New Drugs and Drug News in Pain Management and Palliative Care
Mary Lynn McPherson, PharmD, MA, BCPS, CPE

Home Study Webcast
2 Slides Per Page

freeCE
New Drugs and Drug News in Pain Management and Palliative Care

ACTIVITY DESCRIPTION
It is critically important that pharmacists and pharmacy technicians be knowledgeable about new medications and drug delivery systems introduced to the market to treat pain and advanced illness. Patients, families, caregivers and other healthcare professionals turn to pharmacy professionals to provide accurate and timely information about new drug products including indication, adverse effects, drug interactions and directions for use.

TARGET AUDIENCE
The target audience for this activity is pharmacists, pharmacy technicians and nurses in hospital, community, and retail pharmacy settings.

LEARNING OBJECTIVES
After completing this activity, the pharmacist will be able to:
• List new drugs used to treat pain and non-pain symptoms approved by the FDA in 2016. For each drug, the participant will be able to describe the approved indication, common adverse effects and drug interactions.
• For each new medication approved in 2016, describe the burden-to-benefit ratio of therapy.
• Analyze important drug alerts by the FDA (Public Health Advisories) and implications for patient care.

After completing this activity, the pharmacy technician will be able to:
• List new drugs used to treat pain and non-pain symptoms in 2016
• List new drug alerts by the FDA in 2016

ACCREDITATION
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ACTIVITY TYPE
Knowledge-Based Home Study Webcast

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ABOUT THE AUTHOR
Mary Lynn McPherson, Pharm.D., MA, MDE, BCPS, CPE, is Professor and Executive Director, Advanced Post-Graduate Education in Palliative Care in the Department of Pharmacy Practice and Science at the University of Maryland School of Pharmacy in Baltimore. She also serves as the Program Director for the international Online Master of Science and Graduate Certificate Program in Palliative Care through the University of Maryland, Baltimore. Dr. McPherson has a master's degree in Instructional Systems Development, and a second master's degree in Distance Education and e-Learning.

Dr. McPherson has maintained a practice in hospice and palliative care (local and national) and ambulatory care her entire career. At present, Dr. McPherson is the Director of Pharmacotherapy Services at UniversityCare Heritage Crossing in Baltimore where she works primarily with chronic pain patients and patients with diabetes mellitus. Dr. McPherson teaches extensively in the Doctor of Pharmacy curriculum on pain management and end of life care, including didactic and experiential content. She also developed one of the first and few palliative care pharmacy residencies in the U.S.

Dr. McPherson serves on the Board of the Hospice Network of Maryland, and was founding president of the American Society of Pain Educators. McPherson is a Fellow in the American Society of Health-Systems Pharmacists, the American Pharmacists Association, the American Society of Consultant Pharmacists and the American Society of Pain Educators. She is Board Certified in Pharmacotherapy, a Certified Diabetes Educator and a Certified Pain Educator. She has received many honors for her work, including the American Pharmacists Association Distinguished Achievement Award in Specialized Practice, the Maryland Pharmacists Association Innovative Practice Award, and the Maryland Society of Health-Systems Pharmacists W. Purdum Lifetime Achievement Award. Dr. McPherson has received many awards for teaching including the Presidential Citation from the Hospice and Palliative Nurses Association, Professor of the Year many times from the School of Pharmacy, University of Maryland Baltimore Founder’s Week Teacher of the Year and the Robert Chalmers Distinguished Educator Award from the American Association of Colleges of Pharmacy. She has written four books, including "Demystifying Opioid Conversion Calculations: A Guide for Effective Dosing," and many book chapters and peer-reviewed articles on pain management, palliative care, and other topics.

FACULTY DISCLOSURE
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Objectives

1. List new drugs used to treat pain and non-pain symptoms approved by the FDA in 2016. For each drug the participant will be able to describe the approved indication, common adverse effects and drug interactions.

2. For each new medication approved in 2016, describe the burden-to-benefit ratio of therapy.

3. Analyze important drug alerts by the FDA (Public Health Advisories) and implications for patient care.
Top 10 Most Costly Conditions in US

<table>
<thead>
<tr>
<th>Condition</th>
<th>Annual Cost (Billions)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diabetes</td>
<td>100</td>
</tr>
<tr>
<td>Ischemic heart disease</td>
<td>90</td>
</tr>
<tr>
<td>Low back and neck pain</td>
<td>60</td>
</tr>
<tr>
<td>Hypertension</td>
<td>80</td>
</tr>
<tr>
<td>Injuries from falls</td>
<td>70</td>
</tr>
<tr>
<td>Depressive disorders</td>
<td>65</td>
</tr>
<tr>
<td>Oral-related problems</td>
<td>60</td>
</tr>
<tr>
<td>Vision and hearing problems</td>
<td>50</td>
</tr>
<tr>
<td>Skin-related problems</td>
<td>45</td>
</tr>
<tr>
<td>Pregnancy and postpartum care</td>
<td>20</td>
</tr>
</tbody>
</table>
Reslizumab (Cinqair)

- **Indication:** Add-on maintenance treatment of severe asthma in patients ≥ 18 years old, and with an eosinophilic phenotype
  - Eosinophilic phenotype not well defined, but general means severe disease with high eosinophil levels in blood/sputum despite treatment with a corticosteroid
- IL-5 major cytokine responsible for the growth, differentiation, recruitment and activation of eosinophils
  - Reslizumab binds to IL-5 and blocks its binding to IL-5 receptors
- Shown to reduce asthma exacerbations
- Dose is 3 mg/kg infused IV over 20-50 minutes every 4 weeks
- $2500 a dose

Mepolizumab (Nucala)

- **Indication:**
  - SQ injection as add-on maintenance treatment for severe asthma with an eosinophilic phenotype (≥ 12 yo).
  - Not for other eosinophilic conditions, acute bronchospasm or status asthmaticus
- **Comparative drug:** omalizumab (Xolair), reslizumab (Cinqair)
- **Advantages:**
  - May enhance other asthma therapies in this profile patient
  - May allow reduction in oral corticosteroid doses
  - Unique MOA (interleukin-5 antagonist)
  - Less risk anaphylaxis
Mepolizumab (Nucala)

