Goal. The goal of this lesson is to provide a review of select U.S. Food and Drug Administration (FDA) safety warnings and associated prescribing updates that were issued over the past several months regarding zolpidem-containing products, valproate use in pregnancy, ketoconazole and acetaminophen.

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

1. demonstrate an understanding of the safety warnings and associated prescribing changes, if applicable, issued for each of the entities discussed;
2. identify the patient population at risk for adverse events in relation to the safety warnings for the entities discussed; and
3. list fundamental patient counseling points secondary to the safety warnings and associated prescribing changes, if applicable, for the entities discussed.

Zolpidem-Containing Medications

Zolpidem is a sedative-hypnotic medication used for the treatment of insomnia. In 2011, approximately nine million patients received zolpidem products from U.S. outpatient retail pharmacies, of which over half were dispensed to females.

In January 2013, FDA notified the public that new data indicated that blood levels of zolpidem may be high enough the morning after use to impair activities that require alertness, including driving. While this specific warning focused on zolpidem-containing products such as Ambien, Ambien CR, Edluar, and Zolpimist, drowsiness the day after taking virtually any insomnia product is possible and warrants caution. FDA announced that they were requiring manufacturers to reduce the recommended dose of these agents in order to lower resulting blood levels the following morning. For over 20 years, FDA has received reports of possible driving impairment and motor vehicle accidents associated with zolpidem. However, in most cases it was difficult to determine if the driving impairment was related to zolpidem or a specific zolpidem drug level. The availability of this new data and driving simulation studies has led to the approval of new drug labels reflecting these dosing changes as of May 2013.

The recommended initial dose of immediate-release products Ambien and Edluar is now 5 mg for women and either 5 mg or 10 mg for men. The recommended initial dose of zolpidem extended-release (Ambien CR) is 6.25 mg for women, and either 6.25 mg or 12.5 mg for men. These initial doses are expected to be effective in most patients. However, if they are not, the dose can be increased to 10 mg for immediate-release products and 12.5 mg for zolpidem extended-release with the cautionary statement that the higher dose can increase the risk of next-day impairment of driving and other activities that require full alertness. Because labeling for Intermezzo already recommends a lower dose in women compared to men, FDA is not requiring additional changes. Table 1 lists a summary of these dosing changes.

Data submitted to FDA indicated that individuals with zolpidem blood levels greater than 50 ng/mL may be impaired enough to increase the risk of a motor vehicle accident. In pharmacokinetic trials utilizing zolpidem products at the 10 mg dose, 15 percent of women and 3 percent of men had zolpidem concentrations that exceeded 50 ng/mL eight hours after dosing. Of the total 250 women and 250 men tested, three women and one man had levels exceeding 90 ng/mL.

In trials involving zolpidem extended-release 12.5 mg, 33 percent of women and 25 percent of men had zolpidem blood concentrations exceeding 50 ng/mL, approximately eight hours after dosing. Eight hours following 6.25 mg extended-release doses of zolpidem, 15 percent of adult women and 5 percent of adult men had levels exceeding the proposed threshold. Ten percent of both elderly men and women were also found to have such levels, indicating that in-
increased age may slow the metabolism of zolpidem. 

Hence, data supports that the risk for next-morning impairment is greatest in patients taking the extended-release forms of these drugs (i.e., Ambien CR and generics), in women, and the elderly. The pharmacokinetic trials conducted did not find a relationship between zolpidem blood levels and the body weight or ethnicity of the patient.

FDA notes that next-morning impairment is different than complex sleep-related behaviors. Next-morning impairment occurs in patients who are awake, while complex sleep-related behaviors occur when patients get out of bed and perform activities such as sleepwalk, drive a car, or prepare and eat food while they are not fully awake and without memory of the activity. In 2007, the zolpidem label’s Warnings and Precautions section was updated to reflect the concern of complex sleep-related behaviors. The co-administration of central nervous system (CNS) depressants with zolpidem increases the risk of such behaviors.

