Disclosure

- I have reports no actual or potential conflicts of interest associated with this presentation
Learning Objectives

• Upon successful completion of this activity, participants should be able to:
  ➢ Identify therapeutic indications of drugs recently approved by the FDA.
  ➢ Discuss pharmacological properties of the new medications
  ➢ List side effects, warnings, precautions and significant drug interactions associated with each medication.
  ➢ Identify the normal dose and dosage forms of the drugs presented.
  ➢ Describe limitations to implementing the new medications into clinical practice
New Drug Approval Trends

http://www.fda.gov/drugs/developmentapprovalprocess/druginnovation/ucm474696.htm
Agenda

- Insulin degludec/liraglutide (Xultophy®)
- Insulin glargine/lixisenatide (Soliqua™)
- Plecanatide (Trulance™)
- Naldemedine (Symproic®)
- Sofosbuvir/velpatasvir/voxilaprevir (Vosevi™)
- Glecaprevir/pibrentasvir (Mavyret™)
- Safinamide (Xadago®)
- Valbenazine (Ingrezza™)
- Delafloxacin (Baxdela™)
- Bezlotoxumab (Zinplava™)
- Betrixaban (Bevyxxa®)
The combination of a GLP-1 agonist and long-acting insulin was associated with weight gain in clinical trials.

A. True
B. False
Insulin degludec/Liraglutide (Xultophy®)

• Indication
  • Type 2 diabetes mellitus inadequately controlled on basal insulin (< 50 units) or liraglutide (≤ 1.8 mg daily)

• Pharmacology
  • Ultra long acting insulin
  • GLP-1 agonist
    • Increases glucose-dependent insulin release
    • Decreases glucagon secretion
    • Slows gastric emptying

Xultophy PI 2016.
<table>
<thead>
<tr>
<th>Endpoint</th>
<th>Glargine N = 279</th>
<th>Liraglutide/degludec N = 278</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>A₁C reduction at 26 weeks</strong></td>
<td>1.13%</td>
<td>1.81%</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td><strong>A₁C &lt; 7%</strong></td>
<td>47%</td>
<td>71.6%</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td><strong>Hypoglycemia (events/patient-year)</strong></td>
<td>5.05</td>
<td>2.23</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td><strong>Weight change</strong></td>
<td>+ 1.8 kg</td>
<td>- 1.4 kg</td>
<td>&lt; 0.001</td>
</tr>
</tbody>
</table>

Insulin degludec/Liraglutide (Xultophy®)

• **Dosing**
  • Start at 16 units (16 units of degludec and 0.58 mg of liraglutide)
  • Titrate every 3-4 days by 2 units
  • Max dose of 50 units (50 units of degludec and 1.8 mg of liraglutide)

• **Availability**
  • Only available as a 3 ml pen; packs of 5 pens
  • 100 units/ml of degludec and 3.6 mg/ml of liraglutide

Xultophy PI 2016.
Insulin degludec/Liraglutide (Xultophy®)

• Administration
  • Attach needle
  • Select priming symbol “∙∙—” prior to each use
  • Press button until liquid comes out of needle (may repeat up to 6 times)
  • Then select dose and administer similar to insulin shot
  • Hold button until dose says “0” then count to 6

• Stability/storage
  • Refrigerator until first use then at room temp or refrigerator; protect from light/direct heat
  • Discard 21 days after first use

Xultophy PI 2016.
Insulin glargine/Lixisenatide (Soliqua™)

**Indication**
- Type 2 diabetes mellitus uncontrolled on lixisenatide or basal insulin (< 60 units daily)

**Pharmacology**
- Long acting insulin
- GLP-1 agonist
  - Increases glucose-dependent insulin release
  - Decreases glucagon secretion
  - Slows gastric emptying

