New Drug Update 2015
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SDSU College of Pharmacy
Rapid City Regional Hospital

Pharmacist Objectives
Following this presentation, pharmacists will be able to:
- Identify therapeutic indications and pharmacological properties of specific drugs recently approved by the FDA.
- List side effects, warnings, precautions and significant drug interactions associated with each medication.
- Identify the normal dose and dosage forms of the drugs presented.
- Demonstrate an understanding of how to effectively educate patients who are prescribed each medication.
- Describe how the new drugs presented will be used in clinical practice.

Technician Objectives
Following this presentation, pharmacy technicians will be able to:
- Identify new drugs approved by the FDA and their classification.
- Identify the major uses for the drugs presented.
- Identify the usual dose and route of administration for each medication.
- List the cost associated with each of the new drugs approved by the FDA.

New Drug Approval Trends
ndApproved/DrugandBiologicApprovalReports/NDAandBLAApprovalReports/UCM406851.pdf

Agenda
- Edoxaban (Savaysa™)
- Ivabradine (Corlanor®)
- Sacubitril/valsartan (Entresto™)
- Ceftazidime/avibactam (Avycaz®)
- Ceftolozane/tazobactam (Zerbaxa™)
- Sofosbuvir & ledipasvir (Harvoni®)
- Paritaprevir/ritonovir, omibasvir, dasabuvir (Viekira®)
- Alirocumab (Praluent®)
- Evolocumab (Repatha™)
- Fibanserin (Addyi™)
- Naloxegol (Movantik™)
- Eluxadoline (Viberzi™)
- Dantrolene (Ryanodex®)

“I have had no financial relationship over the past 12 months with any commercial sponsor with a vested interest in this presentation”
Edoxaban should NOT be used in A. fib if:

1. CrCl is < 30 ml/min
2. CrCl is < 50 ml/min
3. CrCl is > 95 ml/min

Edoxaban (Savaysa™)
- **Indication**
  - Reduce stroke and systemic embolism in non-valvular atrial fibrillation
  - Treatment of DVT & PE AFTER 5-10 days of a parenteral anticoagulant
- **Pharmacology**
  - Factor Xa inhibitor

### Pharmacokinetic comparison of oral Factor Xa inhibitors

<table>
<thead>
<tr>
<th></th>
<th>Edoxaban</th>
<th>Apixaban</th>
<th>Rivaroxaban</th>
</tr>
</thead>
<tbody>
<tr>
<td>Peak effect</td>
<td>1-2h</td>
<td>3-4h</td>
<td>2-4h</td>
</tr>
<tr>
<td>T ½</td>
<td>10-14h</td>
<td>~ 12h</td>
<td>5-9h</td>
</tr>
<tr>
<td>Renal clearance</td>
<td>50%</td>
<td>~ 27%</td>
<td>~ 36%</td>
</tr>
<tr>
<td>Metabolism</td>
<td>Minimal</td>
<td>CYP3A4</td>
<td>CYP3A4</td>
</tr>
</tbody>
</table>

### Edoxaban (Savaysa™)
- **Warnings and precautions**
  - Not recommended in mechanical heart valves or moderate to severe mitral stenosis
  - Not recommended for use in non-valvular atrial fibrillation IF the creatinine clearance is > 95 ml/min
  - Not studied in CrCl < 15 ml/min

### Bleeding Rates in Atrial Fibrillation with CrCl ≤ 95 ml/min

<table>
<thead>
<tr>
<th>Bleeding Event</th>
<th>Edoxaban 60 mg n = 5417</th>
<th>Warfarin n = 5485</th>
<th>HR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Major</td>
<td>3.1%</td>
<td>3.7%</td>
<td>0.84 (0.73, 0.97)</td>
</tr>
<tr>
<td>Intracranial hemorrhage</td>
<td>0.5%</td>
<td>1%</td>
<td>0.44 (0.32, 0.61)</td>
</tr>
<tr>
<td>GI bleeding</td>
<td>1.8%</td>
<td>1.3%</td>
<td>1.4 (1.13, 1.73)</td>
</tr>
<tr>
<td>Fatal bleeding</td>
<td>0.2%</td>
<td>0.4%</td>
<td>0.51 (0.3, 0.86)</td>
</tr>
</tbody>
</table>

Savaysa PI 2015.
### Bleeding Rates in VTE

<table>
<thead>
<tr>
<th>Bleeding Event</th>
<th>Edoxaban 60 mg N = 4118</th>
<th>Warfarin N = 4122</th>
<th>HR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clinically Relevant bleeding</td>
<td>8.5%</td>
<td>10.3%</td>
<td>0.81 (0.71, 0.94)</td>
</tr>
<tr>
<td>Major bleeding</td>
<td>1.4%</td>
<td>1.6%</td>
<td>0.84 (0.59, 1.21)</td>
</tr>
<tr>
<td>Intracranial hemorrhage</td>
<td>0.1%</td>
<td>0.3%</td>
<td>NR</td>
</tr>
<tr>
<td>Fatal bleeding</td>
<td>&lt; 0.1%</td>
<td>0.2%</td>
<td>NR</td>
</tr>
</tbody>
</table>

### Efficacy Data in Atrial Fibrillation vs. Warfarin

#### ENGAGE AF-TIMI 48 Trial

<table>
<thead>
<tr>
<th></th>
<th>Edoxaban 60 mg N = 7012</th>
<th>Warfarin N = 7012</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stroke or systemic embolic event</td>
<td>1.18%</td>
<td>1.5%</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

