FDA Safety Warnings and Prescribing Updates: Drospirenone, Citalopram, Dabigatran, Aliskiren, and OTC Topical Pain Relievers

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 a review of significant U.S. Food and Drug Administration (FDA) safety warnings and associated prescribing updates that were issued over the last year regarding drospirenone (DRSP)-containing oral birth control pills, citalopram, dabigatran, aliskiren, and over-the-counter (OTC) topical pain relievers containing menthol, methyl salicylate, or capsicain.

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.

Drospirenone (DRSP)-Containing Oral Birth Control Pills

The Food and Drug Administration has issued several communication bulletins regarding the possible increased risk of blood clots in women taking birth control pills (BCPs) containing drospirenone (e.g., Yasmin®, Beyaz®, Safyral®, and Yaz®) over the past 24 months. The statement issued April 10, 2012 is an update in which FDA has concluded that DRSP-containing birth control pills may be associated with a higher risk for blood clots than other progestin-containing pills. The studies reviewed were observational or epidemiologic in nature. Therefore, they do not take into account the unknown and known patient characteristics that influence prescribing or the risk for blood clots. Thus, it is unclear whether the increased risk for blood clots seen in some of these studies is actually due to DRSP-containing birth control pills. The revised labeling of Yasmin®, Beyaz®, Safyral®, and Yaz® will report that some epidemiologic studies have reported as high as a three-fold increase in the risk of blood clots with DRSP-containing products, when compared to products that contain levonorgestrel or other progestin-containing products. The labeling will also state that other epidemiologic studies found no additional risk with these agents, and will include a summary of an FDA-funded study of the blood clot risk.

The link between combined estrogen-progestin oral contraceptives and venous and arterial thrombosis was made soon after these products were marketed in the early 1960s. At that time, it was thought that the risk was related only to the estrogen component. Early studies revealed that those containing 50mcg or more were associated with a greater risk than those containing a lower dosage, such as 20 to 35mcg. However, by the mid-1990s following the introduction of newer generation progestins in combination with estrogen, it became evident that progestins also contributed to the risk of thromboembolism. A number of theories exist as to why oral estrogen and progestin contraceptives cause thrombosis, but the mechanism is not known. Each generation of progestins has different androgenic (antiestrogenic) potency and activity.

Drospirenone is a fourth-generation progestin. It differs from others as its parent compound is spironolactone, and has some of its antimineralocorticoid and antiandrogenic effects. Hence, DRSP-containing birth control pills carry an additional warning stating that...
they should not be used in patients predisposed to hyperkalemia. Serum potassium concentrations should be checked during the first treatment cycle in women on long-term treatment with medications that may increase serum potassium. DRSP-containing BCPs should not be used in patients with adrenal or renal disease.

The risk of VTE (venous thromboembolism) increases with age (greater than 35 years), smoking, obesity, and a family history of VTE. Therefore, FDA recommends that women who are over the age of 35 and smoke should not take any type of combined oral contraceptive (COC) due to the increased risk of cardiovascular events. Also, women with a history of blood clots, heart attack, or stroke should not take COCs. Providers are reminded that before initiating DRSP-containing birth control pills, the risks and benefits of therapy must be considered in light of the patient’s risk of a VTE.

Health care providers and patients should be aware that the risk of VTE is highest during the first year of COC use. The greatest risk is present after the initial start or restarting (following a four-week or greater pill-free interval) of the same or different COC. It is important to counsel patients on recognizing the symptoms of VTE, such as persistent leg pain, severe chest pain, or sudden shortness of breath, and to contact their health care provider immediately.

FDA adds that while the risk of developing a blood clot for women using any birth control pill is greater than for those who do not, it still remains lower than the risk of developing blood clots in pregnancy and in the postpartum period. Table 1 puts the risk in clinical perspective.

It is also important to note that similar concerns have been raised regarding newer (non-drospirenone) contraceptive methods such as the contraceptive patch, Ortho Evra® and the contraceptive vaginal ring, NuvaRing®. It is hypothesized that since they provide continuous higher exposure to estrogen, thromboembolism risk may be greater. Recent studies have supported an increased risk, and the current Ortho Evra® label contains this warning. Women should talk to a health care professional about their risk for blood clots before deciding which birth control product to use.

