New Drug Update 2015-16
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C. Wayne Weart, Pharm D, FASHP, FAPhA, BCPS
Professor of Clinical Pharmacy and Outcome Sciences
South Carolina College of Pharmacy
Professor of Family Medicine
Medical University of South Carolina
Charleston, South Carolina
weartcw@musc.edu
Faculty Disclosure

• I do not have a vested interest in or affiliation with any corporate organization offering financial support or grant monies for this continuing education activity, or any affiliation with an organization whose philosophy could potentially bias my presentation.

• I do not speak for or consult with any pharmaceutical manufacturer.
Fluticasone furoate / Vilanterol inhalation powder – Breo Ellipta
Fluticasone furoate /Vilanterol inhalation powder –Breo Ellipta

- Maintenance treatment of COPD: 1 inhalation of Breo Ellipta 100 mcg/25 mcg and 200/25 (fluticasone furoate /vilanterol inhalation powder) once daily.
- Cost ~$325.00 Goodrx.com
- The plasma half-life of the components is ~ 24 hours and 21 hours respectively
- FEV1 improvement 214 ml at peak and 144 ml at trough
- FDA Box Warning as with all other LABA containing medications Asthma Related Deaths but NOT indicated for patients with asthma
Fluticasone furoate /Vilanterol inhalation powder – Breo Ellipta

Be careful, every time you move the cover you move to the next dose!
Fluticasone furoate /Vilanterol inhalation powder – Breo Ellipta

- March 19, 2015 the FDA Advisory Committees (Pulmonary, Allergy, Drug safety) voted 16 to 4 to recommend Breo Ellipta for adults 18 y/o and older with asthma but also voted 18-2 against approval for children ages 1-17 y/o.

- The panel also voted 17-3 that the data supported safety in adults but only one panel member voted that safety was supported in children.
Umeclidinium and Vilanterol – Anoro Ellipta Inhaler by GSK

• A combination of umeclidinium, an anticholinergic (LAMA), and vilanterol, a long-acting beta2-adrenergic agonist (LABA), indicated for the long-term, once-daily, maintenance treatment of airflow obstruction in patients with chronic obstructive pulmonary disease (COPD).

• Not indicated for the relief of acute bronchospasm or for the treatment of asthma.
Umeclidinium and Vilanterol – Anoro Ellipta Inhaler
Umeclidinium and Vilanterol – Anoro Ellipta Inhaler

• Inhalation Powder. Inhaler containing 2 double-foil blister strips of powder formulation for oral inhalation. One strip contains umeclidinium 62.5 mcg per blister and the other contains vilanterol 25 mcg per blister.
  – The half-life of both components is about 11 hours
  – Dose is one inhalation once a day.

• FDA Box WARNING: ASTHMA-RELATED DEATH
  – Available as both a 30 dose and 7 dose institutional inhaler
Umeclidinium – Incruse Ellipta Inhaler

• INCURSE™ ELLIPTA® 62.5 mcg/ dose is an anticholinergic indicated for the long-term, once-daily, maintenance treatment of airflow obstruction in patients with chronic obstructive pulmonary disease (COPD), including chronic bronchitis and/or emphysema.

• The effective half-life after once daily dosing is 11 hours.

• Trough FEV1 (mL) at Day 169: Difference From Placebo (95% CI) n = 280 115ml (76, 155)

• Cost ~ $250.00 Goodrx.com
Umeclidinium – Incruse Ellipta Inhaler
Olodaterol - Striverdi Respimat by Boehringer Ingelheim

- FDA approved July 31, 2014 - **Olodaterol** is a long-acting once a day beta-adrenergic agonist (LABA) for the maintenance treatment of patients with chronic obstructive pulmonary disease (COPD), including chronic bronchitis and/or emphysema with airflow obstruction.