#### Efficacy Data in VTE vs. Warfarin

#### Hokusai-VTE Trial

<table>
<thead>
<tr>
<th></th>
<th>Edoxaban 60 mg N = 4118</th>
<th>Warfarin N = 4122</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>1st recurrent VTE or VTE-related death</td>
<td>3.2%</td>
<td>3.5%</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

### Edoxaban (Savaysa™)

#### Dosing
- **Atrial fibrillation**
  - 60 mg daily for CrCl 51-95 ml/min
  - 30 mg daily for CrCl 15-50 ml/min
- **DVT/PE treatment**
  - 60 mg daily
  - 30 mg daily for CrCl 15-50 ml/min or body weight ≤ 60 kg or on certain P-gp inhibitors

### Edoxaban (Savaysa™)

#### Transitioning to edoxaban:
- From warfarin
  - Start when INR < 2.5
- From any other oral anticoagulant or a LMWH
  - Start at next scheduled dose
- From heparin
  - Turn off heparin and start 4 hours later

### Edoxaban (Savaysa™)

#### Transitioning from edoxaban:
- To warfarin
  - Start warfarin and taper edoxaban
    - If on 60 mg decrease to 30 mg
    - If on 30 mg decrease to 15 mg
    - Draw INR immediately prior to edoxaban dose--when INR is > 2 stop edoxaban
  - To any other oral agent, LMWH, or heparin
    - Start alternative agent at time of next scheduled edoxaban dose

### Edoxaban (Savaysa™)

#### Bottom line
- Non-inferior to warfarin for stroke prevention in atrial fibrillation and for DVT/PE treatment
- Use of heparin/LMWH for 5-10 days prior to DVT/PE tx may limit use
- Watch renal function—high and low!
- No specific reversal agent...yet...

#### Additional review
Ivabradine works for heart failure by:
1. Increasing contractility
2. Increasing urine output
3. Slowing the heart rate
4. Reducing afterload

Ivabradine (Corlanor®)

- **Indication**
  - Reduce the risk of hospitalization for worsening heart failure in patients with:
    - Stable, symptomatic chronic heart failure
    - EF ≤ 35%
    - Sinus rhythm
    - Resting heart rate of ≥ 70 BPM
    - On maximum beta-blocker or contraindication to beta-blocker

- **Pharmacology**
  - Inhibits the I$_f$ “funny” current
  - Slows heart rate
  - Effects more pronounced at higher baseline heart rates
  - Does not affect contractility or blood pressure

- **Pharmacokinetics**
  - Cmax in ~ 1 hour
  - Food increases absorption (20-40%)
  - Effective t $\frac{1}{2}$ ~ 6 hours; active metabolite ~ 11 hours
  - CYP3A4 metabolism

- **Contraindications**
  - Resting HR < 60 BPM at initiation
  - BP < 90/50 mmHg
  - Acute decompensated heart failure
  - Sick sinus syndrome
  - Heart block
  - Severe hepatic impairment
  - Moderate-strong CYP3A4 inhibitors or inducers

- **Warnings and precautions**
  - Fetal toxicity
  - Risk of atrial fibrillation (5% vs 3.9% placebo per year)
  - Bradycardia (6% vs. 1.3% placebo per year)

- **Drug interactions**
  - CYP3A4 inducers and inhibitors
### Adverse Reactions from the SHIFT trial

<table>
<thead>
<tr>
<th>Reaction</th>
<th>Ivabradine n = 3232</th>
<th>Placebo n = 3260</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Symptomatic bradycardia</td>
<td>5%</td>
<td>1%</td>
<td>&lt; 0.0001</td>
</tr>
<tr>
<td>Asymptomatic bradycardia</td>
<td>6%</td>
<td>1%</td>
<td>&lt; 0.0001</td>
</tr>
<tr>
<td>Atrial fibrillation</td>
<td>9%</td>
<td>8%</td>
<td>0.012</td>
</tr>
<tr>
<td>Phosphenes*</td>
<td>3%</td>
<td>1%</td>
<td>&lt; 0.0001</td>
</tr>
</tbody>
</table>

*Transient enhanced brightness in a restricted area of the visual field. Lancet. 2010 Sep 11;376:875-85

### Clinical Efficacy from SHIFT trial

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Ivabradine n = 3241</th>
<th>Placebo n = 3264</th>
<th>HR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>CV death or hospital admit for worsening HF*</td>
<td>24%</td>
<td>29%</td>
<td>0.82 (0.75-0.90)</td>
</tr>
<tr>
<td>Hospital admit for worsening heart failure</td>
<td>16%</td>
<td>21%</td>
<td>0.74 (0.66-0.83)</td>
</tr>
<tr>
<td>Death from heart failure</td>
<td>3%</td>
<td>5%</td>
<td>0.74 (0.58-0.94)</td>
</tr>
<tr>
<td>All-cause mortality</td>
<td>16%</td>
<td>17%</td>
<td>0.9 (0.80-1.02)</td>
</tr>
</tbody>
</table>

*primary endpoint Lancet. 2010 Sep 11;376:875-85

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### Ivabradine (Corlanor®)

- **Dosing**
  - 5mg PO BID with meals
  - If after 2 weeks:
    - HR is > 60 BPM increased to 7.5mg BID
    - HR 50-60 BPM remain at 5mg BID
    - HR < 50 BPM decrease to 2.5mg BID
    - May start at 2.5 mg BID if concerned about bradycardia
- **Cost:** ~ $375/month