Soliqua PI. 2016.
## LixiLan-L Trial

<table>
<thead>
<tr>
<th>Endpoint</th>
<th>Glargine N = 365</th>
<th>Glargine/Lixi N = 366</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>A₁C reduction at 30 weeks</strong>*</td>
<td>0.6%</td>
<td>1.1%</td>
<td>&lt; 0.0001</td>
</tr>
<tr>
<td><strong>A₁C &lt; 7%</strong></td>
<td>30%</td>
<td>55%</td>
<td>&lt; 0.0001</td>
</tr>
<tr>
<td><strong>Hypoglycemia (events/patient-year)</strong></td>
<td>4.22</td>
<td>3.03</td>
<td>NR</td>
</tr>
<tr>
<td><strong>Weight change</strong></td>
<td>+ 0.7 kg</td>
<td>- 0.7 kg</td>
<td>&lt; 0.0001</td>
</tr>
</tbody>
</table>

*Primary outcome*
Insulin glargine/Lixisenatide (Soliqua™)

• Starting dose
  • If on lixisenatide or less than 30 units of basal insulin
    • Insulin glargine 15 units/ 5 mcg lixisenatide
    • Displayed as “15” in the dosing window
  • If on 30-60 units of basal insulin
    • Insulin glargine 30 units/10mcg lixisenatide
    • Displayed as “30” in the dosing window

• Availability
  • Only available as a 3 ml pen; packs of 5 pens
  • 100 units/ml of glargine, 33 mcg/ml lixisenatide

Soliqua PI 2016.
Insulin glargine/Lixisenatide (Soliqua™)

• Administration
  • Alcohol swab to rubber seal prior to attaching needle
  • Select “2” units prior to each use
  • Press button until liquid comes out of needle (may repeat up to 3 times)
  • Then select dose and administer similar to insulin shot
  • Hold button until dose says “0” then count to 10

• Stability/storage
  • Store in refrigerator until first use then at room temperature; Protect from light
  • Discard 14 days after first use

Soliqua PI 2016.
Pricing

- Insulin glargine/Lixisenatide (Soliqua)
  - $120 for each 3ml pen

- Insulin degludec/Liraglutide (Xultophy)
  - $160 for each 3 ml pen

Insulin glargine/Lixisenatide (Soliqua™)
Insulin degludec/Liraglutide (Xultophy®)

• Bottom line
  • Combination, once-daily injections
  • Lowers $\text{A}_{1\text{C}}$ vs. insulin monotherapy
  • Useful for patients not controlled on basal insulin and oral agents
  • Rare pancreatitis
  • Weight loss vs. weight gain with insulin monotherapy

• Additional review
Which of the following is a contraindication to plecanatide?

A. Cancer
B. Age less than 6
C. Urinary tract infection
D. Constipation
Plecanatide (Trulance™)

- **Indications**
  - Chronic idiopathic constipation (CIC)

- **Pharmacology**
  - Uroguanylin analog
  - Stimulates guanylate cyclase type-C (GC-C) receptors ➔ increases cGMP ➔ activates CFTR ➔ efflux of chloride from lining of GI tract leading to increased fluid secretion into intestinal lumen
Plecanatide (Trulance™)

• Pharmacokinetics
  • Not systemically absorbed
  • Metabolized to active metabolite in GI tract
  • Degraded into smaller peptides in the GI tract

• Contraindications
  • Bowel obstruction
  • Ages < 6 (due to risk of dehydration; mice data)

• Warnings and precautions
  • Ages 6-17
  • Diarrhea
## Diarrhea Reported from Phase III Trials

<table>
<thead>
<tr>
<th>Adverse reaction</th>
<th>Plecanatide N = 863</th>
<th>Placebo N = 870</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diarrhea</td>
<td>5%</td>
<td>1%</td>
</tr>
<tr>
<td>Severe diarrhea</td>
<td>0.6%</td>
<td>0.3%</td>
</tr>
<tr>
<td>Discontinued due to diarrhea</td>
<td>2%</td>
<td>0.5%</td>
</tr>
</tbody>
</table>

Trulance PI 2017
# Efficacy in Chronic Idiopathic Constipation

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Plecanatide 3 mg (N = 453)</th>
<th>Plecanatide 6 mg (N = 441)</th>
<th>Placebo (N = 452)</th>
</tr>
</thead>
<tbody>
<tr>
<td>*<strong>Response Rate</strong></td>
<td>21%†</td>
<td>19.5%†</td>
<td>10.2%</td>
</tr>
<tr>
<td><strong>First week responders</strong></td>
<td>35.8%†</td>
<td>29.3%†</td>
<td>16.6%</td>
</tr>
<tr>
<td><strong>CSBM within 24 hours</strong></td>
<td>28.7%†</td>
<td>25.2%†</td>
<td>13.3%</td>
</tr>
</tbody>
</table>