- Each actuation from the mouthpiece contains 2.7 mcg olodaterol hydrochloride, equivalent to 2.5 mcg olodaterol. Two actuations equal one dose of 5 mcg at the same time each day.
Olodaterol - Striverdi Respimat

- Cap (A)
- Mouthpiece (B)
- Air vent (C)
- Dose release button (D)
- Safety catch (E)
- Clear base (G)
- Piercing element (I)
- Cartridge (H)
- Dose indicator (F)
Tiotropium – Spiriva Respimat

• FDA approved 9-25-2014; indicated as a maintenance bronchodilator treatment to relieve symptoms of patients with chronic obstructive pulmonary disease (COPD).

• The delivered **dose is 2.5 microgram tiotropium per puff** (2 puffs/dose or 5 mcg) and is equivalent to 3.124 microgram tiotropium bromide monohydrate

• **NOTE there are now two different inhalers!**

• **Cost ~ $350.00 Goodrx.com (both)**
Tiotropium – Spiriva Respimat

• September 16, 2015 the FDA approved SPIRIVA RESPIMAT for the long-term, once-daily, prescription maintenance treatment of asthma in people ages 12 and older. SPIRIVA RESPIMAT is not a treatment for sudden asthma symptoms.

• SPIRIVA RESPIMAT, 1.25 µg/puff (2 puff/dose or 2.5 mcg) is a long-term, once-daily, prescription maintenance treatment of asthma for people 12 years and older.
Tiotropium – Spiriva Respimat
2.5 mcg/inhalation for COPD

Aqua cap color is for COPD
Tiotropium – Spiriva Respimat
1.25 mcg/inhalation for Asthma

- Blue cap color is for patients with asthma!
Glycopyrrolate – Seebri Neohaler by Novartis

- Oct 29, 2015 The U.S. Food and Drug Administration (FDA) approved Seebri Neohaler (glycopyrrolate) inhalation powder, a long-acting muscarinic antagonist (LAMA) indicated for the long-term maintenance treatment of airflow obstruction in patients 18 and older with chronic obstructive pulmonary disease (COPD).

- Dosed twice a day by inhalation (15.6 mcg/capsule for inhalation) ~ $320.00/60 caps
Store SEEBRI capsules in the blister, and only remove IMMEDIATELY BEFORE USE with the NEOHALER device. Each capsule contains approximately 25 mg of lactose monohydrate (which contains trace levels of milk protein).
Combination of Glycopyrrolate and Indacaterol – Utibron Neohaler by Novartis

• Oct 29, 2015 the FDA approved the combo of glycopyrrolate and indacaterol (a BID LABA/LAMA) for the maintenance treatment of patients with COPD.
  — Capsules contain 27.5 mcg of indacaterol and 15.6 mcg glycopyrrolate inhalation powder for use with the NEOHALER device
  — Administered at the same time of the day, (1 capsule in the morning and 1 capsule in the evening), every day. Cost ~ $330.00/60 caps
Store Ytibron capsules in the blister, and only remove IMMEDIATELY BEFORE USE with the NEOHALER device. Each capsule contains approximately 25 mg of lactose monohydrate (which contains trace levels of milk protein).
Combination of Glycopyrrolate and Indacaterol – Utibron Neohaler

• As with all inhaled LABA’s it has a **BOX Warning about asthma related death**

• Use with caution in patients with cardiovascular or convulsive disorders, thyrotoxicosis, sensitivity to sympathomimetic drugs, diabetes mellitus, and ketoacidosis.

• Avoid in patients with narrow angle glaucoma.

• **Avoid administration with other anticholinergic-containing drugs**
Combination of Tiotropium and Olodaterol - Stiolto Respimat

• 5/21/2015 the FDA approved Boehringer Ingelheims Fixed-Dose Combination Tiotropium Plus Olodaterol – Stiolto for Patients with COPD. (LAMA + LABA)
  – The NDA submission for tiotropium + olodaterol FDC is based on results from three global Phase III trials – the 52-week replicate TONADO® 1&2 studies and the 6-week cross-over VIVACITO® dose finding study.
  • The phase III clinical trial program (TOviTO®) for tiotropium + olodaterol includes more than 7,000 people living with varying severities of COPD worldwide.
Tiotropium and Olodaterol - Stiolto Respimat
Tiotropium and Olodaterol - Stioltot Respimat

• Each actuation from the mouthpiece contains 3.124 mcg tiotropium bromide monohydrate, equivalent to 2.5 mcg tiotropium, and 2.736 mcg olodaterol hydrochloride, equivalent to 2.5 mcg olodaterol. (Each dose is two actuations once a day)

• Label also contains the LABA class Box Warning – Asthma Related Death.
Tiotropium and Olodaterol - Stiolto Respimat

• Recommended Dosing: is two inhalations once-daily at the same time of the day. Do not use Stiolto Respimat more than two inhalations every 24 hours.