• **Disadvantages:**
  • Limited indications

• **Risks/Adverse effects:**
  • Hypersensitivity reactions
  • Do not use with acute bronchospasm or status epilepticus
  • Opportunistic infections (Herpes Zoster, helminth infections)
  • Headache (91.9%), injection site reactions (8%), back pain (5%), fatigue (5%)

• **Usual dosage:**
  • 100 mg every 4 weeks SQ into the upper arm, thigh, or abdomen
  • $2500 a dose


Mepolizumab (Nucala)

• **Comments**
  • 400,000 asthma-related hospitalizations/year in the US
  • Multiple cell types, involving eosinophils, and mediators (cytokines) are involved in the inflammatory process occurring in the airways of the lungs
  • Interleukin-5 is a major cytokine responsible for eosinophil activity
  • Mepolizumab is approved for use in combination with other maintenance tx

• **Effectiveness**
  • Corticosteroid reduction in weeks 20-24
    • 23% of mepolizumab patients had 90-100% steroid reduction vs. 11% placebo patients
    • 54% of patients treated with new drug had ≥ 50% reduction in daily prednisone dose, vs. 33% placebo

# COPD Inhalers

<table>
<thead>
<tr>
<th>Drug</th>
<th>Delivery Device</th>
<th>Usual Adult Dosage</th>
<th>Monthly Cost</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>LA Anticholinergic/LA Beta2-Agonst Combinations</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bevespi Aerosphere (glycopyrrolate/formoterol)</td>
<td>Metered dose inhaler</td>
<td>2 inhalations BID</td>
<td>$315.70</td>
</tr>
<tr>
<td>Utibron Neohaler (glycopyrrolate/indacaterol)</td>
<td>Dry powder inhaler</td>
<td>1 inhalation BID</td>
<td>$297.80</td>
</tr>
<tr>
<td>Stiolto Respimat (tiotropium/olodaterol)</td>
<td>Inhalation spray inhaler</td>
<td>2 inhalations once daily</td>
<td>$315.70</td>
</tr>
<tr>
<td>Anoro Ellipta (umeclidium/vilantrol)</td>
<td>Dry powder inhaler</td>
<td>1 inhalation once daily</td>
<td>$315.70</td>
</tr>
</tbody>
</table>

- **Considerations:**
  - Dosing frequency (once vs. twice daily)
  - Ease of use (MDI, DPI, ISI)

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# COPD Inhalers

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<tr>
<td>Seebri Neohaler (glycopyrrolate)</td>
<td>Dry powder inhaler</td>
<td>1 inhalation twice daily</td>
<td>$297.80</td>
</tr>
<tr>
<td>Tudorza Pressair (aclidinium)</td>
<td>Dry powder inhaler</td>
<td>1 inhalation twice daily</td>
<td>$101.10</td>
</tr>
<tr>
<td>Spiriva HandiHaler (tiotropium)</td>
<td>Dry powder inhaler</td>
<td>1 inhalation daily</td>
<td>$315.70</td>
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<tr>
<td>Spiriva Respimat (tiotropium)</td>
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<tr>
<td>Incruse Ellipta (umeclidium)</td>
<td>Dry powder inhaler</td>
<td>1 inhalation daily</td>
<td>$252.60</td>
</tr>
</tbody>
</table>

Same considerations: Dosing frequency and ease of use
Lesinurad (Zurampic)

- **Indication:**
  - In combination with a xanthine oxidase inhibitor for the treatment of hyperuricemia associated with gout in patients not at goal

- **Comparable drugs:**
  - Xanthine oxidase inhibitors (allopurinol, febuxostat [Uloric])

- **Advantages:**
  - Unique MOA – inhibits uric acid transporter 1 (URAT1) and organize anion transporter 4
  - Provides additional reduction in serum uric acid

- **Disadvantages:**
  - Not first-line; limited indications; may cause acute RFx, may reduce reliability of hormonal contraceptives

Lesinurad (Zurampic)

- **Comments:**
  - Increases risk of acute renal failure; monitor renal function
  - Caution in patients with Clcr < 60 ml/min; do not use with CLcr < 45 ml/min
  - Major cardiovascular adverse events
  - Not recommended in severe hepatic impairment
  - Metabolized by 2C9 and affected by inhibitors and inducers
  - ASA > 325 mg per day reduces effectiveness
  - Reduces reliability of hormonal contraceptives

- **Adverse events:**
  - Headache 95%), influenza (5%), GERD (3%), increased serum creatinine concentrations (4%)
Lesinurad (Zurampic)

• **Usual dosage:**
  - 200 mg by mouth once a day with food and water
  - If xanthine oxidase is interrupted, lesinurad should also be interrupted
  - Instruct patients to stay well hydrated (2 liters per day)
  - Gout flare prophylaxis (e.g., colchicine, NSAID) recommended with td initiation
  - DC treatment if CLcr is reduced and persistently < 45 ml/min
  - $370/month

• **Effectiveness:**
  - Inhibits UA transporter 1 and organic anion transporter 4
  - Responsible for majority of reabsorbed UA
  - In combination with allopurinol, reduced UA to target in 55% patients (double those in allopurinol + placebo group)

Spritam (levetiracetam)

• **Spritam**
  - Rapidly disintegrating tablet formulation of levetiracetam
  - For adjunctive treatment of partial onset, myoclonic and primary generalized tonic-clonic seizures
    - Used off-label as monotherapy for partial-onset and generalized seizures, absence seizures, seizures of Lennox-Gastaut syndrome
  - Uses 3D technology
    - 3D printer dispenses powdered medication in layers and a liquid binding agent binds the layers together. It is solid but porous.
    - Disintegrates in 11 seconds when taken with a sip of water


Brivaracetam (Briviact)

**Indication:**
- Administered orally or IV as adjunctive therapy in the treatment of partial-onset seizures in patients ≥ 16 years of age