*more than 3 complete spontaneous bowel movements (CSBM) per week, and increase of more than 1 CSBM/week in 9 of the 12 weeks


† p < 0.001 vs. placebo
Plecanatide (Trulance™)

• Dosing
  • 3 mg PO once daily with or without food
  • May be crushed and mixed in applesauce or water

• Cost
  • Plecanatide = $329.44 per month
  • Linaclotide = $329.38 per month
Plecanatide (Trulance™)

• Bottom line
  • Similar to linaclotide
  • No data beyond 12 weeks
  • Contraindicated in pediatric patients
  • Likely for refractory cases of constipation
  • Irritable bowel data pending

• Additional review
Why is naldemedine a Schedule II controlled substance?

A. High potential for abuse
B. Structurally similar to morphine
C. Easily converted to fentanyl
D. Have no idea—doesn’t make any sense
Naldemedine (Symproic®)

• Indication
  • Opioid-induced constipation in chronic non-cancer pain

• Pharmacology
  • Structurally related to naltrexone
  • Side chain increases size & polarity
  • Decreases ability to penetrate blood-brain barrier
Naldemedine (Symproic®)

- Pharmacokinetics
  - $T\frac{1}{2} \sim 11$ hours
  - Primarily metabolized by CYP3A
  - Majority excreted via kidneys

- Contraindications
  - GI obstruction
Naldemedine (Symproic®)

• Warnings and precautions
  • GI perforation
  • Opioid withdrawal
  • No data in severe hepatic impairment

• Drug interactions
  • Avoid CYP3A inducers (e.g. carbamazepine, phenytoin, rifampin, St. John’s wort)
  • CYP3A inhibitors increase plasma levels (e.g. diltiazem, clarithromycin, fluconazole)
  • P-glycoprotein inhibitors increase plasma levels (e.g. amiodarone, verapamil)
### Adverse Reactions from 12-week Clinical Trials

<table>
<thead>
<tr>
<th>Reaction</th>
<th>Naldemedine N = 542</th>
<th>Placebo N = 546</th>
</tr>
</thead>
<tbody>
<tr>
<td>Abdominal pain</td>
<td>8%</td>
<td>2%</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>7%</td>
<td>2%</td>
</tr>
<tr>
<td>Nausea</td>
<td>4%</td>
<td>2%</td>
</tr>
<tr>
<td>Gastroenteritis</td>
<td>2%</td>
<td>1%</td>
</tr>
</tbody>
</table>
### Efficacy for Opioid Induced Constipation

<table>
<thead>
<tr>
<th>Trial</th>
<th>Naldemedine</th>
<th>Placebo</th>
<th>p-value (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Compose 1 Trial</strong></td>
<td>N = 273</td>
<td>N = 272</td>
<td></td>
</tr>
<tr>
<td>Response rate*</td>
<td>47.6</td>
<td>34.6</td>
<td>0.002 (4.8-21.3)</td>
</tr>
<tr>
<td><strong>Compose 2 Trial</strong></td>
<td>N = 276</td>
<td>N = 274</td>
<td></td>
</tr>
<tr>
<td>Response rate*</td>
<td>52.5%</td>
<td>33.6%</td>
<td>&lt; 0.0001 (10.8-27)</td>
</tr>
</tbody>
</table>

*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

Naldemedine (Symproic®)

- **Dosing**
  - 0.2 mg once daily with or without food

- **Cost**
  - #30 0.2 mg tablets = ???

- **Availability**
  - Expected summer 2017

- **Schedule II controlled substance**
  - Current proposal to deschedule
Naldemedine (Symproic®)

• Bottom line
  • Another agent for opioid-induced constipation
  • Likely 2\textsuperscript{nd} line after less expensive laxatives
  • Currently a C-II

• Additional review
Which of the following is a contraindication to using sofosbuvir/velpatasvir/voxilaprevir?