Corlanor PI 2015

### Ivabradine (Corlanor®)

- **Bottom line**
  - May be used for heart failure AFTER beta-blockers optimized
  - No effect on blood pressure, monitor heart rate
  - Prevents 1 in 25 patients from being hospitalized over 2 years
- **Additional review**

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### Sacubitril should NOT be used with:

1. HCTZ
2. Lisinopril
3. Spironolactone
4. Metoprolol

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### Sacubitril/valsartan (Entresto™)

- **Indication**
  - NYHA Class II-IV to reduce risk of CV death and heart failure hospitalization
- **Pharmacology**
  - Neprilysin inhibitor
  - Blocks the break down of natriuretic peptides

Entresto PI 2015
**Pharmacokinetics**
- Peaks in ~ 2 hours
- T½ ~ 10 hours
- Valsartan has a higher bioavailability in Entresto vs. other formulations
- Sacubitril rapidly metabolized by esterases to active metabolite LBQ657
- Majority excreted via kidneys

**Contraindications**
- History of angioedema due to ACEI or ARB
- Concomitant use with an ACEI
- Avoid within 36 hours
- Concomitant use with aliskiren in diabetics

**Warnings and precautions**
- Hyperkalemia
- Pregnancy
- Hypotension

**Common Adverse Reactions in PARADIGM Trial**

<table>
<thead>
<tr>
<th>Adverse Reaction</th>
<th>Sacubitril/valsartan N = 4187</th>
<th>Enalapril N = 4212</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Symptomatic Hypotension</td>
<td>14%</td>
<td>9.2%</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Potassium &gt; 5.5 mmol/L</td>
<td>16.1%</td>
<td>17.3%</td>
<td>0.15</td>
</tr>
<tr>
<td>Cough</td>
<td>11.3%</td>
<td>14.3%</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Scr &gt; 2.5 mg/dl</td>
<td>3.3%</td>
<td>4.5%</td>
<td>0.007</td>
</tr>
</tbody>
</table>

**Key Outcomes from PARADIGM Trial**

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Sacubitril/valsartan N = 4187</th>
<th>Enalapril N = 4212</th>
<th>HR (95% CI)</th>
<th>NNT</th>
</tr>
</thead>
<tbody>
<tr>
<td><em>Death from CV cause or First hospitalization for worsening HF</em></td>
<td>21.8%</td>
<td>26.5%</td>
<td>0.8 (0.73-0.87)</td>
<td>21</td>
</tr>
<tr>
<td>Death from CV cause</td>
<td>13.3%</td>
<td>16.5%</td>
<td>0.8 (0.71-0.89)</td>
<td>32</td>
</tr>
<tr>
<td>First hospitalization for worsening HF</td>
<td>12.8%</td>
<td>15.6%</td>
<td>0.79 (0.71-0.89)</td>
<td>36</td>
</tr>
</tbody>
</table>

CV = cardiovascular
HF = heart failure
NNT = number need to treat

**Dosing**
- 49/51mg PO BID
- After 2-4 weeks increase to 97/103mg BID as tolerated
- May start at 24/26mg if:
  - Not previously on an ACEI or ARB (or on very low doses)
  - Severe renal impairment (< 30ml/min)
  - Moderate hepatic impairment

**Availability**
- Tablets
  - 24-26 mg
  - 49-51 mg
  - 97-103 mg

**Cost**
- ~ $500 for #60 tabs
- ~ $6000/year
Sacubitril/valsartan (Entresto™)

- **Bottom line**
  - Impressive trial results
  - Potential to become new standard for HF patients but some criticize trial design
  - On-going trials will further define role
  - Long-term safety?
  - Do not use with an ACE inhibitor
- **Additional review**

Avycaz will be used for ____ infections

1. MRSA
2. VRE
3. Gram negative
4. Anaerobic

Ceftazidime-Avibactam (Avycaz™)

- **Indication**
  - Complicated intra-abdominal (cIAI) with metronidazole and complicated urinary tract infections (cUTI)
  - Reserve for use in patients who have limited or no alternative treatment options
- **Pharmacology**
  - 3rd generation, antipseudomonal cephalosporin β-lactamase inhibitor inactivates some β-lactamases and protects ceftazidime from degradation

Adverse Reactions

<table>
<thead>
<tr>
<th></th>
<th>Phase 2 cIAI Trial</th>
<th>Phase 2 cUTI Trial</th>
</tr>
</thead>
<tbody>
<tr>
<td>Avycaz™ plus Metronidazole</td>
<td>Avycaz™</td>
<td>Avycaz™ plus Metronidazole</td>
</tr>
<tr>
<td>N=101</td>
<td>N=68</td>
<td>N=102</td>
</tr>
<tr>
<td>Vomiting</td>
<td>14%</td>
<td>5%</td>
</tr>
<tr>
<td>Nausea</td>
<td>10%</td>
<td>6%</td>
</tr>
<tr>
<td>Constipation</td>
<td>4%</td>
<td>1%</td>
</tr>
<tr>
<td>Abdominal Pain</td>
<td>8%</td>
<td>3%</td>
</tr>
<tr>
<td>Upper Abdominal Pain</td>
<td>1%</td>
<td>0%</td>
</tr>
</tbody>
</table>

Ceftazidime-Avibactam (Avycaz™)

- Avibactam enhances in vitro activity in presence of some β-lactamases
  - TEM
  - SHV
  - CTX-M
  - KPCs
  - AmpC
  - Certain oxacillinases (OXA)
- Not active against all β-lactamases
  - Metallo-β-lactamases
  - Gram negative bacteria that overexpress efflux pumps or have porin mutations

Ceftazidime-Avibactam (Avycaz™)