  – Stiolto Respimat Inhalation Spray is available as:
    • Stiolto Respimat Inhalation Spray: 60 metered actuations (NDC 0597-0155-61)
      – Cost: ~ $325.00
    • Stiolto Respimat Inhalation Spray: 28 metered actuations (NDC 0597-0155-31) (institutional pack)
Arnuity Ellipta (fluticasone furoate inhalation powder) by GSK/Theravance

- FDA approved August 20, 2014 ARNUITY ELLIPTA is a corticosteroid indicated for: once-daily maintenance treatment of asthma as prophylactic therapy in patients aged 12 years and older. Not indicated for relief of acute bronchospasm.

- Cost ~ $150.00 per 100 mcg and ~$200.00/200 mcg Goodrx.com
Arnuity Ellipta (fluticasone furoate inhalation powder)
PROAIR RESPICLICK (albuterol sulfate) inhalation powder by Teva

- FDA approved 4-1-2015 for treatment (1-2 inhalations up to every 4-6 hours) or prevention of bronchospasm in patients 12 years of age and older with reversible obstructive airway disease and prevention of exercise-induced bronchospasm (15-30 min before exercise) in patients 12 years of age and older.
  - 200 actuations per device with a dose counter
  - No priming required! Cost: ~ $55.00
  - Do Not wash or put any part of your inhaler in water
  - DO NOT USE with a spacer!
PROAIR RESPICLICK (albuterol sulfate) inhalation powder

Device Full
200 Doses

Device Empty
0 Doses
Step 2. Hold the inhaler upright as you open the cap fully. See Figure F.

- Open the cap all the way back until you hear a “click”.
- Your PROAIR RESPICLICK inhaler is now ready to use.
- Do not open the cap unless you are taking a dose.
PROAIR RESPICLICK (albuterol sulfate) inhalation powder

- Do not let your lips or fingers block the vent above the mouthpiece.
Flibanserin – Addyi by Sprout/Valeant

• August 18, 2015 Flibanserin (Addyi) was FDA approved for: Treatment of hypoactive sexual desire disorder in premenopausal women (HSDD)

• Dosing regimen: 100 mg tablet orally once daily at bedtime  Cost: ~ $850.00/30 tabs
  – administration during waking hours increases the risks of hypotension, syncope, accidental injury, and central nervous system (CNS) depression (such as somnolence and sedation).
  – Discontinue flibanserin after 8 weeks if the patient does not report an improvement in her symptoms.
Flibanserin - Addyi

• Flibanserin is a new molecular entity that is an agonist at the 5 hydroxytryptamine (5HT) type 1A receptor and an antagonist at the 5HT type 2A receptor. Flibanserin is not approved in any other country.

• First evaluated for the treatment of MDD based upon effects on 5HT but it was not found to be effective and the research switched to HSDD.
Flibanserin - Addyi

• Hypoactive sexual desire disorder (HSDD) is defined in the DSM IV as “Persistently or recurrently deficient (or absent) sexual fantasies and desire for sexual activity. The judgment of deficiency or absence is made by the clinician taking into account factors that affect sexual functioning, such as age and the context of the person’s life.”
  – Occurs in about 7% of premenopausal females.
• The disturbance causes marked distress and interpersonal difficulty.
• The sexual dysfunction is not better accounted for by another Axis I disorder (except another Sexual Dysfunction) and is not due exclusively to the direct physiological effects of a substance (e.g., a drug of abuse, a medication) or a general medical condition.
Flibanserin - Addyi