A. Mild cirrhosis (Child-Pugh A)
B. Rifampin use
C. Failed previous hepatitis C treatment
D. Hepatitis Genotype-3
Sofosbuvir/velpatasvir/voxilaprevir (Vosevi™)

- **Indication**
  - Treatment of hepatitis genotypes 1-6, previously treated with an NS5A inhibitor
  - Treatment of hepatitis genotypes 1a or 3 previously treated with sofosbuvir without an NS5A inhibitor

- **Pharmacology**
  - Block steps of viral replication
  - Sofosbuvir: HCV NS5B RNA polymerase inhibitor
  - Velpatasvir: HCV NS5A protein inhibitor
  - Voxilaprevir: NS3/4A protease inhibitor
## Pharmacokinetics

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Sofosbuvir</th>
<th>Velpatasvir</th>
<th>Voxilaprevir</th>
</tr>
</thead>
<tbody>
<tr>
<td>Effect of food on absorption</td>
<td>↑ 64-144%</td>
<td>↑ 40-166%</td>
<td>↑ 112-435%</td>
</tr>
<tr>
<td>T ½</td>
<td>29h*</td>
<td>17h</td>
<td>33h</td>
</tr>
<tr>
<td>Urinary excretion</td>
<td>80%*</td>
<td>0.4%</td>
<td>0%</td>
</tr>
<tr>
<td>Metabolism</td>
<td>Cathepsin A, CES1, HINT1</td>
<td>CYP2B6, CYP2C8, CYP3A4</td>
<td>CYP3A4</td>
</tr>
</tbody>
</table>

* Active metabolite
Sofosbuvir/velpatasvir/voxilaprevir (Vosevi™)
• Contraindications
  • Rifampin
• Warnings/precautions
  • Moderate to severe hepatic impairment
    • Child-Pugh B & C
  • Hepatitis B reactivation
• Drug interactions
  • Next slide
Sofosbuvir/velpatasvir/voxilaprevir (Vosevi™)

- Drug interactions
  - Many, many many…
  - Amiodarone—bradycardia
  - Avoid with P-gp inducers and moderate-potent CYP inducers
    - Reduces levels of all 3 agents
  - Avoid OATP inhibitors
    - Increases voxilaprevir
  - Acid-reducing drugs decrease velpatasvir absorption
## Common Adverse Reactions

<table>
<thead>
<tr>
<th></th>
<th>POLARIS-1</th>
<th></th>
<th>POLARIS-4</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Sof/Vel/Vox</td>
<td>Placebo</td>
<td>Sof/Vel/Vox</td>
<td>Placebo</td>
</tr>
<tr>
<td></td>
<td>N = 263</td>
<td>N = 152</td>
<td>N = 182</td>
<td>N = 151</td>
</tr>
<tr>
<td>Headache</td>
<td>21%</td>
<td>14%</td>
<td>23%</td>
<td>23%</td>
</tr>
<tr>
<td>Fatigue</td>
<td>17%</td>
<td>15%</td>
<td>19%</td>
<td>23%</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>13%</td>
<td>9%</td>
<td>14%</td>
<td>3%</td>
</tr>
<tr>
<td>Nausea</td>
<td>13%</td>
<td>7%</td>
<td>10%</td>
<td>3%</td>
</tr>
<tr>
<td>Insomnia</td>
<td>6%</td>
<td>3%</td>
<td>3%</td>
<td>1%</td>
</tr>
</tbody>
</table>

Sof/Vel/Vox = Sofosbuvir/velpatasvir/voxilaprevir

Vosevi PI 2017
POLARIS-1 Trial

Sustained Viroligic Response-12 %

- GT-1a: N = 101, 96%
- GT-1b: N = 45, 100%
- GT-2: N = 5, 100%
- GT-3: N = 78, 95%
- GT-4: N = 22, 91%
- GT-5: N = 1, 100%
- GT-6: N = 6, 100%