- **Clinical Studies**
  - Efficacy supported in part by previous findings of the efficacy and safety of ceftazidime for treatment of cIAI and cUTI
  - Contribution of avibactam was established in vitro and in animal models of infection
  - Limited trial data
Ceftazidime/Avibactam (Avycaz™)

- **Dosage**
  - 2.5 g IV q8h
  - 5-14 days for cIAI
  - In combination with metronidazole
  - 7-14 days for cUTI
  - Including pyelonephritis

Renal Dosing Adjustment

<table>
<thead>
<tr>
<th>Estimated CrCl (mL/min)</th>
<th>Recommended Dosage (infused over 2 hours)</th>
</tr>
</thead>
<tbody>
<tr>
<td>&gt;50</td>
<td>2.5 g IV Q8H</td>
</tr>
<tr>
<td>31-50</td>
<td>1.25 g IV Q8H</td>
</tr>
<tr>
<td>16-30</td>
<td>0.94 g IV Q12H</td>
</tr>
<tr>
<td>6-15</td>
<td>0.94 g IV Q24H</td>
</tr>
<tr>
<td>≤5</td>
<td>0.94 g IV Q48H</td>
</tr>
</tbody>
</table>

Ceftazidime/Avibactam (Avycaz™)

- **Bottom line**
  - Pooled analyses support avibactam as an effective extender of ceftazidime activity
  - Need adequate laboratory analysis to determine specific β-lactamase—likely reserved for KPC-producing bacteria
  - More research is needed to solidify efficacy and safety profile
- **Additional review**

Zerbaxa will be used for ____ infections

1. MRSA
2. VRE
3. Gram negative
4. Anaerobic

Ceftolozane/tazobactam (Zerbaxa™)

- **Indication**
  - Complicated intra-abdominal infections (with metronidazole) and complicated urinary tract infections
- **Pharmacology**
  - New cephalosporin combined with tazobactam (beta-lactamase inhibitor)

Ceftolozane/tazobactam (Zerbaxa™)

- **Gram negative**
  - *Enterobacter cloacae*
  - *E. coli*
  - *Klebsiella oxytoca, pneumonia*
  - *Proteus mirabilis*
  - *Pseudomonas aeruginosa*
  - *Bacteroides fragilis*
- **Gram positive**
  - *Streptococcus anginosus, constellatus, salivarius*
Ceftolozane/tazobactam (Zerbaxa™)

- Dosing
  - 1.5 gm (1 gm/0.5 gm) IV q8h
  - Infused over 1 hour
  - cIAI → 4-14 days
  - cUTI → 7 days
- Renal adjustments
  - CrCl 30-50 mL/min → 750 mg q8h
  - CrCl 15-29 mL/min → 375 mg q8h
  - ESRD on HD → single loading dose of 750 mg, followed by 150 mg (100 mg/50 mg) maintenance dose q8h for the remainder of the treatment period
  - On HD days, administer dose ASAP following completion of HD

Compared to the older agents the new hepatitis C medications:

1. Are less expensive
2. Have more side effects
3. Have more drug interactions
4. Require longer treatment duration

New Standard of Care for HCV in 2015 and Beyond

<table>
<thead>
<tr>
<th></th>
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<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Interferon + Ribavirin x 12m SVR ~ 25%</td>
<td>Peginterferon + Ribavirin x 12m SVR ~ 25%</td>
<td>Harvoni® or Viekira® x 2-6m SVR &gt; 90%</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>Interferon + Ribavirin x 12m SVR ~ 25%</td>
<td>Peginterferon + Ribavirin x 12m SVR ~ 25%</td>
<td>Peginterferon + Ribavirin x 12m SVR ~ 25%</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>Interferon + Ribavirin x 12m SVR ~ 25%</td>
<td>Peginterferon + Ribavirin x 12m SVR ~ 25%</td>
<td>Peginterferon + Ribavirin x 12m SVR ~ 25%</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

- Interferon + Ribavirin
- Peginterferon + Ribavirin
- Harvoni® or Viekira®

GT, genotype; P/R, peginterferon/ribavirin
Clinical Significance of Newer Agents

- Significant adverse effects with current CHC medications
  - Ribavirin: hemolytic anemia, fatigue, nausea, headache
  - Interferon and PEG-interferon: flu-like symptoms
- Simple combination regimen
- Enables shorter duration of treatment
- U.S. Preventative Services Task Force: Screen adults born between 1945-1965 for HCV
  - Increased identification of CHC genotype 1 positive patients

Sofosbuvir & Ledipasvir (Harvoni®)

- Indication
  - Genotype 1 hepatitis C
- Mechanism of action
  - Sofosbuvir
    - HCV NS5B RNA polymerase inhibitor
  - Ledipasvir
    - NS5A protein inhibitor

Sofosbuvir & Ledipasvir (Harvoni®) — ION-2 Study

<table>
<thead>
<tr>
<th></th>
<th>SVR12, %</th>
<th>95% CI</th>
<th>95% CI</th>
<th>95% CI</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>LDV/SOF x 12 wks</td>
<td>94%</td>
<td>93%-96%</td>
<td>93%-94%</td>
<td>98%-100%</td>
<td>98%-100%</td>
</tr>
<tr>
<td>LDV/SOF + RBV x 12 wks</td>
<td>96%</td>
<td>95%-97%</td>
<td>95%-96%</td>
<td>99%</td>
<td>99%-100%</td>
</tr>
<tr>
<td>LDV/SOF x 24 wks</td>
<td>99%</td>
<td>98%-100%</td>
<td>99%-100%</td>
<td>100%</td>
<td>99%</td>
</tr>
<tr>
<td>LDV/SOF + RBV x 24 wks</td>
<td>99%</td>
<td>98%-100%</td>
<td>99%-100%</td>
<td>100%</td>
<td>99%</td>
</tr>
</tbody>
</table>

