MEDICATION UPDATE

Kansas Association of Osteopathic Medicine (KAOM)
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Tiffany Shin, PharmD, BCACP
shin@ku.edu
Clinical Assistant Professor
University of Kansas School of Pharmacy - Wichita
Objectives

1. Describe new FDA approved medications and new FDA approved indications related to primary care
2. Summarize the indications, mechanisms of action, adverse effects, and patient safety considerations for each medication or class of medications
3. Compare and contrast the new medications with current standards of care
4. Discuss the implications of the new medications to primary care practice
Keeping up with the Drug Market

- Total new FDA approvals
  - 2014: 79
  - 2015: 67
  - 2016: 10 (and counting)

http://www.centerwatch.com/drug-information/fda-approved-drugs/
Agenda

- Cardiology
- Diabetes
- Obesity/Weight loss
- Respiratory
- Pain Management
- Gastroenterology
- Notable agents
# Heart Failure: Sacubitril/Valsartan (Entresto™) – July 2015

<table>
<thead>
<tr>
<th>FDA approved indication(s):</th>
<th>• Chronic heart failure (NYHA Class II-IV) with reduced ejection fraction to reduce CV death and hospitalization for heart failure</th>
</tr>
</thead>
</table>
| Drug Class                 | • Sacubitril: Neprilysin inhibitor  
• Valsartan: angiotensin receptor blocker (ARB)                                                                                                                                                                                                 |
Sacubitril/Valsartan (Entresto™): MOA

Physiological response

NP system

RAAS

Pathophysiological response

NPs

NPs

Nephrilisin

Inactive fragments

NPR-A receptor

Guanulate cyclase

GTP

cGMP

Angiotensin receptor nephrilisin inhibitor (ARN)

Promotes these effects

Inhibits these effects

Systemic vascular resistance

Sympathetic tone

Aldosterone

Cardiac fibrosis

Ventricular hypertrophy

Natriuresis/diuresis

Heart failure

Systemic vascular resistance

Sympathetic tone

Aldosterone

Cardiac fibrosis

Ventricular hypertrophy

Natriuresis/diuresis

PARADIGM-HF Study

Sacubitril/Valsartan compared to Enalapril in patients with heart failure with reduced ejection fraction

Primary outcome: Composite death from CV causes or first hospitalization from heart failure

Randomized double-blind active comparator phase 3 trial

4817 patients received Sacubitril/Valsartan
4212 patients received Enalapril

Mean Age: 63.8yo
Black Race: 5.1%
NYHA Class II: 70.4%
NYHA Class III: 24%

Diuretic: 80.2%
Digitalis: 30.2%
Beta-Blocker: 93%
Mineralcorticoid antagonist: 55.6%
ICD: 14.8%


ICD: implantable cardioverter-defibrillator
# PARADIGM-HF Results

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Sacubitril/Valsartan (N = 4187)</th>
<th>Enalapril (N = 4212)</th>
<th>Hazard Ratio or Difference (95% CI)</th>
<th>P Value</th>
<th>NNT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Death from CV cause or first hospitalization from worsening HF*</td>
<td>914 (21.8%)</td>
<td>1117 (26.5%)</td>
<td>0.80 (0.73-0.87)</td>
<td>&lt;0.001</td>
<td>22</td>
</tr>
<tr>
<td>Death from CV causes</td>
<td>558 (13.3%)</td>
<td>693 (16.5%)</td>
<td>0.80 (0.71-0.89)</td>
<td>&lt;0.001</td>
<td>32</td>
</tr>
<tr>
<td>First hospitalization from worsening HF</td>
<td>537 (12.8%)</td>
<td>658 (15.6%)</td>
<td>0.79 (0.71-0.89)</td>
<td>&lt;0.001</td>
<td>36</td>
</tr>
<tr>
<td>Death from any cause</td>
<td>711 (17%)</td>
<td>835 (19.8%)</td>
<td>0.84 (0.76-0.93)</td>
<td>&lt;0.001</td>
<td>36</td>
</tr>
<tr>
<td>Change in KCCQ clinical summary score at 8 months</td>
<td>-2.99 ± 0.36</td>
<td>-4.63 ± 0.36</td>
<td>1.64 (0.63-2.65)</td>
<td>0.001</td>
<td>--</td>
</tr>
<tr>
<td>New-onset atrial fibrillation</td>
<td>84 (3.1%)</td>
<td>83 (3.1%)</td>
<td>0.97 (0.72-1.31)</td>
<td>0.83</td>
<td>--</td>
</tr>
<tr>
<td>Decline in renal function</td>
<td>94 (2.2%)</td>
<td>108 (2.6%)</td>
<td>0.86 (0.65-1.13)</td>
<td>0.28</td>
<td>--</td>
</tr>
</tbody>
</table>

CV: cardiovascular; HF: Heart failure; KCCQ: Kansas City Cardiomyopathy Questionnaire

* Primary composite outcome

## Sacubitril/Valsartan (Entresto™): Considerations

<table>
<thead>
<tr>
<th>Adverse Effects</th>
<th>Clinical benefit</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hypotension</td>
<td>Reduced CV-related death and hospitalizations (NNT 22)</td>
</tr>
<tr>
<td>Elevated SCr</td>
<td>Improve survival</td>
</tr>
<tr>
<td>Elevated Potassium</td>
<td>Less risk of cough</td>
</tr>
<tr>
<td>Orthostatic hypotension</td>
<td>Less risk of angioedema</td>
</tr>
<tr>
<td>Dizziness</td>
<td></td>
</tr>
<tr>
<td>Angioedema</td>
<td></td>
</tr>
</tbody>
</table>

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Heart Failure
Sacubitril/Valsartan (Entresto™): The Bottom Line

- New drug class and mechanism with promising benefits
- If used, replaces ACEi/ARB in treatment of HFrEF
  - Must wait 36 hours between ACEi and Entresto dose

**Consider in:**
- Patients with no improvement in NYHA functional class or worsening symptoms on optimal medications
- NYHA Class II or III in HFrEF

**Avoid/caution in:**
- History of angioedema
- ?African American patients?
- Renal dysfunction
- Elevated potassium

HFrEF - heart failure with reduced ejection fraction; ACEi: angiotensin converting enzyme inhibitor; ARB: angiotensin receptor blocker
Honorable Mention: Heart Failure
Ivabradine (Corlanor®) – April 2015

FDA approved indication(s):

• Reduce the risk of hospitalization for worsening heart failure in patients with stable, symptomatic heart failure with LVEF ≤ 35%, in sinus rhythm, resting HR ≥ 70 bpm, and on max tolerated beta-blockers

• Off-label: Chronic stable angina in combination with beta-blocker therapy

Anticoagulation Updates:

- Edoxaban (Savaysa®) – January 2015
  - Factor Xa inhibitor

- Dabigatran (Pradaxa®) – October 2015
  - New Indication: VTE prophylaxis in hip replacement

- Idarucizumab (Praxbind®) – October 2015
  - Dabigatran reversal agent
## Regular Adult Dosing for Oral Anticoagulation

<table>
<thead>
<tr>
<th>Condition</th>
<th>Edoxaban (Savaysa)</th>
<th>Dabigatran (Pradaxa)</th>
<th>Rivaroxaban (Xarelto)</th>
<th>Apixaban (Eliquis)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Stroke prophylaxis in A-Fib (non-valvular)</strong></td>
<td>60mg daily</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>VTE Prophylaxis after Total Knee Replacement</strong></td>
<td>Not FDA Approved</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>VTE Prophylaxis after Total Hip Replacement</strong></td>
<td>Not FDA Approved</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>DVT/PE Treatment</strong></td>
<td>60mg daily</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>DVT/PE Prevention of Recurrence</strong></td>
<td>60mg daily</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Edoxaban (Savaysa®): The Bottom Line

- No clear benefit over other direct oral anticoagulants (DOACs)
- Non-inferior to warfarin in stroke prevention in atrial fibrillation and DVT/PE treatment
- Significantly less major bleeding than warfarin
- Requires parenteral bridge therapy

**Consider in:**
- Poor control with warfarin in the past not due to adherence problems
- Taking many drugs that interact with warfarin (especially intermittent administration)

**Avoid/caution in:**
- CrCl >95mL/min
- CrCl<15mL/min
- Well controlled on warfarin or other anticoagulants

**DOAC Reversal:**

**Idarucizumab (Praxbind®) – Oct 2015**

| **FDA approved indication(s):** | • Reversal of dabigatran (Pradaxa®) anticoagulant effects:
  • For emergency surgery/urgent procedures
  • In life-threatening or uncontrolled bleeding |
<table>
<thead>
<tr>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Drug Class</strong></td>
<td>• Humanized monoclonal antibody fragment (Fab)</td>
</tr>
<tr>
<td><strong>Mechanism of Action</strong></td>
<td>• Binds specifically to dabigatran and its acylglucuronide metabolites with higher affinity than the binding affinity of dabigatran to thrombin, neutralizing the anticoagulant effect</td>
</tr>
</tbody>
</table>

Praxbind: Change of ECT from Baseline in Healthy Subjects

ECT: Ecarin Clotting Time

Re-VERSE AD
(RE-VERSAl Effects of idacucizumab on Active Dabigatran)

- Prospective cohort study
  - Emergency surgery or urgent procedure
  - Life-threatening or uncontrolled bleeding

- Mortality:
  - 26/123 (attributed to complications of index event)

- Thrombotic events:
  - 5/123 (attributed to the underlying medical condition)

- SE: hypokalemia (7%), delirium (7%), constipation (7%), pyrexia (6%), pneumonia (6%)

Idarucizumab (Praxbind®): Dosing

- 5 g IV (provided as 2 separate vials of 2.5g/50mL)
- Limited data to support additional 5 g IV
- Restart anticoagulation as soon as medically appropriate

Idarucizumab (Praxbind®): Bottom Line

- First FDA approved DOAC reversal agent
- For emergent or life-threatening situations only
- Only works for dabigatran (Pradaxa)
- Restart anticoagulation as soon as medically appropriate due to concern with underlying medical condition
- In the pipeline:
  - Andexanet alfa (Factor Xa reversal agent) - submitted to FDA
  - Ciraparantag (Broad-spectrum reversal agent) - Phase II trials
# Hyperdyslipidemia: PCSK9 Inhibitors

| FDA approved products | • Alirocumab (Praluent®) – July 2015  
• Evolocumab (Repatha®) – August 2015 |

| FDA approved indication(s) | • Additional LDL-C lowering adjunct to diet, max tolerated statin, and other LDL-lowering therapies in:  
• Heterozygous familial hypercholesterolemia (HeFH)  
• Homozygous familial hypercholesterolemia (HoFH)  
• Clinical atherosclerotic cardiovascular disease |

| Dosing | Alirocumab | 75 mg subQ q 2 weeks. May ↑150mg q 2 weeks if adequate response not achieved within 4-8 wks  
Evolocumab | 140 mg subQ q 2 weeks or 420 mg monthly |

PCSK9 Inhibitors: MOA

Hyperdyslipidemia

- Binding of PCSK9 to LDLR promotes lysosomal degradation of LDLR
- LDLR recycling
- LDL-C uptake
### PCSK9 Inhibitors: Considerations

<table>
<thead>
<tr>
<th>Adverse Effects</th>
<th>Clinical Benefits</th>
</tr>
</thead>
<tbody>
<tr>
<td>Injection site reactions</td>
<td>• Lowers LDL 40-60% on top of statin regimen</td>
</tr>
<tr>
<td>Liver enzyme abnormalities</td>
<td>• Less cardiovascular events in exploratory analysis</td>
</tr>
<tr>
<td>Back pain, arthralgia, myalgia</td>
<td>• No dose adjustment necessary in hepatic and renal impairment</td>
</tr>
<tr>
<td>Upper respiratory tract infections</td>
<td></td>
</tr>
</tbody>
</table>
Promising Results on CV Events in Exploratory Analysis

Long-term studies to definitively evaluate CV risk reduction are ongoing [ODYSSEY OUTCOMES – alirocimab; FOURIER study – evolocimab]

PCSK9 inhibitors: The Bottom Line

Consider in:
- Statin intolerance
- Maximally tolerated statin in HeFH
- HoFH with other lowering LDL agents
- Atherosclerotic cardiovascular disease with statin

Avoid/caution in:
- Hypersensitivity to drugs
- Latex allergy
- Pregnancy
Cardiology Question #1

Which direct oral anticoagulant (DOAC) now has an FDA approved reversal agent?