• Efficacy and Safety of Flibanserin for the Treatment of Hypoactive Sexual Desire Disorder in Women: A Systematic Review and Meta-Analysis published on-line in JAMA Internal Med 2-29-2016 included

  – Five published and 3 unpublished studies including 5914 women were included. Pooled mean differences for SSE change from baseline were 0.49 (95% CI, 0.32-0.67) between 100-mg flibanserin and placebo, 1.63 (95% CI, 0.45-2.82) for eDiary desire, and 0.27 (95% CI, 0.17-0.38) for FSFI desire. The risk ratio for study discontinuation due to AEs was 2.19 (95% CI, 1.50-3.20). The risk ratio for dizziness was 4.00 (95% CI, 2.56-6.27) in flibanserin vs placebo, somnolence 3.97 (95% CI, 3.01-5.24), nausea 2.35 (95% CI, 1.85-2.98), and fatigue 1.64 (95% CI, 1.27-2.13). Women’s mean global impression of improvement scores indicated minimal improvement to no change.
<table>
<thead>
<tr>
<th>Adverse Effect</th>
<th>Placebo (%) N=1905</th>
<th>Flibanserin 100 mg (%) N= 1543</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dizziness</td>
<td>2.2</td>
<td>11.4</td>
</tr>
<tr>
<td>Somnolence</td>
<td>.1</td>
<td>11.2</td>
</tr>
<tr>
<td>Nausea</td>
<td>3.7</td>
<td>10.4</td>
</tr>
<tr>
<td>Fatigue</td>
<td>5.0</td>
<td>9.2</td>
</tr>
<tr>
<td>Insomnia</td>
<td>2.4</td>
<td>4.9</td>
</tr>
<tr>
<td>Dry mouth</td>
<td>0.9</td>
<td>2.4</td>
</tr>
<tr>
<td>Anxiety</td>
<td>0.9</td>
<td>1.8</td>
</tr>
<tr>
<td>Constipation</td>
<td>0.5</td>
<td>1.6</td>
</tr>
<tr>
<td>Abdominal pain</td>
<td>0.8</td>
<td>1.5</td>
</tr>
<tr>
<td>Sedation</td>
<td>0.2</td>
<td>1.3</td>
</tr>
<tr>
<td>Somnolence or sedation or fatigue (CNS depression)</td>
<td>7.9</td>
<td>20.6</td>
</tr>
</tbody>
</table>
Flibanserin - AddyI

• WARNING: HYPOTENSION AND SYNCOPE IN CERTAIN SETTINGS
  – Contraindicated with Alcohol The use of ADDYI and alcohol increases the risk of severe hypotension and syncope. Therefore, alcohol use is contraindicated in patients taking ADDYI. Before prescribing ADDYI, assess the likelihood of the patient abstaining from alcohol, taking into account the patient’s current and past drinking behavior, and other pertinent social and medical history. Counsel patients who are prescribed ADDYI about the importance of abstaining from alcohol use. Because of the increased risk of hypotension and syncope due to an interaction with alcohol, ADDYI is available only through a restricted program under a Risk Evaluation and Mitigation Strategy (REMS) called the ADDYI REMS Program.
  – Contraindicated with Strong or Moderate CYP3A4 Inhibitors The concomitant use of ADDYI and moderate or strong CYP3A4 inhibitors increases flibanserin concentrations, which can cause severe hypotension and syncope. Therefore, the use of moderate or strong CYP3A4 inhibitors is contraindicated in patients taking ADDYI.
  – Contraindicated in Patients with Hepatic Impairment The use of ADDYI in patients with hepatic impairment increases flibanserin concentrations, which can cause severe hypotension and syncope.
ADDYI REMS Program

ADDYI is available only through a restricted program under a REMS called the ADDYI REMS Program, because of the increased risk of severe hypotension and syncope due to an interaction between ADDYI and alcohol. Notable requirements of the ADDYI REMS Program include the following:

- Prescribers must be certified with the program by enrolling and completing training.
- Pharmacies must be certified with the program and must only dispense to patients pursuant to a prescription from a certified prescriber.
Flibanserin - Addyi

• In the phase 1 DDI study, **alcohol, consumed over 10 minutes and combined with flibanserin**, increased the incidence of somnolence, orthostatic hypotension and syncope.
  – The Applicant’s proposed draft label includes a warning regarding the risks of CNS depression, hypotension and syncope associated with co-administration of flibanserin with alcohol.