An article published in 2011 in the Journal of Clinical Sleep Medicine by Poceta examined a series of clinical and legal cases following the ingestion of zolpidem. The author described cases of zolpidem-associated complex behaviors including daytime automatisms and sleep-related parasomnia, and concluded that risk factors for these behaviors include concomitant ingestion of other sedating drugs, a higher dose of zolpidem, a history of parasomnia, ingestion at times other than bedtime or when sleep is unlikely, poor management of pill bottles, and living alone. Parasomnias are sleep disorders that involve abnormal and unnatural movements, behaviors, emotions, perceptions, and dreams that occur while falling asleep, sleeping, between sleep stages or during arousal from sleep. Family history, sleep deprivation, fever, alcohol, and medications predispose people to parasomnia. FDA states that the new dosing recommendations are expected to decrease both complex sleep-related behaviors and next morning impairment.

The zolpidem drug label carries other noteworthy precautions. Since it is a CNS depressant, its effect can be additive when used concurrently with other CNS depressants such as benzodiazepines, opioids, tricyclic antidepressants, and alcohol. Sleep disturbances can present with physical and/or psychiatric disorder(s). Therefore, symptomatic treatment of insomnia should be prescribed with caution and careful evaluation as well as re-evaluation. Abnormal thinking and behavior changes have been reported in patients treated with sedative-hypnotics such as zolpidem. These changes include decreased inhibition, bizarre behavior, agitation, and depersonalization. Visual and auditory hallucinations have been reported.

Worsening depression and suicidal thoughts and actions have been reported in patients treated with sedative-hypnotics who are primarily depressed. Providers are cautioned to prescribe minimal tablets of zolpidem as intentional overdosage is common in this group of patients.

The risk of respiratory depression when used at hypnotic doses should be considere in patients with respiratory impairment including those with sleep apnea and myasthenia gravis. Patients should be monitored for tolerance, abuse, and dependence of zolpidem. Reports of withdrawal signs and symptoms following rapid dose decrease or abrupt discontinuation have been reported.

In order to reduce the risk of next-morning impairment, patients should take the lowest dose that manages their symptoms. Zolpidem should not be taken if less than seven to eight hours of sleep is anticipated. Poceta suggests instructing the patient to not only “ingest immediately prior to going to bed,” but to add that it should be taken “at your usual bedtime only.”

### Valproate Sodium Use in Pregnancy

FDA alerted health care professionals and women in May 2013 that recent studies provide evidence that the anti-seizure medications, valproate sodium and related products, can cause decreased IQ scores in children whose mothers took them while pregnant. Stronger warnings about use during pregnancy will be added to the drug labels and valproate’s pregnancy category will be changed from “D” to “X” when prescribed for migraines. However, valproate products will remain in pregnancy category “D” for treating epilepsy and manic episodes associated with bipolar disorders. Pregnancy risk category D indicates that adequate well-controlled or observational studies in pregnant women have

<table>
<thead>
<tr>
<th>Table 1</th>
<th>2013 Dosing recommendations for zolpidem*</th>
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<tr>
<td>Ambien, Edluar, Zolpimist</td>
<td>Women: 5 mg once daily, immediately before bedtime</td>
</tr>
<tr>
<td></td>
<td>Men: 5 or 10 mg once daily, immediately before bedtime</td>
</tr>
<tr>
<td>Ambien CR</td>
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<tr>
<td></td>
<td>Men: 6.25 or 12.5 mg once daily, immediately before bedtime</td>
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*for non-elderly adults
demonstrated a risk to the fetus. Yet, the benefits of therapy may outweigh the potential risk such as cases where the drug is needed in a life-threatening situation or serious disease for which safer drugs cannot be used or are ineffective. Pregnancy category X means that adequate well-controlled or observational studies in animals or pregnant women have demonstrated positive evidence of fetal abnormalities or risks. The use of category X agents is contraindicated in women who are or who may become pregnant.

Health care professionals are advised to prescribe these products in pregnant women with epilepsy or bipolar disorders when other medications are not effective or otherwise unacceptable. In addition, for women of childbearing age who are not pregnant, valproate products should be resorted to only when the medication is considered essential and prescribed along with effective birth control.