### Citalopram

Citalopram, a selective serotonin reuptake inhibitor (SSRI), was brought to market as Celexa® after approval in July 2008 for the treatment of depression. Following drug safety communications issued by FDA in August 2011 and March 2012, the newly recommended maximum daily dose of citalopram is 40mg/day (previously 60mg/day) because of the risk of potentially dangerous abnormalities in cardiac electrical activity. Specifically, it can result in prolongation of the QT interval and can lead to torsades de pointes, ventricular tachycardia, and sudden death. Among the top 200 products ranked by number of prescriptions written in 2011, two generic citalopram equivalents made the list at #67 and #84. Additionally, in 2011, approximately 31.5 million prescriptions for citalopram were dispensed from U.S. outpatient retail pharmacies to roughly 7.2 million patients. Prior to this communication, FDA gathered data from U.S. office-based physician practices indicating that 6 percent of citalopram use was at doses above 40mg per day.

This communication is in response to post-marketing reports submitted to FDA along with the results of QT studies assessing the effects of doses of citalopram and its active S-isomer escitalopram (Lexapro®) on the QT interval in adults. The two studies that FDA used to make this decision were randomized, double-blind, placebo-controlled, crossover studies. In the first study, each of the 119 patients received 20mg citalopram per day, 60mg citalopram per day, 400mg moxifloxacin per day, and placebo. Moxifloxacin was presumably included as an active control as it has been previously associated with QT prolongation. Compared to placebo, the mean change in QTc interval prolongation was 8.5msec for the 20mg citalopram per day dose, 18.5msec for 60mg citalopram, and 13.4msec for moxifloxacin.

The second study was designed similarly using escitalopram 10mg and 30mg in 113 subjects. Changes in QTc interval prolongation were present at 4.5msec and 10.7msec respectively when compared to placebo, indicating that while the antidepressant activity is limited to the S-isomer, effects on QTc interval are not. The recommended maximum daily dose of escitalopram is 20mg per day.

FDA wants health care providers to be aware of the following recommendations in conjunction with the new advisory. (1) Citalopram is not recommended at doses greater than 40mg/day, because such doses can result in too great of an effect on the QT interval, and clinical studies do not indicate additional benefit. (2) Citalopram is not recommended in patients with congenital long QT syndrome, bradycardia, hypokalemia, hyp-
magnesemia, recent acute myocardial infarction, uncompensated heart failure, or patients taking other medications that prolong the QT interval. (3) The maximum recommended dose is 20mg per day in patients with hepatic impairment, in those over 60 years of age, in patients who are CYP2C19 poor metabolizers, or in patients taking concomitant cimetidine or another CYP2C19 inhibitor, as these factors may lead to increased levels of citalopram. (4) Electrolyte and/or electrocardiogram (ECG) monitoring is suggested in patients for whom citalopram is not recommended but considered essential. Patients at risk for significant electrolyte disturbances should have baseline and periodic monitoring of serum potassium and magnesium. (5) Providers should discontinue citalopram in patients with persistent QTc measurements greater than 500msec. Patients should be advised to contact a health care provider immediately if they experience dizziness, shortness of breath, palpitations, or syncope which may indicate an abnormal heart rate or rhythm.

Some psychiatrists have expressed concerns over FDA’s new recommendation and contend that there is no convincing evidence that citalopram, when used as prescribed in doses greater than 40mg/day, was associated with an increased risk of QTc interval prolongation and torsades de pointes as long as clinicians paid attention to the risk factors. In one particular evaluation of the cardiac toxicity of citalopram, the author, Howland, points out that the commonly accepted threshold for clinical significance of the QTc interval (i.e., increased risk of developing torsades de pointes) is a QTc ≥500msec or a change in the QTc ≥60msec from baseline. The mean change in the QTc interval was less than 20msec in the study that FDA used to make their decision. Additionally, Howland identifies that FDA did not disclose how many patients exceeded the threshold in the study. Also, it is not known if the post-marketing reports received by FDA regarding citalopram-associated cardiotoxicity are based on therapeutic doses, unusually high dose, or overdoses. In one review including nearly 600 cases of citalopram overdose (most including other drugs), QTc prolongation or other ECG changes are only described in about one-third of the cases, but with no cardiac sequelae or death in the involved patients. These experts argue that there is a subgroup of patients who may benefit from doses of 60mg/day or higher, who could potentially be destabilized if clinicians act on this FDA warning. These psychiatrists also stated that suboptimal treatment of depression is a safety concern.