**Comparable drugs:**
- Levetiracetam (Keppra) (brivaracetam has a 10-30 higher affinity for binding site)

**Advantages:**
- Reduced seizure frequency in some patients who lack control previously

**Disadvantages:**
- Not compared directly to other antiepileptics; limited indications
- Not evaluated < 16 years old
- Twice daily dosing; Schedule V (levetiracetam not controlled)

**Comments:**
- Hypersensitivity reactions may occur; suicidal behavior and ideation
- Psychiatric adverse events, neurological adverse events
- Schedule V
- Metabolized by CYP2C9

**Adverse events:**
- Somnolence/sedation (16%), dizziness (12%), fatigue (9%), nausea/vomiting (5%)

**Dosage:**
- Start at 50 mg twice a day; may be adjusted to 25-100 mg twice daily
- Double dose if rifampin concurrent
- May be given IV over 2-15 minutes at same dose and frequency
Brivaracetam (Briviact)

**Products:**
- Tablets – 10, 25, 50, 75, 100 mg
- Oral solution 50 mg/5 ml

**Effectiveness:**
- Brivaracetam is an analogue of levetiracetam
- Effect due to affinity for synaptic vesicle protein 2A in the brain
- Provides no additional benefit over levetiracetam
- Not directly compared against levetiracetam

<table>
<thead>
<tr>
<th>Drug</th>
<th>Usual Adult Dose</th>
<th>Cost/month</th>
</tr>
</thead>
<tbody>
<tr>
<td>Levetiracetam generic</td>
<td>1000-3000 mg/day PO or IV in 2 divided doses</td>
<td>33.10</td>
</tr>
<tr>
<td>Levetiracetam (Keppra)</td>
<td></td>
<td>$436.40</td>
</tr>
<tr>
<td>Levetiracetam (Spritam)</td>
<td></td>
<td>$433.40</td>
</tr>
<tr>
<td>Brivaracetam (Briviact)</td>
<td>50-200 mg/day PO or IV in 2 divided doses</td>
<td>$910.00</td>
</tr>
</tbody>
</table>


MPR Top Stories 2016

1. **FDA puts restriction on antibiotic drug class**
   - Serious adverse effects of fluoroquinolones outweigh benefits in treatment sinusitis, bronchitis, uncomplicated UTIs (moxifloxacin, ciprofloxacin, gemifloxacin, levofloxacin, ofloxacin)
     - Tendon, muscle, joint, nerve, CNS disorders
     - Confusion, hallucinations
   - FDA recommends these agents be reserved for patients with no alternative options
2. **Proton pump inhibitor safety called into question – new risks**
   - Increased risk of ischemic stroke
   - Previously questioned: hypomagnesemia, increased risk infections (C. diff, pneumonia), increased risk fractures, chronic kidney disease, dementia
   - Mild to moderate esophagitis, GERD
   - Peptic ulcer disease
   - Upper GI symptoms without endoscopy
   - ICU stress ulcer prophylaxis
   - Uncomplicated *H. pylori* treatment
   - Barrett’s esophagus/severe esophagitis
   - H/O bleeding ulcer

3. **CDC – 12 recommendations for prescribing opioids in primary care**
   - Non-pharmacologic and non-opioid therapy preferred for chronic pain
   - Establish treatment goals before starting therapy, especially opioids
   - Before and during opioid therapy, discuss risks and benefits of opioid therapy
   - Start opioid therapy with immediate-release formulations, not long-acting
   - Use lowest opioid dose possible. Caution ~50 MME/day; avoid > 90 MME/day
   - Use lowest dose possible for acute pain; usually 3 days, not to exceed 7 days
   - Evaluate benefits and harm of opioid tx within 1-4 weeks and q3mo after
3. CDC – 12 recommendations for prescribing opioids in primary care
   - Before and during opioid therapy evaluation risk for opioid-related harms (use risk mitigation strategies: naloxone, etc.) Use PDMP data (prescription drug monitoring program)
   - Urine drug testing before starting opioid and at least annually
   - Avoid using opioids and benzodiazepines concurrently when possible
   - Offer or arrange evidence-based treatment (usually medication-assisted treatment with buprenorphine or methadone with behavioral therapies) for patients with opioid-use disorder

4. DEA makes decision in marijuana rescheduling
   - Please, sir, will you remove marijuana from Schedule I status?
5. FDA revises warnings for metformin-containing drugs

- Expanded use in certain patients with reduced renal function
- Widely used drug; in 2014 14.4 million patients received metformin
- Concern with renal impairment is increased risk for lactic acidosis
- Instead of a serum creatinine to determine appropriateness, FDA recommend eGFR
  - eGFR < 30 ml/min before therapy – metformin contraindicated
  - eGFR between 30-45 ml/min before therapy – metformin not recommended
  - eGFR annually (or more frequently as indicated)
    - eGFR < 45 ml/min – assess benefits and risks of continuing treatment
    - eGFR < 30 ml/min – discontinue metformin
- DC metformin before iodinated contrast imaging procedure in patients with eGFR between 30-60 ml/min, liver disease, alcoholism, heart failure

European Medicines Agency said “do what they said” in Nov 2016.

Adlyxin (lixisenatide)

- Once-daily glucagon-like peptide-1 receptor agonist (GLP-1_)
- GLP-1 is a peptide hormone that is released within minutes after eating a meal
  - Suppresses glucagon secretion from pancreatic alpha cells
  - Stimulates glucose-dependent insulin secretion by pancreatic beta cells
  - Slows gastric emptying
- Dose is 20 mcg once daily; price unavailable
- Lowers A1c 0.7-1%; non-inferior to exenatide
- AE – nausea, vomiting, headache, diarrhea, dizziness, hypoglycemia
What else is new in diabetes mellitus?