GT = genotype
POLARIS-4 Trial

Sustained Virologic Response-12%

<table>
<thead>
<tr>
<th>GT</th>
<th>Sofosbuvir/velpatasvir/voxilaprevir</th>
<th>Sofosbuvir/Velpatasvir</th>
</tr>
</thead>
<tbody>
<tr>
<td>GT-1a</td>
<td>98 (N=54)</td>
<td>89 (N=44)</td>
</tr>
<tr>
<td>GT-1b</td>
<td>96 (N=24)</td>
<td>95 (N=22)</td>
</tr>
<tr>
<td>GT-2</td>
<td>100 (N=31)</td>
<td>97 (N=33)</td>
</tr>
<tr>
<td>GT-3</td>
<td>96 (N=54)</td>
<td>85 (N=52)</td>
</tr>
</tbody>
</table>

GT = genotype

N Engl Med 2017; 376:2134-46
Sofosbuvir/velpatasvir/voxilaprevir (Vosevi™)

- **Dosing**
  - One tablet daily **with food** x 12 weeks
  - 400mg/100mg/100mg tablets

- **Cost**
  - $74,760 for 12 weeks
Sofosbuvir/velpatasvir/voxilaprevir (Vosevi™)

• Bottom line
  • First agent approved for those failing other new treatments
  • Convenient dosing
  • Expensive

• Additional review
  • http://www.hcvguidelines.org/
Which of the following is true regarding glecaprevir/pibrentasvir?

A. Relatively cheaper vs. other hepatitis C agents
B. Approved as an 8-week therapy
C. Approved for multiple hepatitis C genotypes
D. All of the above
Glecaprevir/Pibrentasvir (Mavyret™)

• Indication
  • Hepatitis C genotypes 1-6, treatment naïve, may have mild cirrhosis
  • Hepatitis C genotype 1, previously failed an NS5A inhibitor OR an NS3/4A protease inhibitor

• Pharmacology
  • Glecaprevir: HCV NS3/4A protease inhibitor
  • Pibrentasvir: HCV NS5A inhibitor
<table>
<thead>
<tr>
<th>Parameter</th>
<th>Glecaprevir</th>
<th>Pibrentasvir</th>
</tr>
</thead>
<tbody>
<tr>
<td>Effect of food on absorption*</td>
<td>↑ 83-163%</td>
<td>↑ 40-53%</td>
</tr>
<tr>
<td>T ½</td>
<td>6h</td>
<td>13h</td>
</tr>
<tr>
<td>Urinary excretion</td>
<td>0.7%</td>
<td>0%</td>
</tr>
<tr>
<td>Metabolism</td>
<td>CYP3A4 (secondary)</td>
<td>None</td>
</tr>
</tbody>
</table>

*Moderate-high fat meal*
Glecaprevir/Pibrentasvir (Mavyret™)

- **Contraindications**
  - Severe hepatic impairment (Child-Pugh C)
  - Rifampin and atazanavir

- **Warnings/precautions**
  - Moderate hepatic impairment (Child-Pugh B)
  - Hepatitis B reactivation
  - Carbamazepine, efavirenz, & St. John’s wort
Glecaprevir/Pibrentasvir (Mavyret™)

- Drug interactions
  - Both inhibit P-glycoprotein, BCRP, and OATP
  - Both are substrates of P-gp and PCRP
  - Specific medication interactions listed in package insert
  - Specific list of medications NOT interacting listed in package insert
<table>
<thead>
<tr>
<th>Reaction</th>
<th>Glecaprevir/ Pibrentasvir 8 weeks N = 157</th>
<th>Glecaprevir/ Pibrentasvir 12 weeks N = 233</th>
<th>Daclatasvir/ sofosbuvir 12 weeks N = 115</th>
</tr>
</thead>
<tbody>
<tr>
<td>Headache</td>
<td>16%</td>
<td>17%</td>
<td>15%</td>
</tr>
<tr>
<td>Fatigue</td>
<td>11%</td>
<td>14%</td>
<td>12%</td>
</tr>
<tr>
<td>Nausea</td>
<td>9%</td>
<td>12%</td>
<td>12%</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>7%</td>
<td>3%</td>
<td>3%</td>
</tr>
</tbody>
</table>