Dabigatran (Pradaxa®)

Dabigatran (Pradaxa), an oral direct thrombin inhibitor, was initially approved in October 2010 for the prevention of thromboembolic stroke in patients with non-valvular atrial fibrillation based on the results of the RE-LY trial. This study, which compared dabigatran with warfarin, measured the rates of serious bleeding which were found to be similar in the two groups. The trial results indicated that dabigatran was also more effective in preventing strokes. In 2011, the American College of Cardiology Foundation/American Heart Association (ACCF/AHA) produced a focused update for the guidelines on the management of patients with atrial fibrillation, stating that dabigatran was a useful alternative to warfarin when appropriately prescribed. Since its approval through August 2012, a total of approximately 3.7 million prescriptions were dispensed to approximately 725,000 patients from U.S. outpatient retail pharmacies.

FDA has been evaluating new information about the risk of serious bleeding associated with use of dabigatran and warfarin, secondary to a large number of post-marketing reports of bleeding with dabigatran users. The first drug safety communication regarding bleeding risks was issued in December 2011. FDA believed that Pradaxa provided an important health benefit when used as directed, and recommended that clinicians follow the dosing recommendations in the approved drug label, especially for patients with renal impairment, to reduce the risk of bleeding.

On November 2, 2012, the agency issued an updated drug safety communication indicating that they have not changed their recommendation. This decision was based on an assessment that FDA conducted utilizing data from their Mini-Sentinel pilot. Mini-Sentinel is a pilot project sponsored by FDA to create an active surveillance system to monitor the safety of FDA-regulated medical products. The investigation looked at data extracted from insurance claims and administrative data, and examined the actual rates of gastrointestinal bleeding and intracranial hemorrhage. The results of this Mini-Sentinel assessment indicated that bleeding rates associated with new use of dabigatran do not appear to be higher than bleeding rates associated with new use of warfarin, which is consistent with observations from the RE-LY trial.

FDA is also conducting two planned, protocol-based observational assessments which will assess patients taking dabigatran and evaluate bleeding events. FDA feels that comparing the number of post-marketing reports of bleeding in the Adverse Event Reporting System (AERS) between Pradaxa and warfarin is misleading, because reports of bleeding events associated with warfarin have been available for many years and are likely under-reported compared to Pradaxa.

Wychowski and Kouides report a case in which a 66-year-old woman treated with dabigatran for atrial fibrillation developed acute renal failure and upper gastrointestinal bleeding. The patient had been taking dabigatran 150mg orally twice daily, with intermittent renal insufficiency during the previous six months. Laboratory values on
admission included serum creatinine 3.6mg/dL, hematocrit 21 percent, and international normalized ratio (INR) greater than 10. The over-anticoagulated patient was treated with packed red blood cells, prothrombin complex concentrate, and multiple sessions of dialysis. The patient’s renal function never recovered. She remained hemodi-
alysis dependent, and died following a lengthy hospital stay and transfer to a nursing home. This case illustrates the importance of appropriate patient selection and the need to periodically monitor renal function in patients receiving dabigatran.

An audit of bleeding events initiated in collaboration with the Haematology Society of Australia and New Zealand identified 78 episodes of bleeding, of which 12 were major. A review of the cases identified four major factors that played a role in the bleeding: prescriber error, impaired renal function, patient age, and complications arising from the lack of a reversal agent.

The dosing, administration, warnings, and precautions for dabigatran were revised in 2012. For patients with creatinine clearance (CrCL) >30mL/min, the dose is 150mg orally twice daily. For patients with CrCL 15 to 30mL/min, the dose is 75mg orally twice daily. It is not recommended for patients with CrCL <15mL/min. Providers should assess renal function prior to initiation and during therapy, as clinically warranted, followed by dosing adjustments when necessary. Dabigatran should be discontinued in patients who develop acute renal failure, and providers should consider alternative anticoagulant therapy. In patients with moderate renal impairment (CrCL 30 to 50mL/min), concomitant use of the P-gp inhibitor dronedarone or systemic ketoconazole can be expected to produce dabigatran exposure similar to that observed in more severe renal impairment. In this case, reducing the dose to 75mg twice daily should be considered. Generally, the extent of anticoagulation does not need to be assessed. If necessary, the activated partial thromboplastin time (aPTT) or ecarin clotting time (ECT) may be measured, but not the INR.

Pradaxa is contraindicated in patients with active pathological bleeding or with a history of serious hypersensitivity reaction to Pradaxa. Risk factors for bleeding include the concomitant use of other drugs that increase the risk of bleeding such as anti-platelets, heparin, fibrinolytic therapy, and chronic use of NSAIDs.