• FDA warns of pioglitazone and risk of bladder cancer (label change)
  • Risk increases with increasing dose and duration of therapy
• Introduction of Humulin R U 500 and syringe
• Empagliflozin (Jardiance) (SGLT-2 inhibitor) received indication from FDA to be used to reduce the risk of cardiovascular death in T2DM and CVD (benefits seen within a few months of starting therapy)
  • 38% reduction in cardiovascular disease mortality
  • 32% reduction in overall mortality
  • 35% reduction in hospitalization for CHF
• Empagliflozin not indicated with GFR < 45 ml/min
  • Can see acute renal failure; long-term may improve renal function
  • Caution with diuretics, NSAIDs

The holy grail in diabetes!

• FDA approved Minimed 670G
  • A hybrid closed-loop insulin delivery system for use in patients ≥ 14 years old with type 1 diabetes
• System uses an algorithm to automatically adjust basal insulin doses based on readings from a continuous glucose monitor.
• Considered a hybrid system because it still required some action by patient.
  • Patient must manually enter the estimated amount of carbohydrate to be consumed during a meal and accept bolus prandial doses of insulin suggested by the system. Patient must also check BG and enter.
• Available Spring 2017.
### Miscellaneous New Drugs

<table>
<thead>
<tr>
<th>Trade (Generic)</th>
<th>Indication</th>
</tr>
</thead>
<tbody>
<tr>
<td>Afstyla (antihemophilic factor)</td>
<td>Hemophilia A: to treat and control bleeding episodes, for perioperative management, and routine prophylaxis to reduce frequency of bleeding episodes</td>
</tr>
<tr>
<td>Kovaltry (antihemophilic factor)</td>
<td>Hemophilia A: to treat and control bleeding episodes, for perioperative management, and routine prophylaxis to reduce frequency of bleeding episodes</td>
</tr>
<tr>
<td>Idelvion (coagulation Factor IX recombinant)</td>
<td>Hemophilia B: to control and prevent bleeding episodes, for perioperative management, and routine prophylaxis to prevent/reduce frequency of bleeding episodes</td>
</tr>
<tr>
<td>Exondys 51 (eteplisien)</td>
<td>An antisense oligonucleotide for Duchenne muscular dystrophy</td>
</tr>
<tr>
<td>Vonvendi (von Willebrand factor)</td>
<td>On-demand treatment and control of bleeding episodes in adults with von Willebrand disease (VWD)</td>
</tr>
<tr>
<td>Zinbryta (daclizumab)</td>
<td>Treatment of relapsing forms of multiple sclerosis</td>
</tr>
<tr>
<td>Intrarosa (prasterone)</td>
<td>Vaginal insert for treatment of painful sexual intercourse due to menopause</td>
</tr>
<tr>
<td>Vraylar (cariprazine)</td>
<td>Atypical antipsychotic agent (comparators aripiprazole, brexipiprazole)</td>
</tr>
</tbody>
</table>

### Syndros (dronabinol oral solution)

- **Indication** – anorexia associated with AIDS and CINV
- **Pharmaceutical version of tetrahydrocannabinol**
- **Starting dose:**
  - Anorexia - 2.1 mg orally twice daily, one hour before lunch and one hour before dinner; start once a day in elderly. Increase to 4.2 mg twice daily as needed
  - CINV – 4.2 mg/m2 orally 1-3 hours before chemotherapy, then every 2-4 hours after chemotherapy for a total of 4-6 doses
- **Quicker onset than Marinol**
- **Cost ?**
Eluxadoline (Viberzi)

**Indication:** Treatment of adults with IBS and diarrhea

**Comparable:** Alosetron (Lotronex)

**Advantages:**
- Unique MOA (mu-opioid agonist and delta-opioid antagonist)
- Less risk serious GI AE (alosetron has boxed warning re: ischemic colitis and serious complications of constipation)
- Prescribing not restricted (alosetron prescribers/patients must be enrolled)

**Disadvantages:**
- Greater risk of sphincter of Oddi spasm and pancreatitis
- Schedule IV

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Eluxadoline (Viberzi)

**Contraindications:**
- Known/suspected biliary duct obstruction, sphincter of Oddi disease/dysfunction, h/o pancreatitis/pancreatic duct obstruction
- Severe hepatic impairment
- Severe constipation or sequelae from constipation
- Suspected mechanical gastrointestinal obstruction
- Alcohol abuse, alcohol addiction, drinking ≥ 3 alcoholic drinks per day

**Precautions:**
- Reduce dose with OATP 1B1 inhibitors (cyclosporine, gemfibrozil) and strong CYP inhibitors (clarithromycin, paroxetine)
- Concurrent use of constipating drugs
- May increase action of rosvastatin
Eluxadoline (Viberzi)

- **Adverse effects:**
  - Constipation (8%), nausea (7%), abdominal pain (7%)

- **Dosage:**
  - 100 mg twice a day with food (reduce to 75 mg as appropriate)
    - $1,000/month
  - DC if patient has severe constipation for > 4 days

- **Products:** tablets 75, 100 mg

- **Comments:**
  - Mixed opioid receptor activity
  - Effectiveness shown in two placebo-controlled studies

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**Miscellaneous New Drugs (HIV)**

<table>
<thead>
<tr>
<th>Trade (Generic)</th>
<th>Indication</th>
</tr>
</thead>
<tbody>
<tr>
<td>Descovy (emtricitabine, tenofovir and alafenamide)</td>
<td>In combination with other antiretroviral agents, for the treatment of HIV-1 infection in patients ≥ 12 years of age</td>
</tr>
<tr>
<td>Genvoya (elvitegravir, cobicistat, emtricitabine, tenofovir)</td>
<td>Complete regimen for HIV-1 infection in patients who are anti-retroviral treatment-naïve or to replace current antiretroviral regimen in virologically-suppressed patients on a stable ARV regimen for &gt; 6 months with no history of treatment failure or no known substitutions associated with resistance to any components</td>
</tr>
<tr>
<td>Odefsey (emtricitabine, rilpivirine, tenofovir)</td>
<td>Complete regimen for HIV-1 infection in patients who are antiretroviral treatment-naïve with HIV-1 RNA ≤ 100,000 copies/ml or to replace a stable antiretroviral regimen in those who are virologically-suppressed HIV-1 RNA (&lt; 50 copies/ml) for ≥ 6 months with no history of tx failure and no known substitutions associated with resistance</td>
</tr>
</tbody>
</table>
### Miscellaneous New Drugs (ID)