Meador et al. reported a prospective, observational study that involved children of women who were taking one of four anti-epileptic drugs as monotherapy: lamotrigine, carbamazepine, phenytoin, or valproate products. The study compared results of IQ tests of six-year-olds who had been exposed to one of these antiepileptic drugs in utero. Children exposed to valproate products during pregnancy had statistically significant lower IQ scores, when compared to all other monotherapies that were studied. The mean IQ for the valproate was 97 compared to 105, 108, and 108 for carbamazepine, lamotrigine, and phenytoin respectively. Additionally, the mean IQs were higher in groups whose mothers reported periconceptional folate use. However, the authors warn that these findings should be interpreted with caution as the effect of periconceptional folate use was not a primary outcome of the study and the information for this outcome was collected retrospectively. It is important to note that the women studied were exposed to antiepileptic drugs throughout their pregnancies, and it is unknown if the timing of exposure during pregnancy may affect the severity of cognitive effects in children.

Valproate products include: valproate sodium (e.g., Depacon), divalproex sodium (e.g., Depakote, Depakote CP, Depakote ER), valproic acid (e.g., Depakene and Stavzor). While the exact mechanism of action is unknown, their antiepileptic action may be attributed to increased gamma-aminobutyric acid (GABA) levels in the brain. Divalproex sodium is approved for use in simple and complex absence seizures, complex partial epileptic seizures, manic bipolar I disorder, and prophylaxis of migraines. Off label, these agents may also be prescribed for alcohol withdrawal syndrome, maintenance of bipolar I and II disorder, chronic headache disorder, post-traumatic headache, and bipolar type schizoaffective disorder.

The label of valproate products carries a black box warning for the risk of hepatotoxicity which usually occurs within the first six months of treatment. Liver function tests are recommended at the start of therapy and at frequent intervals, particularly during the first six months. Children younger than two years of age and patients with hereditary mitochondrial disease are at a higher risk of developing fatal hepatotoxicity. Use may be contraindicated in these populations.

In addition to impaired cognitive development during prenatal exposure, valproate products may produce major congenital malformations such as neural tube defects (i.e., spina bifida). Life-threatening pancreatitis has also been reported in adults and children taking these agents.

Affected patients should be advised that taking valproate during pregnancy can decrease the child’s IQ score and a higher risk for birth defects exists. These women should speak with their health care professional immediately, but should not stop valproate treatment suddenly as this can cause serious and life-threatening medical problems to both the mother and baby. Health care providers should counsel patients on the importance of effective birth control, if they are not pregnant but of child bearing age. Folic acid supplementation before conception and during early pregnancy has been shown to reduce the chance of neural tube defects in babies and should be routinely recommended.

Additionally, health care providers can share information with their patients about the North American Antiepileptic Drug Pregnancy Registry. The registry was established in 1997 for pregnant women in the United States and Canada at Massachusetts General Hospital in Boston, Massachusetts. The major objective of the registry is to obtain and publish information on the frequency of major malformations (such as heart defects, spina bifida, and cleft lip), with the highest priority placed on new information related to the use of newer antiepileptic drugs (AEDs) marketed in the past ten years. Prior to the creation of this registry, data regarding the safety of antiepileptic drugs was conducted by manufacturers and there was no systematic method to determine whether or not specific anticonvulsants were associated with increases in malformations. As of April 2012, 8,500 women had enrolled in the registry.

The registry’s most recent newsletter, published in 2012, announced new findings on the comparative safety of 11 AEDs used during pregnancy. The newsletter summarizing these findings, as well as additional information for providers and patients, can be found on their website at www.aed-pregnancyregistry.org. The registry staff emphasizes a need for the largest possible sample size as they study the safety of AEDs in order to report accurate findings. Women must register themselves and can do so by calling 1.888.233.2334.