A specific reversal agent is not available for dabigatran. Options include hemodialysis to remove dabigatran or administering activated prothrombin complex concentrations, recombinant Factor VIIa, or concentrate of coagulation factors II, IX, or X. However, clinical experience and clinical data are limited for these treatments. Protamine and vitamin K are not expected to affect the anticoagulant activity of dabigatran. Also new to the product labeling is a statement regarding the use of Pradaxa in patients with mechanical prosthetic heart valves. Pradaxa is contraindicated in this population.

Patients are advised to continue taking Pradaxa as prescribed and to not discontinue therapy without talking to the provider who prescribed it. Patients should be reminded that they may bleed more easily and longer. They should seek emergency treatment if they have any of the following signs or symptoms of bleeding: unusual bruising, pink or brown urine, red or black tarry stools, coughing up blood, vomiting blood, or vomit that looks like coffee grounds. In addition, prompt medical attention is recommended if they experience these additional signs or symptoms of bleeding: unusual bruising, pink or brown urine, red or black tarry stools, coughing up blood, vomiting blood, or vomit that looks like coffee grounds. In addition, prompt medical attention is recommended if they experience these additional signs or symptoms of bleeding: unusual bruising, pink or brown urine, red or black tarry stools, coughing up blood, vomiting blood, or vomit that looks like coffee grounds. In addition, prompt medical attention is recommended if they experience these additional signs or symptoms of bleeding: unusual bruising, pink or brown urine, red or black tarry stools, coughing up blood, vomiting blood, or vomit that looks like coffee grounds. In addition, prompt medical attention is recommended if they experience these additional signs or symptoms of bleeding: unusual bruising, pink or brown urine, red or black tarry stools, coughing up blood, vomiting blood, or vomit that looks like coffee grounds. In addition, prompt medical attention is recommended if they experience these additional signs or symptoms of bleeding: unusual bruising, pink or brown urine, red or black tarry stools, coughing up blood, vomiting blood, or vomit that looks like coffee grounds. In addition, prompt medical attention is recommended if they experience these additional signs or symptoms of bleeding: unusual bruising, pink or brown urine, red or black tarry stools, coughing up blood, vomiting blood, or vomit that looks like coffee grounds. In addition, prompt medical attention is recommended if they experience these additional signs or symptoms of bleeding: unusual bruising, pink or brown urine, red or black tarry stools, coughing up blood, vomiting blood, or vomit that looks like coffee grounds. In addition, prompt medical attention is recommended if they experience these additional signs or symptoms of bleeding: unusual bruising, pink or brown urine, red or black tarry stools, coughing up blood, vomiting blood, or vomit that looks like coffee grounds.

Gastrointestinal adverse reactions such as dyspepsia, burning, nausea, abdominal pain or discomfort, epigastric discomfort, and gastric indigestion may occur and warrant a call to the health care provider.

Patients should inform their health care provider if they are taking Pradaxa before any invasive surgery is scheduled, including dental procedures. Table 2 summa-
rizes pertinent patient counseling tips.

**Aliskiren**

On April 20, 2012, FDA issued a drug safety communication regarding a new warning and contraindication for blood pressure medications containing aliskiren (Tekturna®) which was initially approved in 2007 and marketed by Novartis. Aliskiren is a direct renin inhibitor indicated for the treatment of hypertension. The safety communication states that FDA is warning of possible risks when using blood pressure medicines containing aliskiren with other angiotensin-converting enzyme inhibitors (ACEIs) and angiotensin receptor blockers (ARBs).

The following new recommendations were added to product labels of Tekturna®, Tekturna® HCT® (aliskiren and hydrochlorothiazide), Tekamlo™ (aliskiren and amlodipine), and Amturnide (aliskiren, amlodipine, and hydrochlorothiazide). (1) The use of aliskiren with ACEIs or ARBs is contraindicated in patients with diabetes because of risks of renal impairment, hypotension, and hyperkalemia. (2) Use of aliskiren should be avoided with concomitant use of ARBs or ACEIs in patients with moderate to severe renal impairment (GFR<60mL/min).

