Meet the New Kids on the Block: Ospemifene, Canagliflozin, Levomilnacipran and Dolutegravir

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Goal: To review new medications which gained approval by the Food and Drug Administration (FDA) in 2013, and to discuss their mechanisms of action, place in therapy and other important clinical aspects relevant to pharmacy practice.

Objectives: At the conclusion of this lesson, the reader should be able to:
1. Recognize newly approved medications and their indications.
2. Identify the place in therapy for newly approved medications.
3. Discuss key aspects of newly approved medications, including mechanism of action (MOA) and important counseling points.

Introduction
The FDA approved more than 20 new molecular entities in 2013.\(^1\) The novelty of each of these new drugs varies from innovative mechanisms of action, well-established mechanisms of action in the form of new molecular formulas and new biologic agents that are approved for the treatment of certain cancers.\(^2-6\) New medications discussed in this review focus on the treatment of painful symptoms related to menopause, as well as treatment for chronic disease states such as diabetes, depression and Human Immunodeficiency Virus (HIV).\(^2-5\) The purpose of this review is to explore these new medications in more detail, explaining the mechanisms of action, place in therapy and key aspects that differ from previously used therapies.

Ospemifene (Osphena™)
Ospemifene was approved by the FDA in February 2013.\(^1\) It is the first orally administered agent indicated for moderate to severe dyspareunia (painful intercourse) in postmenopausal females.\(^2\) During menopause, a woman’s estrogen levels will decrease, causing vaginal tissues to become thinner, drier and more fragile. These natural changes are symptoms of vaginal and vulvar atrophy, and often lead to pain during intercourse.\(^7\)

Prior to the approval of ospemifene, a number of over-the-counter (OTC) lubricants and moisturizers, as well as estrogen-containing prescription products were available for treating the symptoms of vaginal atrophy, including painful intercourse.\(^7\) Ospemifene provides a new mechanism of action to treat the underlying issues associated with vaginal atrophy. It is a selective estrogen receptor modulator (SERM) that mimics estrogen on the vaginal tissues and induces changes to increase thickness and decrease fragility.\(^2\)

Similar to conjugated estrogens and other SERMs, ospemifene has a black box warning for cardiovascular events such as deep vein thrombosis (DVT) and stroke. In addition, this medication also carries a black box warning for endometrial cancer for women with an intact uterus not concurrently taking a supplemental progestin, although no reports of endometrial cancer were found in ospemifene clinical studies. Other adverse reactions found in clinical studies include hot flashes (7.5 percent), vaginal discharge (3.8 percent), muscle spasms (3.2 percent), hyperhidrosis (1.6 percent) and genital discharge (1.3 percent).\(^2\)

Nonhormonal lubricants and moisturizers are recommended initially to relieve painful intercourse. When these fail to provide relief, vaginal estrogens are preferred.\(^8\) Ospemifene can be considered for use following treatment failure with vaginal estrogens, or in cases where patients prefer an oral option.\(^8\) Table 1\(^9\) provides a cost comparison of vaginal estrogens and ospemifene.

The recommended dose of ospemifene is 60 mg daily taken with food, for the shortest duration necessary. Postmenopausal women taking this medication should be evaluated periodically to determine if therapy is still necessary. Ospemifene is contraindicated in women with undiagnosed abnormal vaginal bleeding, a history or active DVT or pulmonary embolism (PE), a history of arterial thromboembolic disease, an estrogen-dependent tumor or those who are pregnant or may become pregnant.\(^2\)
Canagliflozin (Invokana®)

Canagliflozin, approved in March 2013 for the treatment of Type 2 diabetes mellitus in adults, brings a new mechanism of action to the treatment of diabetes. This medication acts on the sodium-glucose cotransporter-2 (SGLT-2), which is located in the kidneys and is responsible for reabsorbing glucose that is filtered by the kidneys. SGLT-2 inhibitors block reabsorption, increasing the amount of glucose excreted, and lowering blood glucose concentrations.

In one clinical trial, canagliflozin 100 mg and canagliflozin 300 mg were compared with glimepiride in combination with metformin. The canagliflozin 100 mg, canagliflozin 300 mg and glimepiride groups all showed a similar reduction in hemoglobin A1c from baseline; however, the canagliflozin groups showed a greater than 4 percent reduction in body weight compared to a 1 percent increase in body weight in the glimepiride group. Additionally, the canagliflozin groups experienced a much lower incidence of hypoglycemia compared to the glimepiride group (6 percent vs. 34 percent).

The recommended dose of canagliflozin is 100 mg before the first meal of the day, as this medication can reduce postprandial hyperglycemia.

Due to the mechanism of action of canagliflozin, one of the most commonly experienced side effects is genitourinary infections. Approximately 11 percent of females experienced genital mycotic infections (i.e., vulvovaginal candidiasis) and 6 percent experienced urinary tract infections (UTIs). Male genital mycotic infections occurred in about 4 percent of subjects. Hypotension and hyperkalemia were also reported due to osmotic diuresis.

Levomilnacipran (Fetzima™)

Levomilnacipran, an active enantiomer of the serotonin-norepinephrine reuptake inhibitor (SNRI) milnacipran (Savella®), gained FDA approval in July 2013 and became available to patients in December 2013. This is the fourth SNRI to be approved for major depressive disorder (MDD) in the United States. While this medication does not offer a new mechanism of action, it does offer other potential benefits to patients suffering from MDD.