Ketoconazole

Ketoconazole (Nizoral and others)
is an imidazole antifungal agent that has been prescribed for the treatment of many superficial and systemic fungal infections. During 2012 alone, approximately 600,000 prescriptions for the tablet formulation were dispensed. While it has been associated with drug-induced liver injury for several years, FDA is now requiring the drug label to be updated and requesting that ketoconazole's use be limited. The announcement came from FDA on July 26, 2013 and includes several changes following a negative risk versus benefit assessment that was conducted by the European Medicines Agency (EMA). EMA made a public announcement recommending that marketing authorization of oral ketoconazole be suspended throughout the European Union. Similar action was taken in France, also because of high liver injury associated with ketoconazole use. The foreign agencies state that while hepatitis is a known side effect of other antifungal medicines, both incidence and severity of liver injury with oral ketoconazole were higher than with other antifungals, and it does not appear to be possible to identify measures to reduce the risk. Topical formulations of ketoconazole such as creams, ointments, and shampoo can continue to be used as the amount of drug absorbed throughout the body is low.

Liver damage with ketoconazole is documented for patients receiving high doses for short periods of time or low doses for long periods of time, and may occur in those without obvious risk factors for liver disease. Hepatotoxicity associated with the agent is sometimes reversible upon discontinuation. However, damage leading to liver transplantation or death has occurred. Therefore, oral use is contraindicated in patients with acute or chronic liver disease. The new label recommends that liver function be assessed prior to treatment and monitored routinely (i.e., weekly), as well as at the first signs.

### Table 2
Selected Drugs with Plasma Concentrations Altered by Nizoral®

| Systemic exposure to these drugs is increased significantly by ketoconazole: | Alprazolam, midazolam, triazolam | HMG-CoA reductase inhibitors (lovastatin, simvastatin) |
| Concomitant use is **contraindicated.** | Cisapride | Nisoldipine |
| | Dofetilide | Pimozide |
| | Epileprone | Quinidine |
| | Ergot alkaloids | |

| Systemic exposure to these drugs is increased by ketoconazole: | Alfentanil, fentanyl, sufentanil | Indinavir, saquinavir |
| Careful monitoring, with possible adjustment in dosing, is recommended. | Amlodipine, felodipine, nicardipine, nifedipine | Methylprednisolone |
| | Bosantan | Rifabutin |
| | Buspirone | Sildenafil |
| | Busulfan | Sildenafil |
| | Carbamazepine | Vinca alkaloids |
| | Chlorpromazine | |
| | Cyclosporine | |
| | Digoxin | |
| | Docetaxel, paclitaxel | |
| | Oral anticoagulants | |

*This list is not all-inclusive. From Nizoral package insert.*

### Table 3
Selected Drugs that may Alter Plasma Concentrations of Nizoral®

| Systemic exposure to ketoconazole is significantly reduced by these drugs and concomitant use is not recommended. | Carbamazepine | Nevirapine |
| | Gastric acid suppressants (antacids, antimuscarinics, histamine H₂ blockers, proton pump inhibitors, sucralfate) | Phenytoin |
| | | Rifampin, rifabutin, isoniazid |

| Systemic exposure to ketoconazole is increased significantly by this drug: Dose reduction of ketoconazole should be considered. | Ritonavir | |

*This list is not all-inclusive. From Nizoral package insert.*
or symptoms of possible hepatotoxicity. Signs and symptoms of hepatotoxicity include anorexia, nausea, vomiting, fatigue, jaundice, abdominal pain, or dark urine. Health care professionals should advise patients to avoid alcohol and other potentially hepatotoxic drugs while receiving ketoconazole tablets.

In addition to warning of severe liver injury with ketoconazole, the drug safety communication identified that the antifungal is associated with adrenal insufficiency. Adrenal insufficiency is a decreased ability of the adrenal glands to produce corticosteroids. Health care professionals are advised to monitor adrenal function in patients taking ketoconazole tablets who have existing adrenal insufficiency or in patients experiencing extended periods of stress (i.e., following major surgery or increased stays in intensive care settings).

Lastly, the warning brings attention to the many drug interactions that are possible with ketoconazole which can lead to serious and potentially life-threatening outcomes. FDA is calling for all health care professionals to assess all other concurrent medications that the patient is taking in order to minimize this risk. The current drug label includes a black box warning indicating that ketoconazole is contraindicated with dofetilide, quinidine, pimozide, and cisapride. These combinations can cause elevated plasma concentrations of these drugs which may result in further QT prolongation and possibly life-threatening ventricular dysrhythmias such as torsades de pointes. Co-administration of ketoconazole tablets with oral midazolam, oral triazolam, or alprazolam is also contraindicated as it has resulted in elevated plasma concentrations of these drugs and may potentiate or prolong the sedative and hypnotic effects especially with repeated dosing. Other contraindicated agents include the CYP3A4 metabolized HMG-CoA reductase inhibitors simvastatin and lovastatin, as well as nisoldipine, eplerenone, and ergot alkaloids.