<table>
<thead>
<tr>
<th>Trade (Generic)</th>
<th>Indication</th>
</tr>
</thead>
<tbody>
<tr>
<td>Impavido (miltefosine)</td>
<td>Treatment of visceral, cutaneous and mucosal leishmaniasis due to susceptible <em>Leishmania</em> species</td>
</tr>
<tr>
<td>Epclusa (sofosbuvir and velpatasvir)</td>
<td>HCV genotype 1, 2, 3, 4, 5, 6 in adults without cirrhosis or with compensated cirrhosis; or for use in combination with ribavirin in adults with decompensated cirrhosis</td>
</tr>
<tr>
<td>Zepatier (elbasvir and grazoprevir)</td>
<td>Chronic HCV genotypes 1 o4 4 infection with our without ribavirin</td>
</tr>
<tr>
<td>Impavido (miltefosine)</td>
<td>Treatment of visceral, cutaneous, and mucosal leishmaniasis due to susceptible species</td>
</tr>
<tr>
<td>Vaxchora</td>
<td>Immunization against disease caused by <em>Vibrio cholera</em>, in adults 18-64 of age traveling to cholera-affected areas</td>
</tr>
</tbody>
</table>

### Belbuca (buprenorphine film)

- Buccal film contains buprenorphine, a partial opioid agonist
- Indicated for management of pain severe enough to require daily, around the clock, long-term opioid treatment for which there are no other options.
- Adverse effects
  - Nausea, constipation, vomiting, headache, dizziness, somnolence, QTc prolongation, hepatotoxicity, respiratory depression, severe hypotension, physical and psychological dependence
Belbuca (buprenorphine film)

• **Dose**
  - Opioid-naïve – Belbuca 75 mcg one daily or q12h; after 4 days increase to 150 mcg every 12 hours
  - Opioid-tolerant – Taper opioid down to 30 mg OME or less.
    - < 30 mg oral MSE – start Belbuca 75 mcg po qd-q12h
    - 30-89 mg oral MSE – start Belbuca 150 mcg q12h
    - 90-160 mg oral MSE – start Belbuca 300 mcg q12h
    - 160 mg oral MSE – consider alternate therapy

• **Availability** – 75, 150, 300, 450, 600, 750, 900 mcg

• **Cost** - ~$250 for 75 mcg; ~$700 for 900 mcg

Probuphine (buprenorphine implant)

• Rod-shaped implant – up to 6 months delivery of buprenorphine
  - 4 rods implanted

• Maintenance treatment for stable, opioid-dependent patients receiving 8 mg or less of buprenorphine per day

• Non-inferiority vs. 8 mg SL buprenorphine-naloxone daily
  - Primary outcome – at least 4 months free of illicit opioid use:
    - 96.4% implant vs. 87.6% SL

<table>
<thead>
<tr>
<th>Drug</th>
<th>Target Maintenance Dose</th>
<th>Cost/6 months</th>
</tr>
</thead>
<tbody>
<tr>
<td>Generic buprenorphine</td>
<td>16 mg once/day</td>
<td>$1,671.80</td>
</tr>
<tr>
<td>Probuphine</td>
<td>4 implants for 6 months</td>
<td>$4,950.00</td>
</tr>
</tbody>
</table>

Xtampza ER (oxycodone, abuse deterrent)

- Extended-release, abuse-deterrent capsule formulation of oxycodone
- For management of pain severe enough to require daily, ATC opioid tx
- Formulated as a capsule containing microspheres formulated with oxycodone base and inactive ingredients that make it more difficult to manipulate and abuse. Crushing does not alter abuse deterrence.
- Strengths – 9 (10), 13.5 (15), 18 (20), 27 (30), 36 (40) mg oxycodone
- Oral BAB increases 100-150% when taken with high-fat meal
- Usual opioid adverse effects
- Starting dose, opioid-naïve is Xtampza ER 9 mg po q12h

LA Abuse Deterrent Opioid Formulations

<table>
<thead>
<tr>
<th>Drug</th>
<th>Abuse-Deterrent Mechanism</th>
<th>Cost for 30 days at opioid-naïve starting dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hydrocodone ER</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hysingla ER</td>
<td>Resists crushing and breaking; tablets form a viscous gel when dissolved</td>
<td>$215.80</td>
</tr>
<tr>
<td>Zohydro ER</td>
<td>Contains excipients that form a viscous gel when capsules are crushed or dissolved</td>
<td>$404.90</td>
</tr>
<tr>
<td>Morphine ER/naltrexone</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Embeda</td>
<td>Contains sequestered opioid antagonist, which is released if capsules are crushed or dissolved</td>
<td>$178.50</td>
</tr>
<tr>
<td>Oxycodone ER</td>
<td></td>
<td></td>
</tr>
<tr>
<td>OxyContin</td>
<td>Resists crushing and breaking; tablets form a viscous gel when dissolved</td>
<td>$188.80</td>
</tr>
<tr>
<td>Xtampza ER</td>
<td>Microspheres resist effects of crushing and chewing; melted or dissolved contents of capsules are difficult to inject</td>
<td>$202.20</td>
</tr>
</tbody>
</table>
**Troxyca ER (oxycodone + naltrexone)**

- Extended release capsule formulation of oxycodone plus naltrexone
- For pain severe enough to require daily, ATC, long-term opioid tx
- Opioid-naïve dose: 10 mg/1.2 mg capsule by mouth q12h
- Manufacturer conversion – ½ TDD oral oxycodone as Troxyca ER q12h
- AE – nausea, constipation, vomiting, headache, somnolence
- Cost - ?