• **The incidences of somnolence, dizziness and fatigue were greater among flibanserin treated patients who were on Hormonal Contraceptives than those who were not.** (concurrent use appears to increase flibanserin levels by ~ 40% and the applicant proposed label indicates an increased risk of these side effects.)
Narcan Nasal Spray by Adapt Pharma

- November 18, 2015 the FDA granted fast-track designation and priority review for Narcan nasal spray
- Administering the drug in one nostril delivered approximately the same levels or higher of naloxone as a single dose of an FDA-approved naloxone intramuscular injection, and achieved these levels in approximately the same time frame.
- Cost: ~$37.50/dose
EVZIO (Naloxone) Auto-Injector

Each dose is 0.4mg of naloxone/0.4 ml (IM or SC)
Only comes in boxes of two single dose auto-injectors plus a training auto-injector that may be reused
Cost ~$585.00 for one trainer and two active auto injectors
Extended Release Aspirin – Durlaza by New Haven Pharm

- Sept 2015 FDA approved to:
  - 1. Reduce the risk of death and myocardial infarction (MI) in patients with chronic coronary artery disease, such as patients with a history of MI or unstable angina pectoris or with chronic stable angina
  - 2. Reduce the risk of death and recurrent stroke in patients who have had an ischemic stroke or transient ischemic attack

- Dose is 162.5 mg caps taken once a day
  - To be taken 2 hours before or 1 hour after consuming alcohol and must be swallowed whole (Do Not crush or chew)
  - Cost ~ $190.00/30 tabs GoodRx.com
Extended Release Aspirin – Durlaza

• Limited data suggests that the pharmacodynamic effect of Durlaza 162.5 mg is similar to IR aspirin 81 mg.

• “The mean inhibition of TXB₂ following Durlaza (82%) is lower when compared to IR aspirin 81 mg (93%) after the first dose, but upon repeat administration, near maximal inhibition of serum TBX₂ is achieved, similar to what is achieved following repeated daily doses of IR aspirin.”
Lesinurad – Zurampic by Astra Zeneca

• FDA approved December 22, 2015: Lesinurad is a URAT1 inhibitor indicated in combination with a xanthine oxidase inhibitor for the treatment of hyperuricemia associated with gout in patients who have not achieved target serum uric acid levels (ie. <6.0 mg/dl) with a xanthine oxidase inhibitor alone.

  – Limitations of Use: Lesinurad is not recommended for the treatment of asymptomatic hyperuricemia. Lesinurad should not be used as monotherapy.
Lesinurad - Zurampic

• Lesinurad reduces serum uric acid levels by inhibiting the function of transporter proteins involved in uric acid reabsorption in the kidney. Lesinurad inhibited the function of two apical transporters responsible for uric acid reabsorption, uric acid transporter 1 (URAT1) and organic anion transporter 4 (OAT4). URAT1 is responsible for the majority of the reabsorption of filtered uric acid from the renal tubular lumen. OAT4 is a uric acid transporter associated with diuretic-induced hyperuricemia. Lesinurad does not interact with the uric acid reabsorption transporter SLC2A9 (Glut9).

• Lesinurad produces a dose-dependent decrease in serum uric acid levels and increases in urinary uric acid excretion.
Lesinurad - Zurampic

FDA BOX WARNING:

• RISK OF ACUTE RENAL FAILURE, MORE COMMON WHEN USED WITHOUT A XANTHINE OXIDASE INHIBITOR

• Acute renal failure has occurred with lesinurad and was more common when lesinurad was given alone.

• Lesinurad should only be used in combination with a xanthine oxidase inhibitor. (allopurinol or febuxostat)
Lesinurad - Zurampic

Contraindications:

• Severe renal impairment, end stage renal disease, kidney transplant recipients, or patients on dialysis. Tumor lysis syndrome or Lesch-Nyhan syndrome.