* = All treatment groups had SVR rates superior to adjusted historical response rate of 25% (p<0.001 for all comparisons)
† = One patient in LDV/SOF x 24 weeks withdrew consent after four weeks of treatment

Sofosbuvir & Ledipasvir (Harvoni®) — ION-3 Study

<table>
<thead>
<tr>
<th></th>
<th>SVR12, %</th>
<th>95% CI</th>
<th>95% CI</th>
<th>95% CI</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>LDV/SOF x 8 wks</td>
<td>94%</td>
<td>93%-96%</td>
<td>93%-94%</td>
<td>98%-100%</td>
<td>98%-100%</td>
</tr>
<tr>
<td>LDV/SOF + RBV x 8 wks</td>
<td>93%</td>
<td>92%-94%</td>
<td>93%-94%</td>
<td>98%</td>
<td>98%-99%</td>
</tr>
<tr>
<td>LDV/SOF x 12 wks</td>
<td>95%</td>
<td>95%-96%</td>
<td>95%-97%</td>
<td>99%</td>
<td>99%-100%</td>
</tr>
</tbody>
</table>

* = All treatment groups had SVR rates superior to adjusted historical control rate of 60% (p<0.001 for all comparisons)

Sofosbuvir & Ledipasvir (Harvoni®)

- Drug Interactions
  - Amiodarone — bradycardia
  - Potent P-gp inducers decrease ledipasvir & sofosbuvir plasma concentrations
  - Rifampin, St. John’s wort
  - Antacids/H2’s/PPIs decrease ledipasvir absorption
  - Other medications that can decrease sofosbuvir plasma concentrations
    - Carbamazepine
    - Phenytoin
    - Phenobarbital

Sofosbuvir & Ledipasvir (Harvoni®)

- **Dosage and Administration**
  - One tablet (400mg sofosbuvir/90mg ledipasvir) once daily
  - With or without food
  - May take in evening due to fatigue (13-18%) after administration
  - No dosage adjustment for hepatic dysfunction
  - Sofosbuvir metabolite may accumulate in renal impairment

Sofosbuvir & Ledipasvir (Harvoni®)

- **Bottom line**
  - One tablet, once daily treatment for hepatitis C
  - Cure rates of > 90%
  - Duration of 8-24 weeks
  - Additional review

Paritaprevir/ritonovir, ombitasvir, dasabuvir +/- ribavirin (Viekira®)

- **Indication**
  - Genotype 1 hepatitis C

Paritaprevir/ritonovir, ombitasvir, dasabuvir +/- ribavirin (Viekira®)

- **Pharmacology**
  - Ombitasvir: Inhibits NS5A polymerase
  - Paritaprevir: Inhibits NS3/4A protease
  - Dasabuvir: Inhibits NS5B RNA polymerase
  - Ritonovir: Increases paritaprevir levels thru CYP3A4 inhibition

Clinical Results—No cirrhosis

- **Clinical Results—Cirrhosis**

- **Clinical Results—No cirrhosis**

Paritaprevir/ritonovir, ombitasvir, dasabuvir +/- ribavirin (Viekira®)

- **Drug interactions**
  - Many, many, many
  - Need to utilize databases
  - Ritonavir inhibits CYP3A4
  - Ombitasvir, paritaprevir, dasabuvir and ritonavir are metabolized by p-glycoprotein
  - Detailed tables in packaging


**Hepatitis C Dosage and Cost Summary**

<table>
<thead>
<tr>
<th>HCV Infection</th>
<th>Treatment</th>
<th>Duration</th>
<th>Cost</th>
</tr>
</thead>
<tbody>
<tr>
<td>Genotype 1</td>
<td>Harvoni&lt;sup&gt;®&lt;/sup&gt;</td>
<td>12 weeks&lt;sup&gt;‡&lt;/sup&gt;</td>
<td>$94,500</td>
</tr>
<tr>
<td>Genotype 1′</td>
<td>Viekira Pak™ + ribavirin</td>
<td>12 weeks&lt;sup&gt;†&lt;/sup&gt;</td>
<td>$83,300</td>
</tr>
<tr>
<td>Genotype 2</td>
<td>Sofosbuvir + ribavirin</td>
<td>12 weeks</td>
<td>~ $84,000</td>
</tr>
<tr>
<td>Genotype 3</td>
<td>Sofosbuvir + daclatasvir</td>
<td>24 weeks</td>
<td>~ $168,000</td>
</tr>
<tr>
<td>Genotype 4</td>
<td>Technivie™ + ribavirin</td>
<td>12 weeks</td>
<td>~ $77,000</td>
</tr>
</tbody>
</table>

<sup>‡</sup> For patients receiving prior treatment and having cirrhosis 24 weeks is recommended
<sup>†</sup> For genotype 1b without cirrhosis ribavirin not needed
<sup>§</sup> For 1a with cirrhosis 24 weeks recommended

---

**Alirocumab**

- **Indication**
  - Adjunct to diet and max tolerated statin for adults with heterozygous familial hypercholesterolemia OR clinical atherosclerotic cardiovascular disease who require additional lowering of LDL-C

- **Pharmacology**
  - Proprotein Convertase Subtilisin Kexin Type 9 (PCSK9) inhibitor