---

**Methylnaltrexone (Relistor)**

- Chemical structure comparison between Naltrexone and Methylnaltrexone.
Methylnaltrexone (Relistor)

- OIC in CNCP – tablets and injection
  - Be within close proximity to toilet facilities once administered!
  - Discontinue laxatives prior to use, may use if no response to treatment after 72h
  - Inject 12mg SQ daily OR 450 mg by mouth once daily in the morning
- OIC in adults with advanced illness receiving palliative care who have not responded to laxative therapy – injection
  - Inject 1 dose SQ every other day prn
    - 8 mg for patients 38 kg-61.9 kg
    - 12 mg for patients 62 kg-114 kg
    - Patients <38 kg or >114 kg: 0.15 mg/kg

Methylnaltrexone: Safety

- Creatinine clearance < 60 ml/min:
  - CNCP – reduce oral dose to 150 mg po qd; 6 mg SQ daily
  - Advanced illness – 50% of full SQ dose
- Contraindicated in patients who may have gastrointestinal obstruction or those at high risk
- Warnings and precautions
  - GI perforation, severe or persistent diarrhea, opioid withdrawal


Methylnaltrexone: Adverse Effects

<table>
<thead>
<tr>
<th>Adverse Reaction</th>
<th>Tablets</th>
<th>Injection</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>Abdominal pain</td>
<td>14%</td>
<td>29%</td>
<td>10%</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>5%</td>
<td>6%</td>
<td>2%</td>
</tr>
<tr>
<td>Nausea</td>
<td>12%</td>
<td>5%</td>
<td></td>
</tr>
<tr>
<td>Dizziness</td>
<td>7%</td>
<td>2%</td>
<td></td>
</tr>
</tbody>
</table>

Relistor 150 mg tablets, #90 (450 mg once daily) ~$1,500/month
Relistor 8 mg or 12 mg syringe ~ $110/syringe

Methylnaltrexone – Clinical Efficacy

- OIC – CNCP (ORAL)
  - Defined as < 3 SBM/week and at least one of the following:
    - Bristol Stool Form Scale of 1 or 2 for at least 25% of BMs, straining during ≥ 25% BMs or feeling of incomplete evaluation after at least 25% of BMs.
  - Responder:
    - ≥ 3 SBM/week
    - An increase of 1 or more SBM/week over baseline, for 3 or more out of the first 4 weeks of the treatment period.
  - Oral methylnaltrexone 52% responders (450 mg po qd) vs. 38% placebo
  - NNT = 8
Methylnaltrexone – Clinical Efficacy

- OIC – CNCP (SQ)
  - 4 weeks methylnaltrexone SQ therapy vs. placebo
  - Constipation defined as one or more of the following:
    - Bristol Stool Form scale score of 1 or 2 for at least 25% BMs
    - Straining during at least 25% BMs
    - Sensation of incomplete evacuation after at least 25% of BMs
  - Responder: Proportion of patients \( \geq 3 \) SBMs per week x 4 weeks
  - Methylnaltrexone 12 mg SQ daily – 59% response
  - Placebo – 38% response

---

Miscellaneous New Drugs - Cancer

<table>
<thead>
<tr>
<th>Trade (Generic)</th>
<th>Indication</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alecensa (alectinib)</td>
<td>Anaplastic lymphoma kinase positive NSCLC, with progression or concurrent crizotinib</td>
</tr>
<tr>
<td>Cabometyx (cabozantinib)</td>
<td>Advanced renal cell carcinoma after anti-angiogenic therapy</td>
</tr>
<tr>
<td>Carzalex (daratumumab)</td>
<td>Multiple myeloma s/p ( \geq 3 ) lines of tx (PI and immunomodulatory agent) or who are double-refractory to a PI and immunomodulatory agent</td>
</tr>
<tr>
<td>Empliciti (elotuzumab)</td>
<td>With lenalidomide and dexamethasone for treatment of multiple myeloma s/p 1-3 prior therapies</td>
</tr>
<tr>
<td>Imlygic (talimogene laherparepvec)</td>
<td>Unresectable, cutaneous, subcutaneous and nodal lesions in melanoma recurrent after initial surgery</td>
</tr>
<tr>
<td>Lartruvo (olaratumub)</td>
<td>With doxorubicin, for treatment of adults with soft tissue sarcoma with a histologic subtype for which an anthracycline-containing regimen is appropriate and which is not amenable to curative treatment with radiotherapy or surgery</td>
</tr>
<tr>
<td>Lonsurf (trifluridine and tipiracil)</td>
<td>Treatment of metastatic colorectal cancer in patients previously treated with fluoropyrimidine, oxaliplatin, and irinotecan-based chemotherapy, an anti-VEGF biological therapy, and if RAS wild-type, an anti-EGRF therapy</td>
</tr>
</tbody>
</table>
Miscellaneous New Drugs - Cancer

<table>
<thead>
<tr>
<th>Trade (Generic)</th>
<th>Indication</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ninlaro (ixazomib)</td>
<td>A proteasome inhibitor indicated in combination with lenalidomide and dexamethasone for the treatment of patients with multiple myeloma who have received at least one prior therapy</td>
</tr>
<tr>
<td>Portrazza (necitaumumab)</td>
<td>In combination with gemcitabine and cisplatin, for first-line treatment of metastatic squamous non-small lung cancer</td>
</tr>
<tr>
<td>Tagrisso (osimertinib)</td>
<td>Treatment of patients with metastatic epidermal growth factor receptor mutation positive NSCLC, or have progressed on or after EGFR tyrosine kinase inhibitor therapy</td>
</tr>
<tr>
<td>Tencertiq (atezolizumab)</td>
<td>Locally advanced or metastatic urothelial carcinoma with disease progression during or following platinum-containing chemo, or within 12 months of neoadjuvant or adjuvant treatment with platinum-containing chemotherapy</td>
</tr>
<tr>
<td>Venclexa (venetoclax)</td>
<td>CLL with 17p depletion, who have received at least one prior therapy</td>
</tr>
<tr>
<td>Yondelis (trabectedin)</td>
<td>Unresectable or metastatic liposarcoma or leiomyosarcoma in patients who have received a prior anthracycline-containing regimen</td>
</tr>
</tbody>
</table>