In 2011, approximately 2.4 million prescriptions for aliskiren-containing products were dispensed to 451,000 patients. Also in 2011, data collected from U.S. retail pharmacies indicated that approximately 22 percent of the patients on aliskiren-containing products had concurrent use with ACEIs/ ARBs and diabetic medication, while approximately 30.5 percent of Valturna® (aliskiren/valsartan) patients received concurrent therapy with diabetic medications. Novartis ceased marketing Valturna® in July 2012. The warning is based on preliminary data from the clinical trial, Aliskiren Trial in Type 2 Diabetes using Cardio-Renal Endpoints (ALTITUDE). The purpose of ALTITUDE was to determine whether aliskiren, in addition to conventional therapy, reduces cardiovascular and renal events in patients with type 2 diabetes and chronic kidney disease, cardiovascular disease, or both. The patients were randomized to receive either aliskiren 300mg daily or placebo. Following 27 months of data collection, the trial was terminated early for lack of efficacy. The investigators also found greater risks of renal impairment, hypotension, and hyperkalemia in the aliskiren group. Although the difference in the rate of stroke and/or death was not statistically significant, the aliskiren group was numerically higher. While FDA has not reached a conclusion regarding a link between the drug and death or stroke at the time of writing this lesson, it is important for health care professionals to be aware of the preliminary findings.

Aliskiren is the first and only oral direct renin inhibitor currently available in the U.S. It is the third class of agents joining ACEIs and ARBs in demonstrating antihypertensive effects via the renin-angiotensin-aldosterone system (RAAS). Renin is secreted by the kidneys in response to decreases in blood volume and renal perfusion. Renin cleaves angiotensinogen to form angiotensin I (Ang I) which is then converted to angiotensin II (Ang II) by angiotensin-converting enzyme (ACE). Ang II is a vasoconstrictor and causes the release of catecholamines (i.e., dopamine and norepinephrine), and promotes aldosterone secretion and sodium reabsorption. All of these effects increase blood pressure. Lastly Ang II inhibits renin release, providing a negative feedback to the system and completing the cycle termed RAAS. Aliskiren decreases plasma renin activity and inhibits the conversion of angiotensinogen to Ang I. Because aliskiren, ACEIs and ARBs all suppress the negative feedback loop, there is a compensatory increase in plasma renin concentrations. However, when aliskiren is part of antihypertensive therapy, renin activity, Ang I and Ang II are reduced. Clinical trials indicate that aliskiren lowers blood pressure to a degree comparable to most other agents. When studied in combination with ARBs, it did appear to provide additional antihypertensive effects and end-organ protection, but does lead to an increased risk of hyperkalemia. This combination is currently not preferred.

Aliskiren is prescribed at a starting dose of 150mg by mouth daily, with a routine pattern with regard to meals. The dose may be titrated up to 300mg daily for uncontrolled hypertension. It may take up to two weeks to reach the full effect of the medication. In addition to the new prescribing information previously discussed, the aliskiren label also contains the following warnings and precautions. (1) Anaphylactic reactions and head and neck angioedema have been reported requiring discontinuation of therapy and medical attention. (2) Hypotension may occur in patients who are volume- or sodium-depleted (imbalance should be corrected before initiating therapy). (3) Impaired renal function. (4) Hyperkalemia.

Tekturna® is a pregnancy category D medication (along with ACEIs and ARBs), and carries a black box warning indicating that it may cause injury and/or death to a developing fetus. It should be discontinued as soon as possible if pregnancy is detected. It is not known if Tekturna® is secreted in breast milk, and should be avoided. Concomitant use withitraconazole and cyclosporine should be avoided due to increased levels of aliskiren. Use with an NSAID may lead to an increased risk of renal impairment and loss of antihypertensive effect. Common side effects experienced are dose-dependent diarrhea, cough, dizziness, headache, flu-like symptoms, back pain, tiredness, and hyperkalemia.

**OTC Topical Pain Relievers**

On September 13, 2012, FDA
Injuries, such as first- to third-degree chemical burns at the site of application. The products that were linked to these reports contained either single or multiple ingredients including menthol, methyl salicylate, or capsaicin, and were in various topical formulations such as creams, lotions, ointments, and patches. They are marketed under several brand names including Bengay®, Capzacin®, Flexall®, Mentholatum®, and Icy Hot®.

FDA issued this warning after collecting 43 case reports dated between 1969 and 2011, from database reporting systems and medical literature. Within the series of case reports, all reports were confirmed by health care professionals. Many cases followed a single application of the OTC topical muscle and joint pain reliever, with severe burning or blistering occurring within 24 hours of application. A large number of the second- and third-degree burns followed use of products containing menthol as a single active ingredient, or menthol and methyl salicylate in combination with concentrations exceeding 3 percent and 10 percent, respectively. Only a few case reports involved the use of capsaicin.