- **Pharmacokinetics**
  - Tmax 3-7 days
  - Max PCSK9 inhibition in 4-9 hours
  - LDL nadir in ~ 15 days
  - No data in severe renal or hepatic impairment

- **Contraindication/warnings/precautions**
  - Hypersensitivity reactions
  - Some have required hospitalization

- **Drug interactions**
  - None identified
Adverse Reactions

<table>
<thead>
<tr>
<th>Reaction</th>
<th>Alirocumab (N = 2476)</th>
<th>Placebo (N = 1276)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Injection site reactions</td>
<td>7.2%</td>
<td>5.1%</td>
</tr>
<tr>
<td>Allergic reactions</td>
<td>8.6%</td>
<td>7.8%</td>
</tr>
<tr>
<td>Anti-drug antibodies</td>
<td>4.8%*</td>
<td>0.6%</td>
</tr>
</tbody>
</table>

* Patients had higher rate of injection site reactions (10.2% vs. 5.9%)

Long Term Odyssey Study

% reduction in LDL-C at 24 weeks

Alirocumab (Praluent®)

- Dosing
  - 75mg SQ every 2 weeks
  - If inadequate response after 4-8 weeks may increase to 150 mg SQ every 2 weeks
- Cost
  - ~ $14,600 per year

Alirocumab (Praluent®)

- Administration
  - Warm to room temp for 30-40 min prior to administering
  - Do not use if at room temp for ≥ 24h
  - Inject SQ into thigh, abdomen or upper arm
- Prefilled pens or syringes

Alirocumab (Praluent®)

- Bottom line
  - Highly effective at lowering LDL-C
  - Expensive!!!
  - Need to maximize statin therapy
  - No data on CV morbidity & mortality
  - Awaiting Odyssey Outcomes trial (late 2017?)
- Additional review

Evolocumab (Repatha™)

- Dosing
  - 140 mg SQ every 2 weeks
  - 420 mg SQ once monthly
- Cost
  - Estimated at ~ $7,000-12,000 per year
- Fourier Trial is evaluating mortality
  - Expected results in 2018

https://www.clinicaltrials.gov/ct2/show/NCT02764633?term=evolocumab&rank=18
Flibanserin should not be used:
1. In renal impairment
2. In pre-menopausal women
3. With alcohol
4. With cigarettes

Flibanserin (Addyi™)
- Indication
  ➢ Hypoactive sexual desire disorder (HSDD) in premenopausal women
- Pharmacology
  ➢ Unknown mechanism for HSDD
  ➢ 5-HT1A agonist, 5-HT2A, 5HT2B, 5-HT2C, D4 antagonist

Flibanserin (Addyi™)
- Contraindications
  ➢ Alcohol
  ➢ Moderate to strong CYP3A4 inhibitors
  ➢ Hepatic impairment
- Warnings & precautions
  ➢ Hypotension & syncope
  ➢ Somnolence & sedation

Adverse Reactions from Placebo Controlled Trials

<table>
<thead>
<tr>
<th>Reaction</th>
<th>Flibanserin N = 1543</th>
<th>Placebo N = 1556</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dizziness</td>
<td>11.4%</td>
<td>2.2%</td>
</tr>
<tr>
<td>Somnolence</td>
<td>11.2%</td>
<td>2.9%</td>
</tr>
<tr>
<td>Nausea</td>
<td>10.4%</td>
<td>3.9%</td>
</tr>
<tr>
<td>Fatigue</td>
<td>9.2%</td>
<td>5.5%</td>
</tr>
<tr>
<td>Insomnia</td>
<td>4.9%</td>
<td>5.5%</td>
</tr>
<tr>
<td>Dry mouth</td>
<td>2.4%</td>
<td>1%</td>
</tr>
</tbody>
</table>

Flibanserin (Addyi™)
- Clinical efficacy
  ➢ Three phase 3 trials; 2375 women
  ➢ Increased the number of “satisfying sexual events” per 28 days by 0.5-1 over placebo
  ➢ In two studies the co-primary endpoint (sexual desire) was not significantly better than placebo

Flibanserin (Addyi™)
- Dosing
  ➢ 100 mg at night
  ➢ May cause drowsiness
  ➢ Stop after 8 weeks if no improvement
- Prescribers and pharmacies must be certified through the Addyi REMS program
- www.addyi.rems.com
- Available October 17th, 2015???
Flibanserin (Addyi™)

- Bottom line
  - First drug approved for HSDD
  - Controversial approval
  - Watch for drug interactions and remind patients to avoid alcohol
- Additional review
  - Gellad WF, et al. JAMA; published online July 6, 2015.

When starting naloxegol other laxatives should be:

1. Stopped for at least 3 days
2. Permanently discontinued
3. Tapered over 3 days
4. Continued

Naloxegol (Movantik™)

- Indication
  - Treatment of opioid-induced constipation in adults with chronic non-cancer pain
  - Pharmacology
    - Pegylated naloxone
    - Minimal CNS penetration
    - Displaces opioids from mu receptors in the GI tract

Naloxegol (Movantik™)

- Pharmacokinetics
  - Peaks within 2 hours
  - T ½ 6-11 hours
  - CYP3A4 metabolism
  - Renal excretion ~ 16%
- Contraindications
  - GI obstruction
  - Strong CYP3A4 inhibitors (i.e. ketoconazole or clarithromycin)

Naloxegol (Movantik™)

- Warnings and precautions
  - GI perforation
  - Opioid withdrawal
  - No data in severe hepatic impairment
- Drug interactions
  - Avoid moderate CYP3A4 inhibitors or reduce the dose (avoid grapefruit juice)
  - Avoid strong inducers of CYP3A4