A. Apixaban (Eliquis®)
B. Dabigatran (Pradaxa®)
C. Edoxaban (Savaysa®)
D. Rivaroxaban (Xarelto®)
Cardiology Question #2

How should a patient currently taking lisinopril start taking sacubitril/valsartan (Entresto™) for heart failure with reduced ejection fraction?

A. Direct switch
B. Continue lisinopril and add-on sacubitril/valsartan
C. Hold lisinopril for 36 hours then start sacubitril/valsartan
Diabetes
<table>
<thead>
<tr>
<th>Date Approved</th>
<th>Brand</th>
<th>Generic</th>
<th>Class</th>
<th>Route</th>
</tr>
</thead>
<tbody>
<tr>
<td>2005, Apr</td>
<td>Byetta</td>
<td>Exenatide</td>
<td>GLP-1 Agonist</td>
<td>Injection</td>
</tr>
<tr>
<td>2005, Jun</td>
<td>Levemir</td>
<td>Detemir</td>
<td>Long-Acting Insulin</td>
<td>Injection</td>
</tr>
<tr>
<td>2006, Mar</td>
<td>Januvia</td>
<td>Sitagliptin</td>
<td>DPP-IV Inhibitor</td>
<td>Oral</td>
</tr>
<tr>
<td>2009, Jul</td>
<td>Onglyza</td>
<td>Saxagliptin</td>
<td>DPP-IV Inhibitor</td>
<td>Oral</td>
</tr>
<tr>
<td>2010, Jan</td>
<td>Victoza</td>
<td>Liraglutide</td>
<td>GLP-1 Agonist</td>
<td>Injection</td>
</tr>
<tr>
<td>2011, May</td>
<td>Tradjenta</td>
<td>Linagliptin</td>
<td>DPP-IV Inhibitor</td>
<td>Oral</td>
</tr>
<tr>
<td>2012, Jan</td>
<td>Bydureon</td>
<td>Exenatide ER</td>
<td>GLP-1 Agonist</td>
<td>Injection</td>
</tr>
<tr>
<td>2013, Jan</td>
<td>Nesina</td>
<td>Allogliptin</td>
<td>DPP-IV Inhibitor</td>
<td>Oral</td>
</tr>
<tr>
<td>2013, Mar</td>
<td>Invokana</td>
<td>Canagliflozin</td>
<td>SGLT-2 Inhibitor</td>
<td>Oral</td>
</tr>
<tr>
<td>2014, Jan</td>
<td>Farxiga</td>
<td>Dapagliflozin</td>
<td>SGLT-2 Inhibitor</td>
<td>Oral</td>
</tr>
<tr>
<td>2014, Apr</td>
<td>Tanzeum</td>
<td>Albiglutide</td>
<td>GLP-1 Agonist</td>
<td>Injection</td>
</tr>
<tr>
<td>2014, Jun</td>
<td>Afrezza</td>
<td>Insulin Technosphere</td>
<td>Rapid-acting insulin</td>
<td>Inhaled</td>
</tr>
<tr>
<td>2014, Aug</td>
<td>Jardiance</td>
<td>Empagliflozin</td>
<td>SGLT-2 Inhibitor</td>
<td>Oral</td>
</tr>
<tr>
<td>2014, Sep</td>
<td>Trulicity</td>
<td>Dulaglutide</td>
<td>GLP-1 Agonist</td>
<td>Injection</td>
</tr>
<tr>
<td>2015, Feb</td>
<td>Toujeo</td>
<td>Insulin glargine (U-300)</td>
<td>Long-acting insulin</td>
<td>Injection</td>
</tr>
<tr>
<td>2015, May</td>
<td>Humalog U-200</td>
<td>Insulin lispro (U-200)</td>
<td>Rapid-acting insulin</td>
<td>Injection</td>
</tr>
<tr>
<td>2015, Oct</td>
<td>Tresiba</td>
<td>Insulin degludec</td>
<td>Long-acting insulin</td>
<td>Injection</td>
</tr>
<tr>
<td>2015, Dec</td>
<td>Basaglar</td>
<td>Insulin glargine (U-100)</td>
<td>Long-acting insulin</td>
<td>Injection</td>
</tr>
</tbody>
</table>
New Insulins on the Market

- Rapid acting
  - Insulin technosphere (Afrezza®) – Inhaled – June 2014
  - Insulin lispro U-200 (Humalog® U-200 Kwikpen) – May 2015
- Long-acting
  - Insulin glargine U-300 (Toujeo® Solostar Pen) – Feb 2015
  - Insulin glargine (follow-on biologic) (Basaglar) – Dec 2015
- Ultra long-acting
  - Insulin degludec U-100 (Tresiba® U-100 FlexTouch) – Oct 2015
  - Insulin degludec U-200 (Tresiba® U-200 FlexTouch) – Oct 2015
- Mixed ultra long-acting and rapid acting insulin
  - 70% insulin degludec/ 30% aspart insulin (Ryzodeg® FlexTouch) – Oct 2015
Insulin technosphere (Afrezza®) – Inhaled Insulin – June 2014

- Faster onset than other rapid acting insulins
- Contraindicated in chronic lung disease (asthma/COPD)
- Requires PFTs (baseline, 6 months, then yearly)
- SE: Cough; hypoglycemia
- Dosing in 4 unit increments
Insulin Lispro U-200 (Humalog® U-200) - May 2015

- 200 units/mL
- Similar PK/PD profile to lispro U-100
- Decreased injection volume
- Max 60 units/injection
- Fewer pens per month
- Not indicated for insulin pumps

Humalog (insulin lispro injection) [package insert]. Indianapolis, IN: Eli Lilly and Company, 2015
New Rapid Acting Insulins: The Bottom Line

**Consider in:**
- Afrezza:
  - Unwilling to inject or increase frequency of injections
- Humalog U-200 Kwikpen:
  - On higher doses of bolus insulin (>30 units TIDAC)

**Avoid/caution in:**
- Afrezza:
  - Chronic lung disease
  - Lung cancer
  - Current smokers/recent quitters
  - Patients who need small dose adjustments
  - Doses >12 units
Insulin Glargine U-100 (Basaglar®)  
- December 2015

- Follow-on biologic product of Lantus
- Eli Lilly and Company and Boehringer Ingelheim
- Approved for Type 1 and Type 2 diabetes
  - Clinical Trials: ELEMENT-1 and ELEMENT-2
- Available December 15, 2016
- Cost: Unknown

Basaglar (insulin glargine injection) [package insert]. Indianapolis, IN: Eli Lilly and Company, 2015
Insulin Degludec (Tresiba®) - October 2015

- Ultra-long-acting: Duration of action ~42 hours
- Available in U-100 and U-200 FlexTouch Pens
- May dose once daily any time
- 56 day (8 week) beyond use date
- Compared to glargine U-100 (Lantus®)
  - Less nocturnal hypoglycemia
  - Similar reduction in A1c

Max injection of 80 units (0.8mL)
Max injection of 160 units (0.8mL)

Tresiba (insulin degludec injection) [package insert]. Bagsvaerd, Denmark: Novo Nordisk, 2015
Insulin Degludec/Aspart
(Ryzodeg® 70/30) – Sept 2015

- 70% insulin degludec/ 30% aspart insulin
- U-100 FlexTouch Pens
- Dose daily or BID with meals
- May use with rapid-acting insulin
- 28 day beyond use date
- Max injection of 80 units

Ryzodeg (insulin degludec/aspart injection) [package insert]. Bagsvaerd, Denmark: Novo Nordisk, 2015
New Long-acting Insulins: The Bottom Line

- Multiple insulins > 100 units/mL available now
- Similar efficacy overall; some PK/PD improvements
- 1:1 dose conversion

**Consider in:**
- Patients on high doses of insulin (>60 units/injection)
- History of nocturnal hypoglycemia
- Poor adherence

**Avoid/caution in:**
- Patients doing well on current insulins
# Diabetes: GLP-1 Agonists

| FDA approved products: | • Exenatide (Byetta®)  
|                       | • Exenatide ER (Bydureon®)  
|                       | • Liraglutide (Victoza®)  
|                       | **Albiglutide (Tanzeum®) – April 2014**  
|                       | **Dulaglutide (Trulicity®) – Sept 2014** |
| FDA approved indication: | • Type 2 diabetes mellitus in adults  
|                       | • Adjunct to diet and exercise  
| Route of administration | • Subcutaneous injection  

Micromedex® 2.0, (electronic version). Truven Health Analytics, Greenwood Village, Colorado, USA. Available at: http://www.micromedexsolutions.com/ (cited: 03/30/2016)).
GLP-1 Agonists: Mechanism of Action

- Brain: Appetite down
- Stomach: Gastric emptying down
- Pancreas: Glucose-dependent Glucagon secretion down, Glucose-dependent Insulin secretion up
- Liver: Glucose production down
- Muscle: Glucose Uptake up

Long-term effects demonstrated in animals:
- Increases β-cell mass
- Maintains β-cell function

GLP-1 Agonists: Considerations

**Adverse Effects**
- Nausea (common)
- Vomiting
- Diarrhea/constipation
- Headache
- Injection site reactions
- Pancreatitis
- Black Box Warning:
  - Thyroid C-cell Tumor (Medullary thyroid carcinoma)

**Clinical Benefits**
- ~0.5-1.5% A1c lowering
- Weight Loss (1-5kg)
- Low risk of hypoglycemia
# GLP-1 Agonists: Dosing

<table>
<thead>
<tr>
<th>Drug</th>
<th>Dose</th>
<th>Dosing in Renal Impairment</th>
<th>AWP Price (1 month)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Exenatide (Byetta®)</td>
<td>5mcg SubQ <strong>BID</strong> prior to meal. May increase to 10mcg BID</td>
<td>30-50mL/min: Use caution &lt;30mL/min: Do not use Hemodialysis: Do not use</td>
<td>$694.32 (Kansas Medicaid preferred)</td>
</tr>
<tr>
<td>Exenatide ER (Bydureon®)</td>
<td>2mg SubQ once <strong>weekly</strong></td>
<td>30-50mL/min: Use caution &lt;30mL/min: Do not use Hemodialysis: Do not use</td>
<td>$659.04 (Kansas Medicaid preferred)</td>
</tr>
<tr>
<td>Liraglutide (Victoza®)</td>
<td>0.6mg SubQ <strong>daily</strong> x 1wk, then increase to 1.2mg daily. May increase to 1.8mg daily</td>
<td>No adjustment, use caution Hemodialysis: No adjustment</td>
<td>$554.04 (Kansas Medicaid preferred)</td>
</tr>
<tr>
<td>Albiglutide (Tanzeum®)</td>
<td>30mg SubQ once <strong>weekly</strong>. May increase to 50mg weekly</td>
<td>No adjustment, use caution</td>
<td>$527.24</td>
</tr>
<tr>
<td>Dulaglutide (Trulicity®)</td>
<td>0.75mg SubQ once <strong>weekly</strong>. May increase to 1.5mg weekly</td>
<td>No adjustment, use caution</td>
<td>$689.76</td>
</tr>
</tbody>
</table>