Careful monitoring and dosing adjustments may be required with several other commonly prescribed medications. Tables 2 and 3 include more drug interactions as detailed in the Nizoral package insert.

Under the new label, ketoconazole should not be used as a first-line agent for any fungal infection and should only be used for the treatment of certain fungal infections such as endemic mycoses when alternative antifungal therapies are not available. Indications for which the risk of ketoconazole therapy outweighs the benefit have been removed from the label. Therefore, the use of ketoconazole in Candida and dermatophyte infections is no longer indicated and this oral antifungal is no longer appropriate for fungal infections of the skin or nails. This labeling change will alter prescribing as reports from office-based physicians indicated that the most common diagnosis associated with use in recent years have included superficial skin and nail fungal infections. Ultimately, oral ketoconazole can now only be prescribed for the following infections: blastomycosis, coccidioidomycosis, histoplasmosis, chromomycosis, and paracoccidioidomycosis in patients who have failed other therapies or who are intolerant to them. A patient Medication Guide is now required by law each time a prescription is dispensed, and is summarized in Table 4.

### Acetaminophen

A new safety warning with acetaminophen has been issued. On August 1, 2013, FDA published a statement to warn the public about rare but serious skin reactions that have been reported secondary to acetaminophen use. The skin reactions include Stevens-Johnson Syndrome (SJS), toxic epidermal necrolysis (TEN), and acute generalized exanthematous pustulosis (AGEP), and they can be fatal.

Stevens-Johnson Syndrome is described as severe, widespread vesiculobullous disease of the skin with involvement of two or more mucosal surfaces such as eyes, oral cavity, upper airway or esophagus, gastrointestinal tract, or anogenital mucosa. SJS results in mucosal erosions and epidermal detachment affecting less than 10 percent of the body surface area. TEN is the most extreme form of the disease with
bias occurs when a pharmaceutical agent is inadvertently prescribed for an early manifestation of a disease that has not yet been diagnosed. In this instance, protopathic bias refers to a false increase in the risk of SJS/TENS attributed to acetaminophen when used to treat fever because fever is also an early symptom of SJS/TEN. In one of the studies that did control for protopathic bias, acetaminophen was still associated with SJS/TEN.

FDA states that it is difficult to determine how frequently serious skin reactions occur with acetaminophen due to the widespread use, difference in usage among individuals, and the fact that the medication has been available for so long. FDA is requiring that a warning be added to the labels of acetaminophen-containing prescription drugs and requesting the same from manufacturers of OTC acetaminophen drug products.

While health care professionals should be aware of this risk, they should recall that it is rare and consider other drugs that carry the same warnings in their label. Drugs that are most commonly associated with SJS include anticonvulsants such as phenytoin, phenobarbital, carbamazepine, lamotrigine, and valproic acid; sulfonamides; penicillins; nonsteroidal anti-inflammatory drugs (NSAIDs); allopurinol; and tetracyclines. Drugs that are rarely associated with SJS include: leflunomide, venlafaxine, furosemide, nevirapine, and following vaccination from smallpox and chickenpox. SJS has also occurred rarely following certain fungal and protozoal infections and in children with Epstein-Barr virus and enterovirus infections. Overall incidence of SJS is 0.1 to 0.7 cases per 100,000 per year. It occurs mainly in children and young adults, affecting males two times more than females.

AGEP is most often caused by antibiotics such as aminopenicillins and macrolides, calcium channel blockers, and antimalarials. Among many other drugs, aspirin and NSAIDs such as celecoxib, etodolac, and ibuprofen have been linked. The estimated incidence is one to five cases per million per year. While it can occur at any age, AGEP most often affects adults with a slight female predominance.