<table>
<thead>
<tr>
<th>Common Adverse Reactions</th>
<th>Naloxegol 25 mg n = 446</th>
<th>Naloxegol 12.5 mg n = 441</th>
<th>Placebo n = 444</th>
</tr>
</thead>
<tbody>
<tr>
<td>Abdominal pain</td>
<td>21%</td>
<td>12%</td>
<td>7%</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>9%</td>
<td>6%</td>
<td>5%</td>
</tr>
<tr>
<td>Nausea</td>
<td>8%</td>
<td>7%</td>
<td>5%</td>
</tr>
<tr>
<td>Flatulence</td>
<td>6%</td>
<td>3%</td>
<td>3%</td>
</tr>
</tbody>
</table>
Efficacy for Opioid Induced Constipation

<table>
<thead>
<tr>
<th>KODIAC-4 Trial</th>
<th>Naloxegol 12.5 mg N = 213</th>
<th>Naloxegol 25 mg N = 214</th>
<th>Placebo N = 214</th>
</tr>
</thead>
<tbody>
<tr>
<td>Response rate</td>
<td>40.8%</td>
<td>44.4%</td>
<td>29.4%</td>
</tr>
<tr>
<td>p-value vs. placebo</td>
<td>0.02</td>
<td>0.001</td>
<td>--</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>KODIAC-5 Trial</th>
<th>Naloxegol 12.5 mg N = 232</th>
<th>Naloxegol 25 mg N = 232</th>
<th>Placebo N = 232</th>
</tr>
</thead>
<tbody>
<tr>
<td>Response rate</td>
<td>35%</td>
<td>39.7%</td>
<td>29.3%</td>
</tr>
<tr>
<td>p-value vs. placebo</td>
<td>0.202</td>
<td>0.02</td>
<td>--</td>
</tr>
</tbody>
</table>

*Response rate was defined as at least 3 SBMs/wk, and increase of at least 1 SBM/wk in 9 of the 12 weeks & 3 out of the last 4 weeks.


Naloxegol (Movantik™)

- **Dosing**
  - Normal renal function
  - 25 mg daily in the AM on an empty stomach
  - CrCl < 60ml/min
    - Start at 12.5 mg daily in the AM on an empty stomach
  - Moderate CYP3A4 inhibitors
    - 12.5 mg daily in the AM on an empty stomach
  - Discontinue maintenance laxatives; may resume in 3 days

- **Cost**
  - #30 = ~$300
  - Same price for 12.5 mg or 25 mg
  - Advised not to split or crush

- **Bottom line**
  - Likely used when osmotic laxatives and stimulants not effective
  - No direct comparison vs. other agents
  - Stop laxatives when initiating therapy

- **Additional review**

Eluxadoline should be dose adjusted for:

1. CrCl < 30ml/min
2. Age > 65 years
3. Cholecystectomy
4. Diarrhea

Eluxadoline (Viberzi™)

- **Indication**
  - Treatment of irritable bowel syndrome with diarrhea (IBS-D)

- **Pharmacology**
  - Mu-opioid receptor agonist
  - Delta-opioid receptor antagonist

Movantik PI 2015

Movantik PI 2015

Eluxadoline (Viberzi™)

- **Cmax**: 2-4 hours
- **T ½**: 4-6 hours
- **Metabolism**
  - Unclear, possible glucuronidation
  - Elevated levels in hepatic impairment
- **Minimal renal excretion**

**Contraindications**
- Biliary obstruction, sphincter of Oddi dysfunction, EtOH use, pancreatitis, severe liver impairment, history of chronic or severe constipation, GI obstruction

**Warnings**
- Risk of pancreatitis & sphincter of Oddi spasm

**Drug interactions**
- OATP1B1 Inhibitors
  - Increase levels of eluxadoline
  - Cyclosporine, gemfibrozil, antiretrovirals
- OATP1B1 & BCRP substrates
  - Rosuvastatin levels may increase
  - Drugs causing constipation
  - Anticholinergics, opioids

**Efficacy for IBS-D**

<table>
<thead>
<tr>
<th>Study</th>
<th>Eluxadoline 75 mg BID N = 427</th>
<th>Eluxadoline 100 mg BID N = 426</th>
<th>Placebo N = 427</th>
</tr>
</thead>
<tbody>
<tr>
<td><em>Response rate</em></td>
<td>24%</td>
<td>25%</td>
<td>17%</td>
</tr>
<tr>
<td>p-value vs. placebo</td>
<td>&lt; 0.01</td>
<td>&lt; 0.05</td>
<td>--</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Study</th>
<th>Eluxadoline 75 mg BID N = 381</th>
<th>Eluxadoline 100 mg BID N = 382</th>
<th>Placebo N = 382</th>
</tr>
</thead>
<tbody>
<tr>
<td><em>Response rate</em></td>
<td>29%</td>
<td>30%</td>
<td>16%</td>
</tr>
<tr>
<td>p-value vs. placebo</td>
<td>&lt; 0.001</td>
<td>&lt; 0.001</td>
<td>--</td>
</tr>
</tbody>
</table>

*Simultaneous improvement in the daily worst abdominal pain score by ≥ 30% vs. baseline weekly average AND reduction in the Bristol Stool Scale to ≤ 5 on at least 50% of the days within a 12-week time interval