Micromedex® 2.0, (electronic version). Truven Health Analytics, Greenwood Village, Colorado, USA. Available at: http://www.micromedexsolutions.com/ (cited: 03/30/2016)); prices from Redbook using typical maintenance doses; Kansas Medicaid Preferred Drug list (updated 03/01/2016)
GLP-1 Agonists: Head-to-Head in A1c lowering

* p<0.05 for superiority, ** met non-inferiority criteria, # did not meet non-inferiority criteria

GLP-1 Agonists: Head-to-Head in Weight Loss

GLP-1 Agonists: The Bottom Line

- Liraglutide (Victoza) and dulaglutide (Trulicity) may be more effective in A1c lowering
- At least 1 agent often covered by insurance
- Unique counseling needed for different pens

**Consider in:**
- Not at goal on metformin +/- additional agents, including basal insulin
- Obese
- Adherence problems (weekly dosing)

**Avoid/caution in:**
- Severe renal dysfunction
- History of thyroid cancer
- History of pancreatitis
- Gastroparesis
## Diabetes: SGLT-2 Inhibitors

| FDA approved products: | Canagliflozin (Invokana®) – March 2013  
| Dapagliflozin (Farxiga®) – January 2014  
| Empagliflozin (Jardiance®) – August 2014  
| Combo Products: | Canagliflozin + metformin (Invokamet®)  
| Dapagliflozin + metformin (Xigduo XR®)  
| Empagliflozin + metformin (Synjardy®)  
| Empagliflozin + linagliptin (Glyxambi®)  
| FDA indication: | Type 2 diabetes mellitus in adults  
| Adjunct to diet and exercise  

Increased glucose excretion

50-100g/day urine glucose = 200-400 kcal/day

EMPA-REG OUTCOME Trial

Effect of empagliflozin, in addition to standard of care, on CV morbidity and mortality in type 2 diabetes patients with high CV risk

Primary outcome: Death from CV cause, nonfatal MI, or nonfatal stroke

Randomized double-blind placebo-controlled phase 3 trial

4687 patients received empagliflozin
2333 patients received placebo
3 year follow-up

CAD: 75.6%
Hx MI: 46.6%
Hx stroke: 23.3%
Baseline A1c: 8.1%
Baseline BP: 135/77

Metformin: 74%
Insulin: 48.3%
ACEi: 80.7%
Beta-Blocker: 64.9%
Statin: 77%
Aspirin: 82.6%

CV: cardiovascular; MI: myocardial infarction

## EMPA-REG OUTCOME Trial

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Placebo (N = 2333)</th>
<th>Empagliflozin (N = 4687)</th>
<th>Hazard Ratio (95% CI)</th>
<th>P Value</th>
<th>NNT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Death from CV cause, nonfatal MI, or nonfatal stroke</td>
<td>282 (12.1%)</td>
<td>490 (10.5%)</td>
<td>0.86 (0.74-0.99)</td>
<td>NI: &lt;0.001</td>
<td>63</td>
</tr>
<tr>
<td>Death from any cause</td>
<td>194 (8.3%)</td>
<td>269 (5.7%)</td>
<td>0.68 (0.57-0.82)</td>
<td>&lt;0.001</td>
<td>39</td>
</tr>
<tr>
<td>Death from CV causes</td>
<td>137 (5.9%)</td>
<td>172 (3.7%)</td>
<td>0.62 (0.49-0.77)</td>
<td>&lt;0.001</td>
<td>46</td>
</tr>
<tr>
<td>Fatal or nonfatal MI*</td>
<td>126 (5.4%)</td>
<td>223 (4.8%)</td>
<td>0.87 (0.70-1.09)</td>
<td>0.23</td>
<td>--</td>
</tr>
<tr>
<td>Nonfatal MI*</td>
<td>121 (5.2%)</td>
<td>213 (4.8%)</td>
<td>0.87 (0.70-1.09)</td>
<td>0.22</td>
<td>--</td>
</tr>
<tr>
<td>Fatal or nonfatal stroke</td>
<td>69 (3.0%)</td>
<td>164 (3.5%)</td>
<td>1.18 (0.89-1.56)</td>
<td>0.26</td>
<td>--</td>
</tr>
<tr>
<td>Nonfatal stroke</td>
<td>60 (2.6%)</td>
<td>150 (3.2%)</td>
<td>1.24 (0.92-1.67)</td>
<td>0.16</td>
<td>--</td>
</tr>
<tr>
<td>Hospitalization for HF</td>
<td>95 (4.1%)</td>
<td>126 (2.7%)</td>
<td>0.65 (0.50-0.85)</td>
<td>0.002</td>
<td>72</td>
</tr>
</tbody>
</table>

CV: cardiovascular; MI: myocardial infarction; HF: heart failure; NI: noninferiority; Sup: superiority
*excluding silent MI

# SGLT-2 Inhibitors: Considerations

## Adverse Effects
- Mycotic vulvovaginal infections
- UTIs
- Orthostatic hypotension
- Increased LDL-C
- Hyperkalemia - canagliflozin only
- Increased SCr (usually transient)
- Post-marketing reports of diabetic ketoacidosis (DKA)

## Clinical Benefits
- ~0.7-1% A1c lowering
- Weight Loss (2-3kg)
- Lowers BP (up to 5mmHg)
- Low risk of hypoglycemia
- Not dependent on beta-cell function
- Potential cardiovascular risk benefit
  - EMPA-REG OUTCOME
## SGLT-2 Inhibitors: Dosing

<table>
<thead>
<tr>
<th></th>
<th>Dose</th>
<th>Renal Impairment</th>
<th>Hepatic Impairment</th>
<th>AWP Price (1 month)</th>
</tr>
</thead>
</table>
| Canagliflozin    | 100mg po daily prior to first meal; may increase to 300mg | 45-59mL/min: 100mg daily  
<45mL/min: Not recommended | Mild-moderate: no dose adjustment  
Severe: Not recommended | $435.67 (Kansas Medicaid preferred) |
| (Invokana®)      |                                           |                                          |                                     |                             |
| Dapagliflozin    | 5mg po daily in morning; may increase to 10mg | <60mL/min: not recommended | No adjustment, use caution | $435.68                     |
| (Farxiga®)       |                                           |                                          |                                     |                             |
| Empagliflozin    | 10mg po daily; may increase to 25mg       | <45mL/min: Not recommended | No adjustment, use caution | $435.66 (Kansas Medicaid preferred) |
| (Jardiance®)     |                                           |                                          |                                     |                             |

Micromedex® 2.0, (electronic version). Truven Health Analytics, Greenwood Village, Colorado, USA. Available at: http://www.micromedexsolutions.com/ (cited: 03/30/2016)); prices from Redbook using typical maintenance doses; Kansas Medicaid Preferred Drug list (updated 03/01/2016)
SGLT-2 Inhibitors: The Bottom Line

**Consider in:**
- Type 2 DM not at goal on metformin +/- additional agents
- High CVD risk
- Obese
- Uncontrolled HTN
- Prefer oral

**Avoid/caution in:**
- Poor renal function
- Hyperkalemia (mainly canagliflozin)
- History of frequent vaginal or urinary infections
- Type 1 DM
Diabetes Patient Case

- MM is a 69yoAAM with DM2 (12 yrs), CKD, HTN, HLD, CAD (CABG 2012), obesity, and smokes ½ ppd.
- Currently on metformin 500mg BID, glipizide 10mg qAM, atorvastatin 40mg, lisinopril 20mg, and ASA 81mg.
- Labs/vitals (today): A1c 8.8%, Scr 1.8, eGFR =40mL/min, K+ 4.1; BP 114/70; HR 72, BMI 35
- What do you recommend for diabetes management?
  A. Start empagliflozin (Jardiance®)
  B. Start dulaglutide (Trulicity®)
  C. Start insulin degludec (Tresiba® U-100)
  D. Start inhaled insulin technosphere (Afrezza®)
Weight Loss/Obesity

- 1959: Phentermine
- 1999: Orlistat (Xenical®)
- 2007: Orlistat OTC (Alli®)
- June 2012: Lorcaserin (Belviq®)
- July 2012: Phentermine/Topiramate ER (Qysimia®)
- September 2014: Bupropion/Naloxone (Contrave®)
- December 2014: Liraglutide (Saxenda®)

- **April 2015:** Deoxycholic acid (Kybella™)
- **Jan 2015:** Lisdexamfetamine (Vyvanse®) – new indication
**Binge Eating Disorder: Lisdexamfetamine (Vyvanse®) - Expanded Indication**

| FDA approved indication(s): | • Attention deficit hyperactivity disorder (ADHD)  
|                            | • **Binge eating disorder (moderate to severe)**  
|                            | • **Approved Jan 2015** |

| Drug Class | • Stimulant amphetamine |

| Basic Mechanism of Action | • Pro-drug for dextroamphetamine  
|                          | • Suppresses appetite |

<table>
<thead>
<tr>
<th>Dosing</th>
<th>Initial</th>
<th>Target</th>
<th>Max</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>ADHD</strong></td>
<td>30mg qAM</td>
<td>Treatment response (titrate weekly)</td>
<td>70mg/day</td>
</tr>
<tr>
<td><strong>Binge eating disorder</strong></td>
<td>30mg qAM</td>
<td>50-70mg/day (titrate weekly)</td>
<td>70mg/day</td>
</tr>
</tbody>
</table>

**August 2015: Kansas Board of Healing Arts approved use for binge eating disorder**

Binge Eating Disorder: DSM-5

- Recurrent episodes of eating significantly more food in a shorter time than normal
- Marked by feelings of lack of control and distress
- Occurs, on average, at least once a week over 3 months
- Not associated with inappropriate compensatory behavior (e.g. purging)

## Lisdexamfetamine (Vyvanse®): Considerations

<table>
<thead>
<tr>
<th>Adverse effects</th>
<th>Clinical Benefits</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Dry mouth (36%)</td>
<td>• Decreased binge eating days per week by 1 more day compared to placebo (NNT = 3)</td>
</tr>
<tr>
<td>• Insomnia (20%)</td>
<td>• Improved cessation of binge eating (NNT = 4)</td>
</tr>
<tr>
<td>• Increased HR, jittery,</td>
<td>• 50 and 70mg doses achieved 5% weight loss</td>
</tr>
<tr>
<td>constipation, anxiousness (&gt;5%)</td>
<td></td>
</tr>
<tr>
<td>• Black box warning:</td>
<td></td>
</tr>
<tr>
<td>• Risk of abuse and dependence</td>
<td></td>
</tr>
</tbody>
</table>

