child-Pugh class B) is 50 mg per day. Safinamide should be avoided in patients with severe liver disease.

Xadago® is available in 50 mg and 100 mg tablets. It is important to take it at the same time each day, but the medication can be given without regards to meals.

Xadago® carries some of the same drug-drug interactions and drug-food interactions as other MAO-B inhibitors, but safinamide is a selective inhibitor when dosed at 100 mg or less per day. Although the potential interactions are less in recommended doses, patients
should be made aware of the interactions. Foods that contain high concentrations of tyramine could cause severe hypertension, especially if the patient is taking high doses of the drug. The food-MAO-B interaction can result in hypertensive crisis which is an emergency situation. Pharmacists should provide the patient or caregiver with a list of foods that are high in tyramine.

Abrupt discontinuation or interruption of antiparkinsonian therapy has been associated with a discontinuation syndrome, which may resemble neuroleptic malignant syndrome. Symptoms may include elevated temperature, muscular rigidity, altered consciousness and autonomic instability. Pharmacists should counsel patients on not discontinuing Xadago® abruptly.

Drug-drug interactions can occur with concomitant use of other monoamine oxidase inhibitors or other drugs that are potent inhibitors of monoamine oxidase (linezolid); opioids (meperidine, methadone, propoxyphene, tramadol); serotonin-norepinephrine reuptake inhibitors; tricyclic, tetracyclic, or triazolopyridine antidepressants, cyclobenzaprine, methylphenidate, amphetamine and their derivatives; St. John’s wort; and dextromethorphan. Safinamide is contraindicated with any of these drugs.

Adverse events with Xadago® can include dyskinesia, hypertension, impulse control disorder, and serotonin syndrome. When discontinuing therapy, it is recommended to have patients taking the 100 mg dose taper off by decreasing the dose by half for one week.

The 50 mg and 100 mg tablets are film-coated and not intended to be split. This product became available to the market in July 2017.

Amantadine Hydrochloride (Gocovri™, Adamas Pharmaceuticals) received FDA approval on August 24, 2017 for the treatment of levodopa-induced dyskinesia. This follows its April 2015 FDA orphan drug status.

The manufacturer enrolled over 280 patients in three different placebo-controlled trials to evaluate effectiveness. In the clinical trials, the dose was 340 mg (274 mg equivalent amantadine base) daily at bedtime. This extended-release product was dosed at bedtime so the resulting blood levels were higher upon awakening when the dyskinesia can be the most difficult for patients.

The initial dose is 137 mg daily at bedtime, and then increased after one week to 274 mg as the recommended maximum daily dose. The lower 137 mg daily dose should be recommended to patients with moderate or severe kidney impairment. Gocovri™ can be given without regard to meals. It should be swallowed whole, or the contents can be sprinkled on soft food but swallowed whole without chewing.

Patients should not be abruptly withdrawn from Gocovri™. Amantadine can cause anticholinergic side effects and these can be exaggerated when combined with other drugs with the same effect.

Alcohol should be avoided since it is known to cause a dose dumping effect which destroys the extended-release feature and the entire dose would be released at one time.

Urine pH has been reported to influence the excretion rate of amantadine. The pH of the urine can be affected by diet, drugs such as carbonic anhydrase inhibitors, sodium bicarbonate and clinical disease states such as urinary tract infections. Acidifying the urine can cause amantadine to be eliminated faster, while increasing the alkalinity of the urine can increase blood levels and increase the risk of adverse events.

The most common side effects include hallucination, dizziness, dry mouth, swelling of legs and feet, constipation, and falls.

Immunizing pharmacists should be aware that the antiviral properties of amantadine could potentially interfere with the efficacy of live attenuated vaccines including influenza. Patients should receive live vaccines prior to starting therapy, and therapy should not be initiated until patients have had time to seroconvert with the vaccine. Inactivated influenza vaccine would be the preferred choice in these patients.

Gocovri™ is available in 68.5 mg and 137 mg (expressed as the amantadine base) extended-release capsules.

Summary
This lesson includes a broad overview of drugs approved in 2017 for central nervous system disorders. Pharmacists should consult the patient package insert and other references for more detailed information.

Many pharmacists will not be exposed to some of these newer medications in their practices, but should stay current with new drug and formulation approvals, as well as updates to treatment guidelines that could include these new agents.

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.

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continuing education quiz

New Drugs 2017: Central Nervous System

1. Valbenazine is used in the treatment of tardive dyskinesia by acting as an (a):
   a. VMAT1 inhibitor. c. interleukin-2 receptor blocker.
   b. VMAT2 inhibitor. d. opioid agonist.

2. Which of the following drugs should be taken on an empty stomach for better absorption?
   a. Valbenazine c. Methylphenidate
   b. Deutetrabenazine d. Safinamide

3. Deutetrabenazine has a Boxed Warning for:
   a. cardiovascular events. c. hyponatremia.
   b. liver failure. d. depression.

4. The starting dose for deutetrabenazine for Huntington’s disease is:
   a. 6 mg once daily x 1 week.
   b. 6 mg twice daily x 1 week.
   c. 12 mg once daily x 1 week.
   d. 12 mg twice daily x 1 week.

5. The first drug indicated for both primary progressive and relapsing forms of multiple sclerosis is:
   a. valbenazine. c. ocrelizumab.
   b. deutetrabenazine. d. edaravone.

6. For the treatment of ALS, edaravone acts as a:
   a. VMAT2 inhibitor. c. sympathomimetic amine.
   b. free radical scavenger. d. MAO-B inhibitor.

7. FDA approved Noctiva™ for the treatment of:
   a. diabetes insipidus. c. von Willebrand disease.
   b. hemophilia A. d. nocturnal polyuria.

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