AGEP symptoms include red-dening of the skin, rash, blisters, and detachment of the upper surface of the skin. During the acute phase, fever and leukocytosis can occur. Those who experience symptoms are advised to stop taking the drug and seek medical attention right away. It is important for patients to understand that these reactions can occur with first-time use of acetaminophen or at any time while it is being taken. Individuals who have experienced a serious skin reaction with acetaminophen should not take the medication again.

Summary
The safety information and prescribing updates discussed in this lesson provide a detailed review of FDA drug safety communications recently issued for zolpidem-containing products, valproate use in pregnancy, ketoconazole, and acetaminophen. The updated product leaflets should be consulted for full prescribing information.

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 CE activity and is targeted to pharmacists in all practice settings.

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The Ohio Pharmacists Foundation Inc. is accredited by the Accreditation Council for Pharmacy Education as a provider of continuing pharmacy education.
FDA Safety Warnings and Prescribing Updates: Zolpidem, Valproate, Ketoconazole, and Acetaminophen

1. The recommended initial dose of extended-release zolpidem for women is now:
   a. 5 mg.  c. 10 mg.
   b. 6.25 mg. d. 12.5 mg.

2. Data suggests that the risk for next-morning impairment is greatest in patients taking which of the following formulations of zolpidem?
   a. Immediate-release  c. Sublingual
   b. Oral spray  d. Extended-release

3. Zolpidem’s effects can be additive with all of the following drugs EXCEPT:
   a. alcohol.  c. tricyclic antidepressants.
   b. benzodiazepines. d. ketoconazole.

4. Zolpidem should not be taken if fewer than how many hours of sleep are anticipated?
   a. 5 to 6 hours   b. 7 to 8 hours

5. The pregnancy category for valproate products prescribed for migraines is now:
   a. Category X.  c. Category C.
   b. Category D.  d. Category B.

6. It has been confirmed that the timing of exposure to valproate during pregnancy affects the severity of cognitive effects in children.
   a. True   b. False

7. The label of valproate products carries a black box warning for the risk of:
   a. renal toxicity.  c. hepatotoxicity.
   b. respiratory depression.  d. adrenal insufficiency.

8. The major objective of the North American Antiepileptic Drug Pregnancy Registry is to publish information on the frequency of:
   a. major malformations in babies.
   b. colonic obstruction.
   c. fistulas and perianal disease.
   d. small bowel obstruction.

9. Liver damage with ketoconazole is documented in patients receiving all of the following EXCEPT:
   a. low doses for short periods of time.
   b. low doses for long periods of time.
   c. high doses for short periods of time.

10. In addition to severe liver injury, ketoconazole is associated with:
    a. renal toxicity.  c. pancreatitis.
    b. respiratory depression.  d. adrenal insufficiency.

11. All of the following medications are contraindicated with ketoconazole EXCEPT:
    a. alprazolam.  c. carbamazepine.
    b. dofetilide.  d. simvastatin.

12. Ketoconazole is appropriate therapy for fungal infections of the skin or nails.
    a. True   b. False

13. Patients taking ketoconazole should be advised to avoid:
    a. alcohol.  c. caffeine.
    b. acetaminophen.  d. NSAIDs.

14. Rare but serious skin reactions associated with acetaminophen use include all of the following EXCEPT:
    a. AGEP.  c. TEN.
    b. SJS.  d. LDE.

15. The estimated incidence of acute generalized exanthematous pustulosis is:
    a. 0.1 to 0.7 cases per 100,000 per year.
    b. 1 to 5 cases per million per year.

Completely fill in the lettered box corresponding to your answer.

1. [a] [b] [c] [d]  6. [a] [b]  11. [a] [b] [c] [d]
2. [a] [b] [c] [d]  7. [a] [b] [c] [d]  12. [a] [b]
3. [a] [b] [c] [d]  8. [a] [b] [c] [d]  13. [a] [b] [c] [d]
4. [a] [b]  9. [a] [b] [c]  14. [a] [b] [c] [d]
5. [a] [b] [c] [d]  10. [a] [b] [c] [d]  15. [a] [b]

☐ I am enclosing $5 for this month’s quiz made payable to: Ohio Pharmacists Association.

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