Effect on cardiovascular morbidity and mortality not yet established

Lisdexamfetamine (Vyvanse®): The Bottom Line

- Only FDA approved product for binge eating disorder
- Not approved for weight loss, but may help
- Long-term efficacy unknown

**Consider in:**
- Addition to psychotherapy and nutrition counseling
- Failed or are not candidates for SSRIs

**Avoid/caution in:**
- Hx of mania or seizures
- Concerns for abuse
- Other eating disorders
- Cardiovascular concerns
**FDA approved indication(s):**
- Improvement in appearance of moderate-to-severe convexity or fullness associated with submental fat in adults

**Drug Class**
- Cytolytic drug

**Basic Mechanism of Action**
- Destroys the cell membrane causing lysis

**Route of administration**
- Multiple in-office injections under the chin

---

Not approved for fat anywhere else on the body

Respiratory
### Asthma: Tiotropium (Spiriva®) - Expanded Indication

| FDA approved indication(s): | • COPD (maintenance treatment)  
• **Asthma (maintenance treatment)**  
• **Approved September 2015** |
<table>
<thead>
<tr>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Drug Class</strong></td>
<td>• Long-acting muscarinic receptor antagonist</td>
</tr>
<tr>
<td><strong>Dosing</strong> Asthma</td>
<td>• Respimat: 2 inhalations (5mcg) once daily</td>
</tr>
<tr>
<td>COPD:</td>
<td>• Respimat: 2 inhalations (5mcg) once daily</td>
</tr>
<tr>
<td></td>
<td>• Handihaler: Inhale 1 capsule (18mcg) once daily</td>
</tr>
<tr>
<td><strong>Side Effects</strong></td>
<td>• Dry mouth, sore throat, bronchitis, headache, sinus infection</td>
</tr>
</tbody>
</table>
PrimoTinA- Asthma 1 and 2 trials

Tiotropium in asthma poorly controlled with standard combination therapy

Primary endpoints:
- Peak and trough FEV$_1$ response change from baseline to week 24
- Time to first severe asthma exacerbation

Excluded:
- Past diagnosis of COPD
- Serious coexisting illnesses
- Concurrent use of anticholinergic bronchodilator

912 patients included
- Mean Age: 53yo
- Mean Baseline FEV1: 62% of predicted value

Randomized, double-blind, placebo-controlled, parallel group, 48 week study period

Significant improvement in peak and trough FEV1 at week 24
- 21% less severe asthma exacerbations

Tiotropium (Spiriva®) for Asthma: The Bottom Line

Consider in:
- Asthma patients not controlled on ICS/LABA
  - Add on therapy

Avoid/caution in:
- Urinary retention
- Narrow angle glaucoma
- Severe renal impairment
- Handihaler formulation
Asthma: ProAir® RespiClick (albuterol) – April 2015

ProAir RespiClick (albuterol sulfate) [package insert]. Horsham, PA: Teva Respiratory, LLC; 2015.
ProAir RespiClick: The Bottom Line

- First dry powder rescue inhaler
- No hand-breath coordination or spacer needed
- Requires deep inhalation at time of use
- Approved for bronchospasm and exercise-induced bronchospasm

Consider in:
- Patients with poor hand-breath coordination

Avoid/caution in:
- Patients doing well on current rescue inhaler
- Children <12 years
Recent Approvals: Inhalers and Devices for COPD

<table>
<thead>
<tr>
<th>Brand Name</th>
<th>Stiolto Respimat</th>
<th>Utibron Neohaler</th>
<th>Seebri Neohaler</th>
</tr>
</thead>
<tbody>
<tr>
<td>Generic Medication (Class)</td>
<td>Tiotropium Bromide (LAMA)/ Olodaterol (LABA)</td>
<td>Glycopyrrolate (LAMA)/ Indacaterol (LABA)</td>
<td>Glycopyrrolate (LAMA)</td>
</tr>
<tr>
<td>Indication(s)</td>
<td>COPD</td>
<td>COPD</td>
<td>COPD</td>
</tr>
<tr>
<td>Dosing frequency</td>
<td>Inhale 2 puffs once daily</td>
<td>Inhale 1 capsule BID</td>
<td>Inhale 1 capsule BID</td>
</tr>
<tr>
<td>Approved</td>
<td>May 2015</td>
<td>October 2015</td>
<td>October 2015</td>
</tr>
<tr>
<td>Picture</td>
<td><img src="image" alt="Stiolto Respimat" /></td>
<td><img src="image" alt="Utibron Neohaler" /></td>
<td><img src="image" alt="Seebri Neohaler" /></td>
</tr>
</tbody>
</table>

LABA: Long-acting beta-agonist; LAMA: Long-acting muscarinic antagonist

Micromedex® 2.0, (electronic version). Truven Health Analytics, Greenwood Village, Colorado, USA. Available at: http://www.micromedexsolutions.com/ (cited: 03/30/2016); prices from Redbook using typical maintenance doses
## Summary of Newer Inhalers

<table>
<thead>
<tr>
<th>Brand Name</th>
<th>Generic Medication (Class)</th>
<th>Indication(s)</th>
<th>Frequency</th>
<th>Form</th>
</tr>
</thead>
<tbody>
<tr>
<td>ProAir RespiClick</td>
<td>Albuterol sulfate (SABA)</td>
<td>Asthma</td>
<td>1-2 puffs q4-6h prn</td>
<td>DPI</td>
</tr>
<tr>
<td>Breo Ellipta</td>
<td>Fluticasone furoate (ICS)/Vilanterol trifenate (LABA)</td>
<td>Asthma COPD</td>
<td>Inhale once daily</td>
<td>DPI</td>
</tr>
<tr>
<td>Anoro Ellipta</td>
<td>Umeclidinium bromide(LAMA)/Vilanterol trifenate (LABA)</td>
<td>COPD</td>
<td>Inhale once daily</td>
<td>DPI</td>
</tr>
<tr>
<td>Stiolto Respimat</td>
<td>Tiotropium Bromide (LAMA)/Olodaterol (LABA)</td>
<td>COPD</td>
<td>Inhale 2 puffs once daily</td>
<td>MDI</td>
</tr>
<tr>
<td>Utibron Neohaler</td>
<td>Glycopyrrolate (LAMA)/Indacaterol (LABA)</td>
<td>COPD</td>
<td>Inhale 1 cap BID</td>
<td>Cap</td>
</tr>
<tr>
<td>Striverdi Respimat</td>
<td>Olodaterol (LABA)</td>
<td>COPD</td>
<td>Inhale 2 puffs once daily</td>
<td>MDI</td>
</tr>
<tr>
<td>Arcapta Neohaler</td>
<td>Indacaterol (LABA)</td>
<td>COPD</td>
<td>Inhale 1 cap BID</td>
<td>Cap</td>
</tr>
<tr>
<td>Incruse Ellipta</td>
<td>Umeclidinium bromide (LAMA)</td>
<td>COPD</td>
<td>Inhale once daily</td>
<td>DPI</td>
</tr>
<tr>
<td>Seebri Neohaler</td>
<td>Glycopyrrolate (LAMA)</td>
<td>COPD</td>
<td>Inhale 1 cap BID</td>
<td>Cap</td>
</tr>
<tr>
<td>Arnuity Ellipta</td>
<td>Fluticasone furoate (ICS)</td>
<td>Asthma</td>
<td>Inhale once daily</td>
<td>DPI</td>
</tr>
</tbody>
</table>

SABA: short-acting beta-agonist; ICS: Inhaled corticosteroid; LABA: Long-acting beta-agonist; LAMA: Long-acting muscarinic antagonist; DPI: Dry powder inhaler; MDI: Metered dose inhaler; Cap: Inhaled capsule

Micromedex® 2.0, (electronic version). Truven Health Analytics, Greenwood Village, Colorado, USA. Available at: http://www.micromedexsolutions.com/ (cited: 03/30/2016)
## Honorable Mentions: New Treatments for Eosinophilic Asthma

| FDA approved products | • Mepolizumab (Nucala®) – November 2015  
| | • Reslizumab (Cinqair®) – March 2016 |
| FDA approved indication(s) | • Add-on maintenance treatment of patients with severe eosinophilic asthma |
| Mechanism of Action | • Interleukin-5 (IL-5) antagonist monoclonal antibody  
| | • Mepolizumab: IgG1 kappa  
| | • Reslizumab: IgG4 kappa |
| Dosing | Mepolizumab 100 mg subcutaneously every 4 weeks  
| | Reslizumab 3mg/kg IV infusion every 4 weeks |
| Benefits | ↓ exacerbations, ↓ hospitalizations, ↑ FEV1 |

Guideline Update: March 2016

Special Communication

CDC Guideline for Prescribing Opioids for Chronic Pain—United States, 2016

Deborah Dowell, MD, MPH; Tamara M. Haegerich, PhD; Roger Chou, MD

**IMPORTANCE** Primary care clinicians find managing chronic pain challenging. Evidence of long-term efficacy of opioids for chronic pain is limited. Opioid use is associated with serious risks, including opioid use disorder and overdose.

**OBJECTIVE** To provide recommendations about opioid prescribing for primary care clinicians treating adult patients with chronic pain outside of active cancer treatment, palliative care, and end-of-life care.

**PROCESS** The Centers for Disease Control and Prevention (CDC) updated a 2014 systematic review on effectiveness and risks of opioids and conducted a supplemental review on benefits and harms, values and preferences, and costs. CDC used the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) framework to assess

http://www.cdc.gov/drugoverdose/prescribing/guideline.html

### Opioid Overdose: Narcan (naloxone) Nasal Spray – Nov 2015

<table>
<thead>
<tr>
<th>FDA approved indication(s):</th>
<th>Emergency treatment of known or suspected opioid overdose</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Drug Class</strong></td>
<td>Opioid receptor antagonist</td>
</tr>
<tr>
<td><strong>Dosing</strong></td>
<td>Single spray into one nostril (4mg)</td>
</tr>
<tr>
<td></td>
<td>May repeat q2-3minutes prn until medical assistance arrives</td>
</tr>
</tbody>
</table>

Off-Label Use with Nasal Atomizer

Naloxone: The Bottom Line

- Multiple dosage forms available (IM, nasal spray, nasal atomizer)
- Risk of naloxone use is very low
- Essential to educate patients/caregivers
  - [www.Prescribetoprevent.org](http://www.Prescribetoprevent.org)

**Consider in:**
- History of overdose
- History of substance use disorder
- Higher opioid doses (≥50 mg morphine equivalent/day)
- Difficulty accessing emergency services
- Concurrent benzodiazepine use
- Any increase in risk of respiratory depression

Osteoarthritis:
Vivlodex® (meloxicam) – Oct 2015

Low-dose SoluMatrix® meloxicam

Vivlodex® (meloxicam): The Bottom Line

- Dosing not equivalent to regular meloxicam
- 30% lower dose needed

**Consider in:**
- High risk for NSAID adverse effects who need an NSAID

**Avoid/caution in:**
- Patients doing well on other NSAIDs
- High CV risk
- High GI bleeding risk
- Kidney dysfunction
Evolution of Hepatitis C Treatment

SVR: sustained virologic response; DAA: Direct acting antivirals; IFN: (peg)interferon; RBV: ribavirin