Miscellaneous New Drugs – Reformulations

<table>
<thead>
<tr>
<th>Trade (Generic)</th>
<th>Combination</th>
<th>Indication</th>
</tr>
</thead>
<tbody>
<tr>
<td>Byvalson</td>
<td>Nebivolol and valsartan</td>
<td>Hypertension</td>
</tr>
<tr>
<td>Yosprala</td>
<td>Aspirin and omeprazole</td>
<td>Cardiovascular/cerebrovascular protection</td>
</tr>
<tr>
<td>Sustol</td>
<td>Granisetron</td>
<td>Extended-release injectable formulation to prevent CINV</td>
</tr>
<tr>
<td>Soliqua</td>
<td>Insulin glargine and lixisenatide</td>
<td>Combo LA insulin and GLP-1 agonist for T2DM • 100/33 five solostar pens of 3 ml - $675</td>
</tr>
<tr>
<td>Epaned</td>
<td>Enalapril</td>
<td>Oral solution formulation • 150 ml of 1 mg/ml • $300 • 10 mg a day ~ $600/month</td>
</tr>
<tr>
<td>GoNitro</td>
<td>Nitroglycerin</td>
<td>Sublingual powder formulation for prophylaxis/relief of angina</td>
</tr>
</tbody>
</table>
Nitroglycerin Formulations

<table>
<thead>
<tr>
<th>Drug</th>
<th>Formulation</th>
<th>Tmax</th>
<th>Usual Dosage</th>
<th>Cost (units)</th>
</tr>
</thead>
<tbody>
<tr>
<td>SL powder (GoNitro)</td>
<td>0.4 mg single-use packets</td>
<td>7 minutes</td>
<td>1-2 packets, then 1 packet q5min PRN</td>
<td>$653.30 for 96 packets</td>
</tr>
<tr>
<td>Sublingual tablets (generic) (Nitrostat)</td>
<td>0.3, 0.4, 0.6 mg tabs</td>
<td>6.4-7.2 min</td>
<td>0.3-0.6 mg q5min PRN</td>
<td>$38.20 $43.60</td>
</tr>
<tr>
<td>Translingual spray (generic) (Nitrolingual Pumpspray)</td>
<td>0.4 mg/spray</td>
<td>7.5 min</td>
<td>1-2 sprays, then 1 spray q5min PRN</td>
<td>$279.30 $401.70</td>
</tr>
<tr>
<td>Translingual aerosol spray (generic) (NitroMist)</td>
<td>0.4 mg/spray</td>
<td>8 min</td>
<td>1-2 sprays, then 1 spray q5min PRN</td>
<td>$279.00 $633.30</td>
</tr>
</tbody>
</table>


Oh my aching knees...

• Vivlodex
  • Low dose formulation of meloxicam (NSAID)
  • 5 mg, 10 mg capsule containing submicron particles (tabs are 7.5/15 mg)
    • More rapid absorption – 10 mg Vivlodex vs. 15 mg tablet \( t_{\text{max}} \) was 2 vs. 4 hours
    • Lower systemic meloxicam exposure (AUC) by 33% with Vivlodex
  • Clinical trials showed superior to placebo
  • AE – diarrhea, nausea, abdominal discomfort:
    • 2-3% Vivlodex
    • 0-1% placebo

<table>
<thead>
<tr>
<th>Meloxicam</th>
<th>Formulations</th>
<th>Usual Adult Dose</th>
<th>Cost/mo</th>
</tr>
</thead>
<tbody>
<tr>
<td>Generic</td>
<td>7.5, 15 mg tablets</td>
<td>7.5-15 mg/day</td>
<td>$2.30</td>
</tr>
<tr>
<td>Mobic</td>
<td>7.5, 15 mg tablets</td>
<td>7.5-15 mg/day</td>
<td>$208.60</td>
</tr>
<tr>
<td>Vivlodex</td>
<td>5, 10 mg capsules</td>
<td>5-10 mg once/day</td>
<td>$594.00</td>
</tr>
</tbody>
</table>

Medical Letter 2016;58;33-34.
Xiidra (Lifitegrast)

- 5% ophthalmic solution of lifitegrast, a lymphocyte function-associated antigen-1 antagonist for treatment of dry eye (firstie)
- Dry eye disease – ocular surface inflammation
- Standard treatment – artificial tears, ocular insert devices, ocular anti-inflammatory agents, tetracyclines
- MOA lifitegrast – reduces ocular surface inflammation
- Modestly effective; 1 drop each eye BID; $426/month
- AE – eye irritation, dysgeusia, reduced visual acuity
  - Mostly mild to moderate

Pimavanserin tartrate (Nuplazid)

- **Indication**: Treatment of hallucinations and delusions associated with Parkinson’s disease psychosis.
- **Advantages**
  - First drug with demonstrated efficacy in treatment of hallucinations and delusions associated with Parkinson’s disease psychosis
  - Unique mechanism of action
    - Inverse agonist and antagonist activity at serotonin 5-HT2A receptors
    - Does not act at DA receptors; unless to cause EPS
    - Less likely to cause serious adverse effects (TD, NMS)
- **Disadvantages**:  
  - More likely to cause QTc prolongation/arrhythmia
Pimavanserin tartrate (Nuplazid)

• **Risks/Drug Interactions:**
  - Increased risk of death in elderly patients with dementia-related psychosis
  - QT prolongation or risk factors
  - Class 3 antiarrhythmics, antipsychotic medications
  - Antibacterials (moxifloxacin), 3A4 inhibitors and inducers

• **Adverse Effects:**
  - Nausea (7%), peripheral edema (7%), confusional state (6%)

• **Usual Dose:**
  - 34 mg (2 x 17 mg tabs) once a day
  - 17 mg a day with strong CYP3A4 inhibitor


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Pimavanserin tartrate (Nuplazid)

• **Clinical Data:**
  - Approval based on a 6-week, randomized, double-blind, placebo-controlled trial in 199 patients with PD psychosis
  - Outcome: change in score on the Parkinson’s disease-adapted scale for assessment of positive symptoms
    - -5.79 with pimavanserin
    - -2.73 with placebo
  - No effect on motor function

• **Conclusion:**
  - Consider concurrent use of other QTc prolonging drugs
  - Strong evidence of pimavanserin effectiveness; long-term benefit/risks?
  - Expected to “dramatically change the landscape” of PDP.