**Dosing**
- 100 mg BID with food
- 75 mg BID if:
  - No gallbladder
  - Mild-moderate hepatic impairment
  - Does not tolerate 100 mg BID
  - Taking OATP1B1 inhibitor
  - Discontinue if constipation develops and lasts for > 4 days
Eluxadoline (Viberzi™)
- Bottom line
  - Another option for IBS-D patients
  - No active comparator trials
  - Opioid-agonist; will be a controlled substance; awaiting scheduling
  - Expected first quarter 2016?
- Additional review

Dantrolene (Ryanodex®)
- Indication
  - Treatment of malignant hyperthermia
- Pharmacology
  - Direct skeletal muscle relaxant
  - Produces relaxation by affecting contractile response of muscle at a site beyond myoneuronal junction
  - Dissociates the excitation-contraction coupling, probably interfering with release of Ca²⁺ from sarcoplasmic reticulum

Available IV Products
- Revonto®
  - 20 mg lyophilized dantrolene sodium powder for solution
- Ryanodex®
  - 250 mg lyophilized dantrolene powder for suspension

Dosage and Reconstitution

<table>
<thead>
<tr>
<th></th>
<th>Revonto®</th>
<th>Ryanodex®</th>
</tr>
</thead>
<tbody>
<tr>
<td>Initial</td>
<td>1 mg/kg</td>
<td>1 mg/kg</td>
</tr>
<tr>
<td>Maximum</td>
<td>10 mg/kg</td>
<td>10 mg/kg</td>
</tr>
<tr>
<td>Malignant Hyperthermia Crisis</td>
<td>2.5 mg/kg</td>
<td>2.5 mg/kg</td>
</tr>
<tr>
<td>Vial</td>
<td>20 mg</td>
<td>250 mg</td>
</tr>
<tr>
<td>Reconstitution</td>
<td>60 mL SWFI</td>
<td>5 mL SWFI</td>
</tr>
<tr>
<td></td>
<td>without</td>
<td>without</td>
</tr>
<tr>
<td></td>
<td>bacteriostatic agent</td>
<td>bacteriostatic agent</td>
</tr>
</tbody>
</table>

Patient Case
- TD is a 78 kg female patient. She quickly deteriorates after scheduled procedure ends and anesthetic is stopped. She shows signs of increased temperature, rigid muscles, hyperkalemia, and tachycardia. Physician diagnoses TD with malignant hyperthermia. Patient requires 500 mg of dantrolene treatment to abate symptoms.
### RCRH Dantrolene Expenditure

<table>
<thead>
<tr>
<th>Drug</th>
<th>Cost per Vial</th>
<th>Vials/OR Crash Cart</th>
<th>Cost per OR Crash Cart</th>
</tr>
</thead>
<tbody>
<tr>
<td>Revonto</td>
<td>$65.00</td>
<td>12</td>
<td>$780.00</td>
</tr>
<tr>
<td>Ryanodex</td>
<td>$2,070.00</td>
<td>1</td>
<td>$2,070.00</td>
</tr>
</tbody>
</table>

### RCRH Dantrolene Expenditure

<table>
<thead>
<tr>
<th>Drug</th>
<th>Total Vials in Stock</th>
<th>Total Shelf Drug Cost</th>
<th>Shelf Life</th>
<th>Times Cycled Inventory in 10yrs</th>
<th>Cost every 10 years</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dantrolene</td>
<td>60</td>
<td>$3,900.00</td>
<td>3 years</td>
<td>3</td>
<td>$11,700.00</td>
</tr>
<tr>
<td>Ryanodex</td>
<td>5</td>
<td>$10,350.00</td>
<td>2 years</td>
<td>5</td>
<td>$51,750.00</td>
</tr>
</tbody>
</table>

### Cost Increase Over 10 yrs

<table>
<thead>
<tr>
<th>Category</th>
<th>Amount</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cost Increase Over 10 yrs</td>
<td>$40,050.00</td>
</tr>
<tr>
<td>Percent of Cost Increase</td>
<td>342%</td>
</tr>
</tbody>
</table>

### Bottom line

- Ryanodex requires less intensive means to prepare for patients in a malignant hyperthermia crisis
- Cost of Ryanodex may be considered prohibitive
- Additional review
  - Malignant Hyperthermia Association of the United States. MHAUS. http://www.mhaus.org

### Edoxaban should NOT be used in A. fib if:

1. CrCl is < 30 ml/min
2. CrCl is < 50 ml/min
3. CrCl is > 95 ml/min

- Response Counter:
  - 15% for < 30 ml/min
  - 20% for < 50 ml/min
  - 30% for > 95 ml/min
Ivabradine works for heart failure by:
1. Increasing contractility
2. Increasing urine output
3. Slowing the heart rate
4. Reducing afterload

Sacubitril should NOT be used with:
1. HCTZ
2. Lisinopril
3. Spironolactone
4. Metoprolol

Avycaz will be used for ____ infections
1. MRSA
2. VRE
3. Gram negative
4. Anaerobic

Zerbaxa will be used for ____ infections
1. MRSA
2. VRE
3. Gram negative
4. Anaerobic

Compared to the older agents the new hepatitis C medications:
1. Are less expensive
2. Have more side effects
3. Have more drug interactions
4. Require longer treatment duration

Alirocumab has been shown to reduce:
1. LDL-C
2. Mortality
3. Bank accounts
4. 1 & 2
5. 1 & 3
6. All of the above
Flibanserin should not be used:

1. In renal impairment
2. In pre-menopausal women
3. With alcohol
4. With cigarettes

When starting naloxegol other laxatives should be:

1. Stopped for at least 3 days
2. Permanently discontinued
3. Tapered over 3 days
4. Continued

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