New Hepatitis C Treatments

- Polymerase Inhibitors:
  - Sofosbuvir (**Sovaldi**) – Dec 2013

- NS5A Inhibitor/ Polymerase Inhibitor:
  - Lediprasvir/ Sofosbuvir (**Harvoni**) – Dec 2013
  - Daclatasvir/ Sofosbuvir (**Daklinza**) – July 2015

- NS5A Inhibitor/ Protease Inhibitor
  - Elbasvir and grazoprevir (**Zepatier**) – January 2016

- NS5A Inhibitor/ Protease Inhibitor/ CYP3A Inhibitor:
  - Ombitasvir/ Paritaprevir/ Ritonavir (**Technivie**) – July 2015

- NS5A Inhibitor/ Protease Inhibitor/ CYP3A Inhibitor/ Polymerase Inhibitor:
  - Ombitasvir/ Paritaprevir/ Ritonavir/ Dasabuvir (**Viekira Pak**) – Dec 2014
HCV Medications: MOA

Modified from medical illustrator: David Schumick
# New Hepatitis C Treatments: Considerations

<table>
<thead>
<tr>
<th>Adverse effects</th>
<th>Clinical Benefits</th>
</tr>
</thead>
<tbody>
<tr>
<td>Headache</td>
<td>Less side effects than older HCV medications</td>
</tr>
<tr>
<td>Fatigue</td>
<td>High cure rates</td>
</tr>
<tr>
<td>Anemia</td>
<td>12 to 24 week duration</td>
</tr>
<tr>
<td>Insomnia</td>
<td>Multiple genotypes indicated, though may need to combo RBV+/−PEG</td>
</tr>
<tr>
<td>Bradycardia</td>
<td></td>
</tr>
<tr>
<td>Itching</td>
<td></td>
</tr>
</tbody>
</table>
## Hepatitis C Treatments

<table>
<thead>
<tr>
<th>Approved</th>
<th>Brand</th>
<th>Generic</th>
<th>Class</th>
<th>Genotypes</th>
<th>Frequency</th>
<th>Combo with</th>
<th>Cost (AWP), 12 wk</th>
</tr>
</thead>
<tbody>
<tr>
<td>2001</td>
<td>PegIntron</td>
<td>Peginterferon alfa-2b</td>
<td>Interferon</td>
<td>All</td>
<td>SQ Weekly</td>
<td>RBV</td>
<td>$10,831-12,538</td>
</tr>
<tr>
<td>2002</td>
<td>Pegasys</td>
<td>Peginterferon alfa-2a</td>
<td>Interferon</td>
<td>All</td>
<td>SQ Weekly</td>
<td>RBV</td>
<td>$12,477.84</td>
</tr>
<tr>
<td>2002</td>
<td>Copegus</td>
<td>Ribavirin (RBV)</td>
<td>Nucleoside analog</td>
<td>1, all*</td>
<td>Oral BID</td>
<td>PEG</td>
<td>$690.48-5004.72</td>
</tr>
<tr>
<td>2011, May</td>
<td>VICTRELIS</td>
<td>Boceprevir</td>
<td>PI: NS3/4A</td>
<td>1</td>
<td>Oral TID</td>
<td>PEG + RBV</td>
<td>$6017.76</td>
</tr>
<tr>
<td>2013, Nov</td>
<td>Olysio</td>
<td>Simeprevir</td>
<td>PI: NS3/4A</td>
<td>1, 4*</td>
<td>Oral daily</td>
<td>PEG + RBV</td>
<td>$79,632</td>
</tr>
<tr>
<td>2013, Dec</td>
<td>Sovaldi</td>
<td>Sofosbuvir</td>
<td>Poly I: NS5B</td>
<td>1,2,3,4, 5*,6*</td>
<td>Oral daily</td>
<td>RBV +/- PEG</td>
<td>$100,800</td>
</tr>
<tr>
<td>2013, Dec</td>
<td>Harvoni</td>
<td>Lediprasvir</td>
<td>NS5A Inhibitor</td>
<td>1, 4, 5, 6</td>
<td>Oral daily</td>
<td>None</td>
<td>$113,400</td>
</tr>
<tr>
<td>2014, Dec</td>
<td>Viekira Pak</td>
<td>Ombitasvir</td>
<td>NS5A inhibitor</td>
<td>1</td>
<td>2 tabs oral daily</td>
<td>+/- RBV</td>
<td>$99,982.80</td>
</tr>
<tr>
<td>2014, Dec</td>
<td></td>
<td>Paritaprevir</td>
<td>PI: NS3/4A</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2014, Dec</td>
<td></td>
<td>Ritonavir</td>
<td>Booster</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2014, Dec</td>
<td></td>
<td>Dasabuvir</td>
<td>Poly I: NS5B</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2015, July</td>
<td>Daklinza</td>
<td>Daclatasvir</td>
<td>NS5A inhibitor</td>
<td>3</td>
<td>Oral daily</td>
<td>None</td>
<td>$75,600</td>
</tr>
<tr>
<td>2015, July</td>
<td>Technivie</td>
<td>Ombitasvir</td>
<td>NS5A inhibitor</td>
<td>4 without cirrhosis</td>
<td>2 tabs oral daily</td>
<td>None</td>
<td>$91,983.60</td>
</tr>
<tr>
<td>2015, July</td>
<td></td>
<td>Paritaprevir</td>
<td>PI: NS3/4A</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2015, July</td>
<td></td>
<td>Ritonavir</td>
<td>Booster</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2016, Jan</td>
<td>Zepatier</td>
<td>Elbasvir</td>
<td>NS5A Inhibitor</td>
<td>1, 4</td>
<td>Oral daily</td>
<td>+/- RBV</td>
<td>$65,520</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Grazoprevir</td>
<td>PI: NS3/4A</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*Off label
PI: Protease Inhibitor
Poly I: Polymerase Inhibitor

Micromedex® 2.0, (electronic version). Truven Health Analytics, Greenwood Village, Colorado, USA. Available at: http://www.micromedexsolutions.com/ (cited: 03/30/2016)); prices from Redbook using typical maintenance doses
New Hepatitis C Treatments: The Bottom Line

- Cure for hepatitis C is achievable for many patients with only oral agents
- Improved side effect profile and tolerability
- Minimal monitoring required (CBC, LFTs, etc.)
- Consider genotype, treatment experience (e.g. naïve; prior failure), and presence of cirrhosis to determine regimen and treatment duration
  - FibroSure/FibroTest
- Very expensive
**IBS-D: Eluxadoline (Viberzi®) – May 2015**

<table>
<thead>
<tr>
<th>FDA approved indication(s):</th>
<th>• Treatment of irritable bowel syndrome with diarrhea (IBS-D)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Mechanism of Action</strong></td>
<td>• Mixed mu-opioid receptor agonist, delta opioid receptor antagonist, and kappa opioid receptor agonist which acts locally to reduce abdominal pain and diarrhea in patients with IBS-D without constipating side effects</td>
</tr>
</tbody>
</table>
| **Dosing**                | • 100mg po BID with food  
• 75 mg po BID with food in patients who:  
  • Do not have a gallbladder  
  • Are unable to tolerate the 100 mg dose  
  • Are receiving concomitant OATP1B1 inhibitors  
  • Have mild or moderate hepatic impairment |

## Eluxadoline (Viberzi®): Considerations

<table>
<thead>
<tr>
<th>Adverse Effects</th>
<th>Clinical Benefits</th>
</tr>
</thead>
<tbody>
<tr>
<td>Constipation, nausea, vomiting, abdominal pain, rash, dizziness</td>
<td>Can improve stool consistency as well as abdominal pain</td>
</tr>
<tr>
<td>Sphincter of Oddi spasm</td>
<td></td>
</tr>
<tr>
<td>Pancreatitis</td>
<td></td>
</tr>
</tbody>
</table>
# IBS-D: Rifaxamin (Xifaxin®) – Expanded Indication

| FDA approved indication(s): | • Treatment of travelers’ diarrhea caused by non-invasive strains of E.coli in age ≥12 years  
| | • Reduce risk of overt hepatic encephalopathy recurrence in adults  
| | • **Treatment of irritable bowel syndrome with diarrhea in adults - Approved May 2015**  |
| **Mechanism of Action** | • Inhibits bacterial RNA synthesis by binding to bacterial DNA-dependent RNA polymerase  |
| **Dosing** | • **IBS-D**: 550mg po TID x 14 days, may repeat 2 times if symptoms reoccur  |

### Rifaxamin (Xifaxin®): Considerations

<table>
<thead>
<tr>
<th>Adverse Effects</th>
<th>Clinical Benefits</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nausea/vomiting</td>
<td>□ Improves global IBS symptoms and bloating</td>
</tr>
<tr>
<td>Abdominal pain</td>
<td>□ Repeat treatment has similar efficacy to the first course of rifaximin</td>
</tr>
<tr>
<td>Dizziness</td>
<td></td>
</tr>
<tr>
<td>Headache</td>
<td></td>
</tr>
<tr>
<td>Increased liver enzymes</td>
<td></td>
</tr>
</tbody>
</table>
New IBS-D: The Bottom Line

- Two new mechanisms approved to treat IBS-D
- Target both bowel pattern and abdominal pain
- Expensive

**Consider in:**
- Not controlled or not tolerating other IBS-D medications
- Rifaximin:
  - Non adherent patients or those who do not like taking meds
    - 10 weeks of relief with just 2 weeks of medication

**Avoid/caution in:**
- Eluxadoline:
  - Gallbladder disease
  - Pancreatitis history
- Rifaximin:
  - Current antibiotic use
  - Hepatic impairment
Notable Agents
### FDA approved indication(s):
- Acquired, generalized hypoactive sexual desire disorder (HSDD) in pre-menopausal women that causes marked distress or interpersonal difficulty and is NOT due to:
  - Co-existing medical or psychiatric condition,
  - Problems with the relationship, or
  - Effect of a medication or other substance

### Basic Mechanism of Action
- Agonist at 5-HT$_{1A}$ and antagonist at 5-HT$_{2A}$
- Moderate antagonist activity at 5-HT$_{2B}$, 5-HT$_{2C}$, and dopamine D$_4$ receptor

### Dosing
- 100mg tab po once daily at bedtime

---

Flibanserin (Addyi®): Considerations

### Adverse effects
- Dizziness, somnolence, nausea (>10%)
- Fatigue, insomnia, dry mouth (>2%)
- **Black Box Warning:** Hypotension and syncope
- Contraindicated
  - Alcohol use
  - Moderate-strong CYP3A4 inhibitors
  - Hepatic impairment

### Clinical Benefits
- Improved change from baseline in sexual desire and in monthly satisfying sexual events (SSE) at week 24
  - Mean age 36.6 years
  - SSE 2.5 (flibanserin) vs 1.5 (placebo)
  - Effects after 4 weeks, peaks at 8 weeks

Flibanserin (Addyi®): The Bottom Line

- Must be taken daily for at least 4 weeks to see effect
- Not for enhanced sexual performance
- REMS program for prescribers and pharmacies

**Consider in:**
- Patients with HSDD for at least 6 months with marked distress and desire to improve sexual arousal

**Avoid/caution in:**
- <18 years, elderly, pregnant
- Hepatic dysfunction
- Mental health disorder (e.g. depression, anxiety, etc.)
- Polypharmacy
  - CYP2C19, 3A4 inhibitors
- Relationship discord
**Gout: Lesinurad (Zurampic®) – Dec 2015**

| FDA approved indication(s):                      | • Hyperuricemia associated with gout  
|                                               | • In combination with a xanthine oxidase inhibitor (XOI)  
|                                               | • Not for asymptomatic hyperuricemia  
|                                               | • Not as monotherapy  |

**Drug Class**

- Urate-anion exchanger transporter 1 (URAT1) inhibitor

**Mechanism of Action**

- Decreases uric acid reabsorption in the kidneys through inhibition of URAT1 (major) and OAT4 (minor).