• Not recommended for patients with severe hepatic impairment.
Lesinurad - Zurampic

- Most common adverse reactions in 12-month controlled clinical trials (occurring in greater than or equal to 2% of patients treated with lesinurad in combination with a xanthine oxidase inhibitor and more frequently than on a xanthine oxidase inhibitor alone) were headache, influenza, blood creatinine increased, and gastroesophageal reflux disease.
- May cause nephrolithiasis and renal failure especially with higher than recommended doses.
- As with other drugs approved for gout it may also cause mobilization gout.
In clinical trials, major adverse cardiovascular events (defined as cardiovascular deaths, non-fatal myocardial infarctions, or non-fatal strokes) were observed with lesinurad. A causal relationship with lesinurad has not been established.
Lesinurad - Zurampic

• Study 1 and Study 2 enrolled patients with gout who were on a stable dose of allopurinol of at least 300 mg (or 200 mg for moderate renal impairment) that had a serum uric acid > 6.5 mg/dL and reported at least 2 gout flares in the prior 12 months. Mean years since gout diagnosis were 12 years. More than half of the patients (61%) had mild or moderate renal impairment and 19% of the patients had tophi. Patients continued their allopurinol dose and were randomized 1:1:1 to receive lesinurad 200 mg, lesinurad 400 mg, or placebo once daily. The average dose of allopurinol in the studies was 310 mg (range: 200-900 mg).
Lesinurad - Zurampic

- Study 3 enrolled **gout patients with measurable tophi**. Patients received febuxostat 80 mg once daily for 3 weeks and then were randomized 1:1:1 to once daily doses of lesinurad 200 mg, lesinurad 400 mg, or placebo in combination with febuxostat. A total of 66% of patients had mild or moderate renal impairment. Fifty percent of patients did not reach target serum uric acid < 5.0 mg/dL at Baseline after 3 weeks of febuxostat treatment.
Lesinurad - Zurampic

Proportion of patients achieving a serum uric acid level <6.0 mg/dl

<table>
<thead>
<tr>
<th>Study</th>
<th>Time point</th>
<th>Placebo + allopurinol</th>
<th>Lesinurad 200mg + allopurinol</th>
</tr>
</thead>
<tbody>
<tr>
<td>Study 1 (N=603)</td>
<td>6 months</td>
<td>28%</td>
<td>54%</td>
</tr>
<tr>
<td>Study 2 (N=610)</td>
<td>6 months</td>
<td>23%</td>
<td>55%</td>
</tr>
</tbody>
</table>

The reduction in average serum uric acid levels to < 6 mg/dL was noted for lesinurad 200 mg in combination with allopurinol at the Month 1 visit and was maintained throughout the 12-month study.

Proportion of patients with tophi achieving a serum uric acid level < 5.0mg/dl

<table>
<thead>
<tr>
<th>Study</th>
<th>Time point</th>
<th>Placebo + febuxostat 80 mg</th>
<th>Lesinurad 200 mg + febuxostat 80 mg</th>
</tr>
</thead>
<tbody>
<tr>
<td>Study 3</td>
<td>6 months</td>
<td>47%</td>
<td>57%</td>
</tr>
</tbody>
</table>

The reduction in average serum uric acid levels to < 5 mg/dL was noted for lesinurad 200 mg in combination with febuxostat at the Month 1 visit and was maintained throughout the 12-month study.
Lesinurad - Zurampic

• **Dosage:** is recommended at **200 mg once daily** in combination with a xanthine oxidase inhibitor, including allopurinol or febuxostat. The maximum daily dose of lesinurad is 200 mg

• **Cost:**
  – Failure to take lesinurad with a xanthine oxidase inhibitor may increase the risk of renal adverse reactions.
  – Lesinurad tablets should be **taken in the morning with food and water.**
  – Patients should be instructed to **stay well hydrated (2 liters/day)**
  – Assess renal function before initiating lesinurad.
  – **Do not initiate lesinurad if eCLcr is below 45 mL/min** and discontinue lesinurad if eCLcr persistently falls below 45 mL/min.