When recommending these agents, FDA reminds health care providers to counsel their patients on proper use of the products, and inform them about the risk of serious burns. At the time of writing this lesson, FDA is not requiring manufacturers of these products to carry this warning on the labels.

Proper counseling should include the following information. (1) Areas where the OTC topical product will be applied should not be bandaged tightly. (2) Local heat, such as heating pads, lamps, or hot water in bags or bottles, should not be applied as it can increase the risk of serious burns and increase drug absorption. (3) These products should not be applied to wounds or damaged, broken, or irritated skin. (4) Contact with eyes or mucous membranes (skin inside nose, mouth, or genitals) should be avoided. (5) In addition, these agents should only be applied to the needed areas and sparingly, not to the whole body. These agents will produce a local sensation of warmth or coolness. However, if patients experience pain, swelling, or blistering of the skin where the topical agent was applied, advise patients to discontinue use of the product and seek medical attention.

Adverse events with OTC topical muscle and joint pain relievers should be reported to the FDA MedWatch program (http://www.fda.gov/Safety/MedWatch/). Consumers should also be informed that there is no way to predict who will experience a serious burn from the agents discussed, and that the number of reported cases, compared to the number of individuals who purchase these products, is very small. Table 3 contains a summary of counseling tips for patients using OTC topical analgesic agents.
FDA Safety Warnings and Prescribing Updates: Drospirenone, Citalopram, Dabigatran, Aliskiren, and OTC Topical Pain Relievers

1. Revised labeling for drospirenone-containing products indicates that studies have reported as high as a three-fold increase in the risk of blood clots.
   a. True  b. False

2. DRSP-containing birth control pills should not be used in patients predisposed to:
   a. hypomagnesemia  c. hypokalemia.
   b. hypermagnesemia  d. hyperkalemia.

3. Symptoms of VTE include all of the following EXCEPT:
   a. persistent leg pain  c. unusual bruising.
   b. shortness of breath  d. severe chest pain.

4. The newly recommended maximum daily dose of citalopram is:
   a. 20mg/day  c. 60mg/day.
   b. 40mg/day  d. 80mg/day.

5. The recommended daily dose of citalopram was reduced because of which cardiac abnormality?
   a. Atrial fibrillation  c. QT interval prolongation
   b. ST elevation  d. Ventricular hypertrophy

6. Citalopram is not recommended in patients with all of the following EXCEPT:
   a. hypermagnesemia  c. bradycardia.
   b. hypokalemia  d. recent acute MI.

7. A 75mg dose of dabigatran, orally twice daily, is recommended for patients with a creatine clearance of:
   a. <15mL/min  c. >30mL/min.
   b. 15 to 30mL/min.

8. A specific reversal agent is available for dabigatran.
   a. True  b. False

9. Patients taking dabigatran should be advised to seek emergency treatment for all of the following signs or symptoms of bleeding EXCEPT:
   a. pink or brown urine  c. vomiting blood.
   b. red or black tarry stools  d. shortness of breath.

10. The use of aliskiren with ACEIs or ARBs is contraindicated in patients with diabetes because of the risk of all of the following EXCEPT:
    a. hypermagnesemia  c. hypotension.
    b. renal impairment  d. hyperkalemia.

11. Aliskiren exhibits its antihypertensive effect by:
    a. blocking angiotensin II receptors.
    b. directly inhibiting renin.
    c. inhibiting angiotensin-converting enzyme.

12. A new FDA warning alerts patients to which of the following effects of certain OTC topical pain relievers?
    a. Localized itching
    b. Redness at the site of application
    c. First- to third-degree chemical burns

13. Reports of serious skin injury were linked to all of the following ingredients after topical application EXCEPT:
    a. benzocaine  c. menthol.
    b. capsaicin  d. methyl salicylate.

14. A large number of second- and third-degree burns followed use of products containing which single active ingredient?
    a. Benzocaine  c. Menthol
    b. Capsaicin  d. Methyl salicylate

15. At the time of writing this lesson, FDA is not requiring manufacturers of OTC topical pain relievers to carry the risk of serious burns on product labeling.
    a. True  b. False

To receive CE credit, your quiz must be received no later than April 15, 2016. A passing grade of 80% must be attained. All quizzes received after July 1, 2012 will be uploaded to the CPE Monitor and a statement of credit will not be mailed. Send inquiries to opa@ohiopharmacists.org.

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