**Dosing**

- 200mg po daily with XOI (allopurinol or febuxostat)  
  - Do not initiate if CrCl < 45 mL/min

_Zurampic (lesinurad) [package insert]. Wilmington, DE: AstraZeneca Pharmaceuticals LP; 2015._
Lesinurad (Zurampic®): The Bottom Line

- Improves uric acid levels but did not show change in rate of gout flares

**Consider in:**
- Patients with hyperuricemia and recurrent gout flares despite treatment with XOI who want to try additional therapy

**Avoid/caution in:**
- Asymptomatic hyperuricemia
- CrCl < 45mL/min
- CYP2C9 inhibitors (fluconazole, amiodarone)
- CYP2C9 inducers (rifampin, carbamazepine)

Zembrace SymTouch (sumatriptan) 3mg Subcutaneous Injection

Onzeta Xsail (sumatriptan nasal powder) 11 mg per nosepiece

New Formulations in ADHD Treatment

- Dyanavel XR (amphetamine) Extended-Release Oral Suspension
  - October 2015

- QuilliChew ER (methylphenidate hydrochloride) Extended Release Chewable Tablets
  - December 2015

- Adzenys XR-ODT (amphetamine) Extended-Release Orally Disintegrating Tablets
  - January 2016
Cost Considerations and Tips

- Generic vs. Brand
- Insurance formulary variations and changes
- Take advantage of manufacturer savings cards
- Medication Assistance Programs (MAP) if no insurance
  - www.RxOutreach.org
  - www.Needymeds.org
  - www.GoodRx.com
Objectives

1. Describe new FDA approved medications and new FDA approved indications related to primary care
2. Summarize the indications, mechanisms of action, adverse effects, and patient safety considerations for each medication or class of medications
3. Compare and contrast the new medications with current standards of care
4. Discuss the implications of the new medications to primary care practice
Medications Reviewed

- **Cardiology**
  - Sacubitril/Valsartan (Entresto)
  - *Ivabradine* (Corlanor)
  - Edoxaban (Savaysa)
  - Pradaxa (Dabigatran) - update
  - Idarucizumab (Praxbind)
  - PCSK9 Inhibitors

- **Diabetes**
  - New Insulins
  - GLP-1 agonists
  - SGLT-2 inhibitors

- **Obesity/Weight loss**
  - Lisdexamfetamine (Vyvanse)
  - Deoxycholic acid (Kybella)

- **Respiratory**
  - Spiriva (tiotropium) – new indication
  - ProAir Respiclick (albuterol)
  - Stiolt (tiotropium and olodaterol)
  - Utibron (indacaterol and glycopyrrolate)
  - Seebri (glycopyrrolate)
  - *Mepalizumab* (Nucala)
  - *Resilizumab* (Cinqair)

- **Pain Management**
  - CDC Guideline update
  - Narcan (naloxone) nasal spray
  - Vivlodex (meloxicam)

- **Gastroenterology**
  - Hepatitis C treatments
  - Viberzi (eluxadoline)
  - Xifaxin (rifaxamin) – new indication

- **Notable Agents**
  - Flibanserin (Addyi)
  - Zurampic (lesinurad) - Gout
  - Sumatriptan new dosage forms
  - ADHD new dosage forms

Tiffany Shin, PharmD, BCACP
shin@ku.edu
MEDICATION UPDATE

Kansas Association of Osteopathic Medicine (KAOM)
April 9, 2016

Tiffany Shin, PharmD, BCACP

shin@ku.edu

Clinical Assistant Professor
University of Kansas School of Pharmacy - Wichita
## Insulin Types: Pharmacokinetics

<table>
<thead>
<tr>
<th>Class</th>
<th>Product</th>
<th>Onset</th>
<th>Peak</th>
<th>Duration</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Bolus Insulin</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Inhaled Insulin</td>
<td>Inhaled Insulin</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rapid-acting insulin</td>
<td>Insulin technosphere (Afrezza)</td>
<td>~15 min</td>
<td>1 hour</td>
<td>160 min</td>
</tr>
<tr>
<td>Rapid-acting insulin</td>
<td>Lispro (Humalog U-100)</td>
<td>~15 min</td>
<td>1-2 hours</td>
<td>3-6 hours</td>
</tr>
<tr>
<td></td>
<td>Lispro (Humalog U-200)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Aspart (Novolog)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Glulisine (Apidra)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Short-acting insulin</strong></td>
<td>Regular Insulin (Humulin R, Novolin R)</td>
<td>30-60 min</td>
<td>2-4 hours</td>
<td>6-10 hours</td>
</tr>
<tr>
<td><strong>Intermediate-acting insulin</strong></td>
<td>NPH Insulin (Humulin N, Novolin N)</td>
<td>2-4 hours</td>
<td>4-6 hours</td>
<td>10-24 hours</td>
</tr>
<tr>
<td><strong>Long-acting insulin</strong></td>
<td>Glargine U-100 (Lantus, Basaglar)</td>
<td>1-2 hours</td>
<td>Usually no peak</td>
<td>&lt;24 hours</td>
</tr>
<tr>
<td></td>
<td>Detemir (Levemir)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Long-acting insulin</strong></td>
<td>Glargine U-300 (Toujeo)</td>
<td>Over 6 hours</td>
<td>No peak</td>
<td>36 hours</td>
</tr>
<tr>
<td><strong>Ultra long-acting insulin</strong></td>
<td>Degludec U-100 (Tresiba)</td>
<td>30-90 min</td>
<td>No peak</td>
<td>42 hours</td>
</tr>
<tr>
<td></td>
<td>Degludec U-200 (Tresiba)</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

## Mixed Insulins: Pharmacokinetics

<table>
<thead>
<tr>
<th>Product</th>
<th>Mixture</th>
<th>Onset</th>
<th>Peak</th>
<th>Duration</th>
</tr>
</thead>
<tbody>
<tr>
<td>Humulin 70/30</td>
<td>70% NPH/ 30% Regular insulin</td>
<td>30 min</td>
<td>2-12 hours</td>
<td>18-24 hours</td>
</tr>
<tr>
<td>Novolin 70/30</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Humalog 75/25</td>
<td>75% lispro protamine/25% lispro insulin</td>
<td>~15 min</td>
<td>1-6.5 hours</td>
<td>Up to 24 hours</td>
</tr>
<tr>
<td>Humalog 50/50</td>
<td>50% lispro protamine/50% lispro insulin</td>
<td>~15 min</td>
<td>0.8-4.8 hours</td>
<td>22 hours or more</td>
</tr>
<tr>
<td>Novolog 70/30</td>
<td>70% aspart protamine /30% aspart insulin</td>
<td>~15 min</td>
<td>1-4 hours</td>
<td>Up to 24 hours</td>
</tr>
<tr>
<td>Ryzodeg</td>
<td>70% insulin degludec/30% aspart insulin</td>
<td>~15 min</td>
<td>30-60 min</td>
<td>42 hours</td>
</tr>
</tbody>
</table>

# Summary of Newer Inhalers

<table>
<thead>
<tr>
<th>Brand Name</th>
<th>Generic Medication (Class)</th>
<th>Indication(s)</th>
<th>Frequency</th>
<th>Form</th>
</tr>
</thead>
<tbody>
<tr>
<td>Breo Ellipta</td>
<td>Fluticasone furoate (ICS)/Vilanterol trifenate (LABA)</td>
<td>Asthma/COPD</td>
<td>Inhale once daily</td>
<td>DPI</td>
</tr>
<tr>
<td>Anoro Ellipta</td>
<td>Umeclidinium bromide (LAMA)/Vilanterol trifenate (LABA)</td>
<td>COPD</td>
<td>Inhale once daily</td>
<td>DPI</td>
</tr>
<tr>
<td>Stiolto Respimat</td>
<td>Tiotropium Bromide (LAMA)/Olodaterol (LABA)</td>
<td>COPD</td>
<td>Inhale 2 puffs once daily</td>
<td>MDI</td>
</tr>
<tr>
<td>Utibron Neohaler</td>
<td>Glycopyrrolate (LAMA)/Indacaterol (LABA)</td>
<td>COPD</td>
<td>Inhale 1 cap BID</td>
<td>Cap</td>
</tr>
<tr>
<td>Striverdi Respimat</td>
<td>Olodaterol (LABA)</td>
<td>COPD</td>
<td>Inhale 2 puffs once daily</td>
<td>MDI</td>
</tr>
<tr>
<td>Arcapta Neohaler</td>
<td>Indacaterol (LABA)</td>
<td>COPD</td>
<td>Inhale 1 cap BID</td>
<td>Cap</td>
</tr>
<tr>
<td>Incruse Ellipta</td>
<td>Umeclidinium bromide (LAMA)</td>
<td>COPD</td>
<td>Inhale once daily</td>
<td>DPI</td>
</tr>
<tr>
<td>Seebri Neohaler</td>
<td>Glycopyrrolate (LAMA)</td>
<td>COPD</td>
<td>Inhale 1 cap BID</td>
<td>Cap</td>
</tr>
<tr>
<td>Arnuity Ellipta</td>
<td>Fluticasone furoate (ICS)</td>
<td>Asthma</td>
<td>Inhale once daily</td>
<td>DPI</td>
</tr>
</tbody>
</table>

ICS: Inhaled corticosteroid; LABA: Long-acting beta-agonist; LAMA: Long-acting muscarinic antagonist
DPI: Dry powder inhaler; MDI: Metered dose inhaler; Cap: Inhaled capsule

Micromedex® 2.0, (electronic version). Truven Health Analytics, Greenwood Village, Colorado, USA. Available at:
http://www.micromedexsolutions.com/ (cited: 03/30/2016)
# Hepatitis C Treatments