I’ve got my eye on you…

<table>
<thead>
<tr>
<th>Product Name</th>
<th>Potential Signal of a Serious Risk / New Safety Information</th>
<th>Additional Information (as of 9-30-16)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Antidepressants</td>
<td>Stress cardiomyopathy</td>
<td>FDA is evaluating need for regulatory action</td>
</tr>
<tr>
<td>Beta Interferons ((Avonex, Betaseron, Extavia, Rebi), etc.)</td>
<td>Drug-induced lupus</td>
<td>FDA is evaluating need for regulatory action</td>
</tr>
<tr>
<td>Corlanor (ivabradine)</td>
<td>Concomitant use with drugs that slow HR (beta blockers, clonidine, digoxin, diltiazem, verapamil.)</td>
<td>No action necessary at this time. &quot;Drug Interactions&quot; section for other negative chronotropes updated to include ivabradine</td>
</tr>
<tr>
<td>Diphenhydramine</td>
<td>QT Prolongation</td>
<td>FDA is evaluating need for regulatory action</td>
</tr>
<tr>
<td>Direct-acting antivirals (daclatasvir, ledipasvir/sofosbuvir, etc.)</td>
<td>Hepatitis B reactivation</td>
<td>HCV drugs will received boxed warning about risk of HBV reactivation in co-infected individuals</td>
</tr>
<tr>
<td>Entresto (sacubitril/valsartan)</td>
<td>Risk of rhabdomyolysis with concomitant use of statin therapy</td>
<td>FDA is evaluating need for regulatory action</td>
</tr>
<tr>
<td>HMG-CoA reductase inhibitors</td>
<td>Interstitial lung disease</td>
<td>FDA is evaluating need for regulatory action</td>
</tr>
<tr>
<td>SGLT2 inhibitors (dapagliflozin, empagliflozin, canagliflozin)</td>
<td>Acute pancreatitis</td>
<td>FDA is evaluating need for regulatory action</td>
</tr>
</tbody>
</table>

In the news…

- A new branded formulation of cannabidiol (Epidiolex)
- Orphan drug that is pharmaceutical cannabidiol
- Used to treat pediatric epilepsy
  - Dravet syndrome
  - Lennox-Gastaut syndrome
- Children in trials had tried 10 other anti-epileptic drugs, and were having approximately 3 seizures/day (90 a month)
  - Epidiolex reduced seizures by 42% vs. 19% for placebo
- Filing NDA with FDA first half of 2017
More stuff in the news...

• AcelRx Pharmaceuticals submitted NDA for sublingual sufentanil
  • For moderate-severe acute pain; relief within 15 minutes
  • To be administered in a medically supervised setting using a disposable, pre-filled, single-dose applicator

• Fast track designation for novel gastroparesis therapy
  • Velusetrag – highly selective agonist with high intrinsic activity at the human-5-hydroxytryptamine 4 receptor
  • For symptoms associated with idiopathic and diabetic gastroparesis

• FDA grants priority review to oral anticoagulant
  • Betrixaban for extended-duration prophylaxis of VTE in acute medically ill patients with risk factors for VTE

Mind BLOWN!

• Psilocybin for cancer-related emotional distress
  • Psilocybin is a naturally occurring psychedelic compound produced by more than 200 species of mushrooms, collectively known as psilocybin mushrooms.

• Three large Phase 2 studies
  • Harbor-UCLZ Medical Center;
  • Johns Hopkins University;
  • New York University

• 92 patients – all showed statistically significant improvement with enduring effects for months after a single psilocybin treatment session

http://heffter.org/cancer-distress/
Exam Questions:

1. Which of the following is the most costly disease to manage in the US?
   a. Pregnancy and postpartum care
   b. Oral-related problems
   c. Diabetes mellitus
   d. Low back and neck pain

2. Reslizumab (Cinqair) and mepolizumab (Nucala) are indicated for severe asthma of what type?
   a. Restrictive and inflammatory
   b. Eosinophilic phenotype
   c. Lymphocytic type
   d. Mixed asthma/COPD

3. Lesinurad (Zurampic) is used to treat which of the following?
   a. Hyperuricemia/gout
   b. Hyperglycemia/diabetes
   c. Hypertension
   d. Dyslipidemia

4. What is the advantage of Spritam (levetiracetam) over generic levetiracetam?
   a. Less costly
   b. More rapid dissolution
   c. Fewer adverse effects
   d. Indicated for children in addition to adults

5. Which of the following are adverse effects associated with proton pump therapy?
   a. Hypomagnesemia
   b. Chronic kidney disease
   c. Dementia
   d. All of the above
6. The CDC recommends primary care practitioners try not to exceed what dose of oral morphine equivalent per day for chronic pain?
   a. 20 mg
   b. 50 mg
   c. 90 mg
   d. 120 mg

7. The FDA added a warning about pioglitazone increasing the risk for which of the following?
   a. Glioblastoma
   b. Increased fertility
   c. Vitamin B12 deficiency
   d. Bladder cancer

8. GoNitro is what kind of formulation?
   a. Sublingual powder
   b. Sublingual tablet
   c. Translingual spray
   d. Translingual aerosol spray

9. Xiidra (lifitegrast) is used to treat which of the following indications?
   a. Osteoarthritis of the knees
   b. Dry eye
   c. Asthma of the eosinophilic genotype
   d. Parkinson’s disease

10. Pimavanserin tartrate (Nuplazid) affects which neurotransmitter?
    a. Dopamine
    b. Epinephrine
    c. Serotonin
    d. Norepinephrine