During clinical trials, levomilnacipran was found to have twice the potency for norepinephrine reuptake inhibition relative to serotonin reuptake inhibition, and 17 and 27 times higher selectivity for norepinephrine reuptake inhibition compared with venlafaxine and duloxetine (both SNRIs), respectively. Since there are not currently selective norepinephrine reuptake inhibitors approved for the treatment of depression in the US, this may be an important characteristic for this drug. Levomilnacipran potentially could be used as a first or second line option following failure with SSRIs or SNRIs, or as an add on to other antidepressants.

In addition to the benefit of providing more selective norepinephrine reuptake, levomilnacipran is an extended-release capsule, and is only taken once daily. All other SNRIs used for MDD are dosed twice daily. This medication comes in a titration pack, as the starting dose is 20 mg daily for two days followed by 40 mg daily, with a maximum dose of 120 mg daily.

Because levomilnacipran is an extended-release capsule, it is important to note that it should be taken whole, and not crushed or chewed. Side effects related to levomilnacipran are similar to other SNRIs, and include gastrointestinal disturbances such as nausea, vomiting and constipation. Patients may also experience tachycardia and palpitations. Also, like other SNRIs, levomilnacipran has a black box warning for suicidal thoughts and behaviors upon initiation in young adults, and in fact, is not indicated for children.

Dolutegravir (Tivicay®)

Dolutegravir was approved for the treatment of Human Immunodeficiency Virus (HIV) in adults and children ages 12 and older in August 2013. This is the third integrase inhibitor to be approved in the United States, blocking the

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### Table 9

<table>
<thead>
<tr>
<th>Product</th>
<th>Brand Name</th>
<th>Dose</th>
<th>Cost</th>
</tr>
</thead>
<tbody>
<tr>
<td>Estradiol Cream (topical)</td>
<td>Estrace®</td>
<td>2-4 g/day for 1-2 weeks</td>
<td>$169.96</td>
</tr>
<tr>
<td>Estradiol Ring (vaginal)</td>
<td>Estrace®</td>
<td>2 mg, lasts 90 days</td>
<td>$268.12</td>
</tr>
<tr>
<td>Estradiol Tablets (vaginal)</td>
<td>Vagifem®</td>
<td>1 tab/day for 2 weeks, then 1</td>
<td>$103.10</td>
</tr>
<tr>
<td>Conjugated Estrogen Cream</td>
<td>Premarin®</td>
<td>1 g/day</td>
<td>$241.25</td>
</tr>
<tr>
<td>Ospemifene Tablets (oral)</td>
<td>Osphena™</td>
<td>60 mg daily</td>
<td>$189.60</td>
</tr>
</tbody>
</table>
new drugs, approved in 2013, appear to have received a great deal of recognition in the pharmaceutical world. We should all be on the lookout for the increased use of the medications and how to best educate our patients on their use.

References:
1. U.S. Food and Drug Administration. Drug Approval Reports


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1. Choose the statement that makes ospemifene unique from previously marketed drugs for moderate to severe dyspareunia.
A. It is an orally administered medication.
B. It is a SERM.
C. It should not be used in pregnant women.
D. A & B.
E. All of the above.

2. One of the most common side effects of ospemifene is:
A. Itching.
B. Hot flashes.
C. Discharge.
D. Blurry vision.
E. Excessive thirst.

3. Canagliflozin works by:
A. Increasing glucose reabsorption.
B. Decreasing glucose reabsorption.
C. Inhibiting SGLT-2.
D. A & C.
E. B & C.

4. Adverse effects seen in canagliflozin clinical trials include:
A. Hypokalemia.
B. Hypertension.
C. Genital mycotic infections.
D. A & B.
E. B & C.

5. Canagliflozin may offer a benefit over glimepiride in which area?
A. Improved weight loss
B. Fewer adverse effects
C. Decreased HbA1c
D. Improved adherence
E. Utility in type 1 diabetes

6. What is a potential benefit of levomilnacipran?
A. Once daily dosing
B. Greater selectivity for norepinephrine reuptake inhibition
C. Fewer adverse effects
D. A & B
E. All of the above

7. Levomilnacipran carries a Black Box Warning for:
A. Suicidal thoughts and behavior.
B. Cardiovascular death.
C. Development of diabetes.
D. Neutropenia.
E. Pancreatitis.

8. Dolutegravir is in which drug class?
A. Protease inhibitors
B. Integrase inhibitors
C. Nucleoside reverse transcriptase inhibitors
D. Non-nucleoside reverse transcriptase inhibitors
E. Combination integrase inhibitor/nucleoside reverse transcriptase inhibitor

9. Clinical studies on dolutegravir have shown:
A. Non-inferiority to raltegravir in treatment-naïve patients.
B. Non-inferiority to raltegravir in treatment-experienced patients.
C. Benefit in treatment resistant patients.
D. A & C
E. All of the above

10. Which is true regarding dolutegravir and raltegravir?
A. Dolutegravir is dosed twice daily and raltegravir is dosed once daily
B. Dolutegravir has less side effects than raltegravir
C. Dolutegravir is resistant to mutations affecting raltegravir
D. Dolutegravir cannot be used in ages 12 and up while raltegravir can
E. All of the above