<table>
<thead>
<tr>
<th>Approved</th>
<th>Brand</th>
<th>Generic</th>
<th>Class</th>
<th>Approved Genotype</th>
<th>Dosing Frequency</th>
<th>Combo with</th>
<th>Cost (AWP), 12 wks</th>
</tr>
</thead>
<tbody>
<tr>
<td>2001</td>
<td>PegIntron</td>
<td>Peginterferon alfa-2b</td>
<td>Interferon</td>
<td>All</td>
<td>SQ Weekly</td>
<td>RBV</td>
<td>$10,831-12,538</td>
</tr>
<tr>
<td>2002</td>
<td>Pegasys</td>
<td>Peginterferon alfa-2a</td>
<td>Interferon</td>
<td>All</td>
<td>SQ Weekly</td>
<td>RBV</td>
<td>$12,477.84</td>
</tr>
<tr>
<td>2002</td>
<td>Copegus</td>
<td>Ribavirin (RBV)</td>
<td>Nucleoside analog</td>
<td>1, all*</td>
<td>Oral BID</td>
<td>Peginterferon (PEG)</td>
<td>$690.48-5004.72</td>
</tr>
<tr>
<td>2011, May</td>
<td>Victrelis</td>
<td>Boceprevir</td>
<td>PI: NS3/4A</td>
<td>1</td>
<td>Oral TID</td>
<td>PEG + RBV</td>
<td>$6017.76</td>
</tr>
<tr>
<td>2013, Nov</td>
<td>Olysio</td>
<td>Simeprevir</td>
<td>PI: NS3/4A</td>
<td>1, 4*</td>
<td>Oral daily</td>
<td>PEG + RBV</td>
<td>$79,632</td>
</tr>
<tr>
<td>2013, Dec</td>
<td>Sovaldi</td>
<td>Sofosbuvir</td>
<td>Poly I: NS5B</td>
<td>1,2,3,4, 5*,6*</td>
<td>Oral daily</td>
<td>RBV +/- PEG</td>
<td>$100,800</td>
</tr>
<tr>
<td>2013, Dec</td>
<td>Harvoni</td>
<td>Lediprasvir</td>
<td>NS5A Inhibitor</td>
<td>1</td>
<td>Oral daily</td>
<td>None</td>
<td>$113,400</td>
</tr>
<tr>
<td>2014, Dec</td>
<td>Viekira Pak</td>
<td>Ombitasvir</td>
<td>NS5A inhibitor</td>
<td></td>
<td>2 tabs oral daily</td>
<td>+/- RBV</td>
<td>$99,983.52</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Paritaprevir</td>
<td>PI: NS3/4A</td>
<td>1</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Ritonavir</td>
<td>Booster</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Dasabuvir</td>
<td>Poly I: NS5B</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2015, July</td>
<td>Daklinza</td>
<td>Daclatasvir</td>
<td>NS5A inhibitor</td>
<td>3</td>
<td>Oral daily</td>
<td>None</td>
<td>$75,600</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Sofosbuvir</td>
<td>Poly I: NS5B</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2015, July</td>
<td>Technivie</td>
<td>Ombitasvir</td>
<td>NS5A inhibitor</td>
<td>4 without cirrhosis</td>
<td>2 tabs oral daily</td>
<td>None</td>
<td>$91,983.36</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Paritaprevir</td>
<td>PI: NS3/4A</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Ritonavir</td>
<td>Booster</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*Off label
PI: Protease Inhibitor
Poly I: Polymerase Inhibitor

### Antiplatelet: Vorapaxar (Zontivity®) – May 2014

<table>
<thead>
<tr>
<th><strong>FDA approved indication(s):</strong></th>
<th>Reduction of thrombotic cardiovascular events in patients with history of MI or with peripheral arterial disease</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Drug Class</strong></td>
<td>Protease-activated receptor antagonist</td>
</tr>
<tr>
<td><strong>Mechanism of Action</strong></td>
<td>Inhibits thrombin-induced and thrombin receptor agonist peptide (TRAP)-induced platelet aggregation</td>
</tr>
<tr>
<td><strong>Dosing</strong></td>
<td>1 tablet (2.08 mg) po once daily</td>
</tr>
<tr>
<td><strong>Adverse Effects</strong></td>
<td>Bleeding, anemia, depression, rash</td>
</tr>
</tbody>
</table>
Vorapaxar (Zontivity®): Considerations and Bottom Line

- Reduces risk of CV death, MI, stroke, or urgent revascularization in addition to standard of care in post-MI or PAD patients
- No antidote, platelet inhibition lasts ≥4 weeks after discontinuation

**Consider in:**
- Patients who fail clopidogrel or aspirin therapy for prevention of thrombotic cardiovascular events as add-on

**Avoid/caution in:**
- Anticoagulant use
- Strong CYP3A4 inhibitors or inducers
- Contraindicated in hx of stroke, TIA, or intracranial hemorrhage

MI: Myocardial infarction; PAD: Peripheral artery disease, TIA: transient ischemic attack
Weight Loss: Bupropion SR/Naltrexone SR (Contrave®) – Sept. 2014

| FDA approved indication(s):                                                                 | • Adjunct to diet and exercise  
|                                                                                     | • Chronic weight management in adults with an initial body mass index (BMI) of:  
|                                                                                     |   • ≥ 30 kg/m² (obese) or  
|                                                                                     |   • ≥ 27 kg/m² (overweight) plus at least one weight-related comorbidity (e.g., HTN, Type 2 DM, or dyslipidemia) |
| Drug Classes                                                                       | • Bupropion: weak inhibitor of neuronal uptake of dopamine and serotonin  
|                                                                                     | • Naltrexone: Opioid antagonists |
| Basic Mechanism of Action                                                          | • Decrease appetite through hypothalamic melanocortin system  
|                                                                                     | • Modulation of mesolimbic reward pathways |
| Usual Dosing                                                                       | • Titrate to 2 tablets (16 mg naltrexone/180 mg bupropion)  
|                                                                                     | BID over 4 weeks |

Bupropion SR/Naltrexone SR (Contrave®): Considerations

Adverse effects

- Nausea (21-43%)
- Constipation, headache, or vomiting (>10%)
- Dizziness, insomnia, dry mouth, diarrhea (>5%)
- Increases BP and HR
- Contraindications:
  - Suicidal ideation
  - Seizure history
  - Uncontrolled HTN
  - Chronic opioid use

Drug interactions

- Inhibits CYP2D6
- Affected by CYP2B6 inhibitors/inducers
- MAOIs

Clinical Benefits

- 5% weight loss
- D/C if not achieved within 12 weeks

Effect on cardiovascular morbidity and mortality not yet established
Bupropion SR/Naltrexone SR (Contrave®): The Bottom Line

- Comparable to other long-term medications for weight loss

**Consider in:**
- Obese/overweight with risk factors who have not reached goal with lifestyle modifications alone
- Uncontrolled depression
- History of addictive behavior

**Avoid/caution in:**
- Uncontrolled HTN
- Seizure disorder
- Drug/alcohol withdrawal
- Chronic opioid use
- CYP2D6 substrates
- CYP2B6 inhibitors/inducers:
  - Clopidogrel
  - Protease inhibitors
**Weight Loss: Liraglutide (Saxenda®) – December 2014**

| **FDA approved indication(s):** | • Adjunct to a reduced-calorie diet and increased physical activity  
• Chronic weight management in adults with an initial body mass index (BMI) of:  
  • ≥ 30 kg/m² (obese) or  
  • ≥ 27 kg/m² (overweight) plus at least one weight-related comorbidity (e.g., HTN, Type 2 DM, or dyslipidemia) |
<table>
<thead>
<tr>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Drug Class</strong></td>
<td>• GLP-1 agonist</td>
</tr>
</tbody>
</table>
| **Basic Mechanism of Action** | • Slows gastric emptying  
• Enhances satiety  
• ↑ Glucose-dependent insulin secretion  
• ↓ Glucose-dependent glucagon secretion |
| **Usual Dosing**              | • Slowly titrate to 3mg subQ daily over 5 weeks                                                               |

Liraglutide (Saxenda®): Considerations

<table>
<thead>
<tr>
<th>Adverse effects</th>
<th>Clinical Benefits</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nausea (39%)</td>
<td>4% weight loss</td>
</tr>
<tr>
<td>Diarrhea (21%)</td>
<td>D/C if not achieved within 16 weeks</td>
</tr>
<tr>
<td>Constipation (19%)</td>
<td>Decreases A1c in DM type 2</td>
</tr>
<tr>
<td>Vomiting (16%)</td>
<td></td>
</tr>
<tr>
<td>Dyspepsia 9.6%</td>
<td></td>
</tr>
<tr>
<td>Acute pancreatitis</td>
<td></td>
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<tr>
<td>Gallbladder disorder</td>
<td></td>
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<tr>
<td>Black Box:</td>
<td></td>
</tr>
<tr>
<td>Thyroid C-cell Tumor</td>
<td></td>
</tr>
<tr>
<td>(Medullary thyroid carcinoma)</td>
<td></td>
</tr>
</tbody>
</table>

Effect on cardiovascular morbidity and mortality not yet established
Liraglutide (Saxenda®): The Bottom Line

- Comparable to other long-term medications for weight loss
- Most expensive weight loss medication
- Additional weight loss from 1.8mg dose but no additional A1c lowering

**Consider in:**
- Obese/overweight with risk factors who have not reached goal with lifestyle modifications alone
- Type 2 diabetes not on GLP-1 agonist

**Avoid/caution in:**
- Severe renal dysfunction
- History of thyroid cancer
- History of pancreatitis
- History of gastroparesis
Briviact (brivaracetam) - Epilepsy

- **Briviact** (brivaracetam) Tablets, Solution and Injection
  - Company: UCB, Inc.
  - Date of Approval: February 19, 2016
  - Treatment for: Epilepsy

- Briviact (brivaracetam) is a selective, high-affinity synaptic vesicle protein 2A ligand and analog of levetiracetam indicated for the treatment of partial-onset seizures in patients with epilepsy.

- **FDA Approves Briviact (brivaracetam) to Treat Partial Onset Seizures** - February 19, 2016

- **UCB Announces US and EU Regulatory Filings for the Investigational Antiepileptic Drug Brivaracetam** - January 21, 2015

- **Briviact FDA Approval History**
Plaque Psoriasis

- **Taltz (ixekizumab) Injection**
  - Company: Eli Lilly and **Company**
  - Date of Approval: March 22, 2016
  - Treatment for: **Plaque Psoriasis**

- Taltz (ixekizumab) is a humanized interleukin-17A antagonist indicated for the treatment of adults with moderate-to-severe plaque psoriasis.

- **FDA Approves Taltz (ixekizumab) for Plaque Psoriasis** - March 22, 2016
- **Taltz FDA Approval History**
Plaque Psoriasis

- **Sernivo** (betamethasone dipropionate) Topical Spray
  - Company: Promius Pharma, LLC
  - Date of Approval: February 5, 2016
  - Treatment for: Plaque Psoriasis

- Sernivo Spray (betamethasone dipropionate) is a topical corticosteroid indicated for the treatment of mild to moderate plaque psoriasis.

- **Promius Pharma Receives FDA Approval for Sernivo (betamethasone dipropionate) Spray** - February 7, 2016

- **Sernivo FDA Approval History**
APAP Overdose

- **Cetylev** (acetylcysteine) Effervescent Tablets for Oral Solution
- Company: Arbor Pharmaceuticals, LLC
  Date of Approval: January 29, 2016
  Treatment for: Acetaminophen Overdose

- Cetylev (acetylcysteine) is an antidote for acetaminophen overdose indicated to prevent or lessen liver damage after the ingestion of a potentially hepatotoxic quantity of acetaminophen.

- Arbor Pharmaceuticals Announces FDA Approval of Cetylev - February 9, 2016
- Cetylev FDA Approval History
Hep C

- **Zepatier** (elbasvir and grazoprevir) Tablets
  - Company: Merck & Co., Inc.
  - Date of Approval: January 28, 2016
  - Treatment for: **Chronic Hepatitis C**

- Zepatier (elbasvir and grazoprevir) is a once-daily, single tablet, NS5A replication complex inhibitor and NS3/4A protease inhibitor combination for the treatment of chronic hepatitis C virus (HCV) genotypes 1 and 4 infections.

- **FDA Approves Zepatier (elbasvir and grazoprevir) for Chronic Hepatitis C Genotypes 1 and 4** - January 28, 2016

- **Merck Announces FDA Acceptance of NDA for Grazoprevir/Elbasvir for Chronic Hepatitis C Genotypes 1, 4 and 6 Infection** - July 28, 2015

- **Merck Submits NDA for Grazoprevir/Elbasvir for Chronic Hepatitis C Genotypes 1, 4, and 6 Infection** - May 28, 2015

- **Zepatier FDA Approval History**
Hep C – Harvoni expanded indication

- **Harvoni** (ledipasvir and sofosbuvir)
- New Indication Approved: November 12, 2015

- FDA Approves New Indications for Harvoni to Include Patients with Genotypes 4, 5 and 6 HCV and Patients Co-Infected with HIV
- Harvoni (ledipasvir and sofosbuvir) FDA Approval History
Narcan (naloxone) Nasal Spray

- Date of Approval: November 18, 2015
- Company: Adapt Pharma, Inc.
- Treatment for: Opioid Overdose

Narcan Nasal Spray (naloxone) is an intranasal opioid antagonist formulation indicated for the emergency treatment of known or suspected opioid overdose.

- FDA Approves Narcan (naloxone) Nasal Spray to Treat Opioid Overdose
- Narcan (naloxone) FDA Approval History
Migraine

- **Zembrace SymTouch** (sumatriptan) Injection
- Company: Dr. Reddy’s Laboratories Ltd.
  Date of Approval: January 28, 2016
  Treatment for: **Migraine**

- Zembrace SymTouch (sumatriptan) is a selective 5-HT$_{1B/ID}$ receptor agonist in a prefilled, ready-to-use, single-dose disposable autoinjector for the treatment of acute migraine episodes, with or without aura.

- **Dr. Reddy’s Laboratories Ltd. Receives FDA Approval for Zembrace SymTouch (sumatriptan succinate) Injection for the Acute Treatment of Migraines** - January 29, 2016

- **Zembrace SymTouch FDA Approval History**
Migraine

- **Onzetra Xsail** (sumatriptan) Inhalation Powder - formerly AVP-825
  - Company: Avanir Pharmaceuticals, Inc.
  - Date of Approval: January 27, 2016
  - Treatment for: Migraine

- Onzetra Xsail (sumatriptan) is a fast-acting, intranasal serotonin 5-HT_{1B/1D} receptor agonist (triptan) indicated for the acute treatment of migraine with or without aura.

- **FDA Approves Onzetra Xsail (sumatriptan nasal powder) for the Acute Treatment of Migraine** - January 28, 2016
- **Avanir Pharmaceuticals Receives Complete Response Letter (CRL) from FDA on AVP-825 NDA** - November 26, 2014
- **Avanir Pharmaceuticals Announces Preliminary Feedback from the FDA on AVP-825 for the Acute Treatment of Migraine** - November 7, 2014
- **Avanir Pharmaceuticals Announces Publication of Pivotal Phase III Results from AVP-825 Acute Migraine Study** - October 30, 2014
- **Avanir Pharmaceuticals Announces Acceptance of NDA for AVP-825 for the Acute Treatment of Migraine** - March 26, 2014
- **Avanir Pharmaceuticals Announces Submission of New Drug Application for AVP-825 for the Acute Treatment of Migraine** - January 30, 2014
- **Onzetra Xsail FDA Approval History**
ADHD

- **Adzenys XR-ODT** (amphetamine) Extended-Release Orally Disintegrating Tablets
  - Company: Neos Therapeutics, Inc.
  - Date of Approval: January 27, 2016
  - Treatment for: **Attention-Deficit Hyperactivity Disorder (ADHD)**

- Adzenys XR-ODT (amphetamine) is a central nervous system (CNS) stimulant indicated for the treatment of Attention Deficit Hyperactivity Disorder (ADHD) in patients 6 years and older.

- Neos Therapeutics Announces FDA Approval of Adzenys XR-ODT (Amphetamine Extended-Release Orally Disintegrating Tablet) for ADHD - January 27, 2016

- Adzenys XR-ODT FDA Approval History
ADHD

- **QuilliChew ER** (methylphenidate hydrochloride) Extended Release Chewable Tablets
- **Date of Approval:** December 7, 2015
  **Company:** Pfizer Inc.
  **Treatment for:** Attention Deficit Hyperactivity Disorder

QuilliChew ER (methylphenidate hydrochloride) is a central nervous system (CNS) stimulant indicated for the treatment of Attention Deficit Hyperactivity Disorder (ADHD).

- **Pfizer Receives FDA Approval for QuilliChew ER (methylphenidate hydrochloride) Extended-Release Chewable Tablets**
- **QuilliChew ER (methylphenidate hydrochloride) FDA Approval History**
ADHD

- **Dyanavel XR** (amphetamine) Extended-Release Oral Suspension
- Date of Approval: October 19, 2015
  Company: Tris Pharma, Inc.
  Treatment for: **Attention Deficit Hyperactivity Disorder (ADHD)**

- Dyanavel XR (amphetamine) is an extended-release central nervous system (CNS) stimulant in an oral suspension formulation for the treatment of Attention Deficit Hyperactivity Disorder (ADHD).

- **Tris Pharma Receives FDA Approval of Dyanavel XR (amphetamine) Once-Daily Liquid for ADHD in Children**
- **Dyanavel XR (amphetamine) FDA Approval History**
Pain - OA

- **Vivlodex** (meloxicam) Capsules
- Date of Approval: October 22, 2015
  Company: Iroko Pharmaceuticals, LLC
- Treatment for: **Osteoarthritis**

- Vivlodex (meloxicam) is a low dose nonsteroidal anti-inflammatory drug (NSAID) indicated for the management of osteoarthritis pain.
- [FDA Approves Vivlodex (meloxicam) for Osteoarthritis Pain](#)
- [Vivlodex (meloxicam) FDA Approval History](#)
Vaccinations

- **Gardasil 9** (human papillomavirus 9-valent vaccine, recombinant)


- FDA Approves Expanded Age Indication for Gardasil 9 in Males
- Gardasil 9 (human papillomavirus 9-valent vaccine, recombinant) FDA Approval History
Fluad (influenza vaccine, adjuvanted) Injection

Date of Approval: November 24, 2015
Company: Seqirus
Treatment for: Influenza Prophylaxis

Fluad (influenza vaccine, adjuvanted) is an inactivated influenza vaccine indicated for the prevention of seasonal influenza in people 65 years of age and older.

FDA Approves Fluad (influenza vaccine, adjuvanted) for Prevention of Seasonal Influenza

Fluad (influenza vaccine, adjuvanted) FDA Approval History
Gout

- **Zurampic** (lesinurad) Tablets
  - Company: AstraZeneca Pharmaceuticals LP
  - Date of Approval: December 22, 2015
  - Treatment for: **Hyperuricemia Associated with Gout**

  Zurampic (lesinurad) is a URAT1 inhibitor indicated for the combination treatment of hyperuricemia associated with gout.

  - [FDA Approves Zurampic (lesinurad) to Treat High Blood Uric Acid Levels Associated with Gout](#) - December 22, 2015
  - [FDA Advisory Committee Recommends the Approval of Lesinurad for Gout Patients](#) - October 23, 2015
  - [Zurampic FDA Approval History](#)
Asthma (Eosinophilic)

Nucala (mepolizumab) Injection
Date of Approval: November 4, 2015
Company: GlaxoSmithKline plc
Treatment for: Asthma

Nucala (mepolizumab) is an interleukin-5 antagonist monoclonal antibody (IgG1 kappa) indicated for the add-on maintenance treatment of patients with severe eosinophilic asthma.

• FDA Approves Nucala (mepolizumab) to Treat Severe Asthma

Nucala (mepolizumab) FDA Approval History
Cinqair (reslizumab) Injection

Company: Teva Pharmaceutical Industries Ltd.
Date of Approval: March 23, 2016
Treatment for: Asthma

Cinqair (reslizumab) is an interleukin 5 antagonist monoclonal antibody (IgG4 kappa) indicated for add-on maintenance treatment of patients with eosinophilic asthma.

FDA Approves Cinqair (reslizumab) to Treat Severe Asthma - March 23, 2016

FDA Advisory Committee Recommends Approval of Teva’s Asthma Biologic Reslizumab - December 10, 2015

Cinqair FDA Approval History
Diabetes

- **Basaglar** (insulin glargine) Injection

  - Company: Eli Lilly and Company and Boehringer Ingelheim
  - Date of Approval: December 16, 2015
  - Treatment for: **Diabetes Type 1, Diabetes Type 2**

  - Basaglar (insulin glargine injection) is a long-acting human insulin analog indicated to improve glycemic control in patients with type 1 and type 2 diabetes mellitus.

  - **FDA Approves Basaglar (insulin glargine) for Type 1 and Type 2 Diabetes** - December 17, 2015

  - **Basaglar FDA Approval History**
Antipsychotic: Brexpiprazole (Rexulti®) – July 2015

| FDA approved indication(s): | • Adjunct therapy to antidepressants for major depressive disorder (MDD)  
|                            | • Treatment of schizophrenia |
| Drug Class                 | • Atypical antipsychotic     |
| Basic Mechanism of Action  | • Efficacy may be mediated through partial agonist activity at and 5-HT<sub>1A</sub> and D<sub>2</sub> receptors and antagonist activity at 5-HT<sub>2A</sub> receptors. |
| Dosing (once daily)        | | |
|                           | Initial | Recommended | Max |
| MDD                       | 0.5-1mg/day | 2mg/day | 3mg/day |
| Schizophrenia             | 1mg/day | 2-4mg/day | 4mg/day |
| Adverse effects           | • Weight gain, akathisia  
|                           | • Somnolence, constipation, tremor |

Brexpiprazole (Rexulti®): The Bottom Line

- “Me-too” atypical antipsychotic

**Consider in:**
- Schizophrenia who are uncontrolled on conventional therapy
- MDD not controlled on optimally dosed antidepressant therapy

**Avoid/caution in:**
- Elderly patients with dementia-related psychosis
- CYP2D6 and CYP3A4 inhibitors and inducers
Antipsychotic: Cariprazine (Vraylar®) – Sept 2015

| FDA approved indication(s): | • Treatment of adults with:  
| | • Schizophrenia  
| | • Bipolar I disorder (acute treatment of manic or mixed episodes) |
| Drug Class | • Atypical antipsychotic |
| Basic Mechanism of Action | • Efficacy may be mediated through a combination of partial agonist activity at central dopamine (D$_3$) and 5-HT$_{1A}$ receptors and antagonist activity at 5-HT$_{2A}$ receptors. |
| Dosing (once daily) | Initial | Recommended |
| Schizophrenia | 1.5 mg/day | 1.5 – 6 mg/day |
| Bipolar Mania | 1.5 mg/day daily | 3 – 6 mg/day |
| Adverse Effects | • Akathisia, nausea, constipation  
| | • Tremor (high dose) |

Cariprazine (Vraylar®): Considerations and Bottom Line

- Higher affinity for $D_3$ receptors than other atypical antipsychotics
- Less affinity for $H_1$ and $5-HT_{2C}$ receptors may result in less metabolic and QT prolonging effects
- May have late occurring adverse reactions

**Consider in:**
- Schizophrenia or acute episode of Bipolar I who are uncontrolled on conventional therapy
- Metabolic and/or QT prolonging effects are especially concerning

**Avoid/caution in:**
- Elderly patients with dementia-related psychosis
- CYP3A4 inhibitors and inducers