Mavyret PI 2017
<table>
<thead>
<tr>
<th>Study (Genotype)</th>
<th>Population</th>
<th>SVR12</th>
<th>Treatment Duration</th>
</tr>
</thead>
<tbody>
<tr>
<td>ENDURANCE-4/SURVEYOR-1 (5, 6)</td>
<td>Treatment Naïve and IFN/RBV/Sof Experienced without cirrhosis</td>
<td>100% (57/57)</td>
<td>12 weeks</td>
</tr>
<tr>
<td>Surveyor-2 (2,4,5,6)</td>
<td>Treatment Naïve and IFN/RBV/Sof Experienced without cirrhosis</td>
<td>97% (248/255)</td>
<td>8 weeks</td>
</tr>
<tr>
<td>ENDURANCE-1 (1)</td>
<td>Treatment Naïve and IFN/RBV/Sof Experienced without cirrhosis</td>
<td>99% (348/351)</td>
<td>8 weeks</td>
</tr>
<tr>
<td>EXPEDITION-1 (1,2,4,5,6)</td>
<td>Treatment Naïve and IFN/RBV/Sof Experienced + cirrhosis</td>
<td>99% (145/146)</td>
<td>12 weeks</td>
</tr>
</tbody>
</table>

SVR12 = sustained virologic response at 12 weeks after end of treatment
# ENDURANCE-3
(Treatment Naïve, Genotype 3, without cirrhosis)

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Glecaprevir/Pibrentasvir 8 weeks N = 157</th>
<th>Glecaprevir/Pibrentasvir 12 weeks N = 233</th>
<th>Daclatasvir/sofosbuvir 12 weeks N = 115</th>
</tr>
</thead>
<tbody>
<tr>
<td>SVR12</td>
<td>94.9%</td>
<td>95.3%</td>
<td>96.5%</td>
</tr>
</tbody>
</table>

SVR12 = sustained virologic response at 12 weeks after end of treatment

Mavyret PI 2017
Glecaprevir/Pibrentasvir (Mavyret™)

- **Dosing**
  - 100mg/40mg tablets
  - Take 3 tablets once daily with food
  - 4-week or 8-week supply
    - Wallets of 3 tablets each

- **Cost**
  - $26,400 for 8 weeks
  - $39,600 for 12 weeks

Mavyret PI 2017
### Glecaprevir/Pibrentasvir Duration: Treatment Naïve Patients

<table>
<thead>
<tr>
<th>HCV Genotype</th>
<th>Treatment Duration</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No cirrhosis</td>
</tr>
<tr>
<td>1-6</td>
<td>8 weeks</td>
</tr>
</tbody>
</table>

### Glecaprevir/Pibrentasvir Duration: Treatment-Experienced Patients

<table>
<thead>
<tr>
<th>HCV Genotype</th>
<th>Previous regimen</th>
<th>No cirrhosis</th>
<th>Child-Pugh A</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>NS5A inhibitor</td>
<td>16 weeks</td>
<td>16 weeks</td>
</tr>
<tr>
<td></td>
<td>NS3/4A protease inhibitor</td>
<td>12 weeks</td>
<td>12 weeks</td>
</tr>
<tr>
<td>1,2,4,5,6</td>
<td>Interferon, ribavirin or sofosbuvir</td>
<td>8 weeks</td>
<td>12 weeks</td>
</tr>
</tbody>
</table>
Glecaprevir/Pibrentasvir (Mavyret™)

• Bottom line
  • First 8-week treatment for all genotypes
  • Certain subtypes require 12 or 16 weeks
  • GT-1 patients failing previous treatment with new agents
  • Significantly cheaper list price vs. other approved treatments
  • May be used in renal failure

• Additional review
  • http://www.hcvguidelines.org/
Safinamide’s mechanism is similar to which agent?

A. Rasagiline
B. Pramipexole
C. Levodopa
D. Entacapone
Safinamide (Xadago®)

• **Indication**
  - Add-on treatment for Parkinson’s disease
  - Reduces “off” episodes

• **Pharmacology**
  - Selective monoamine oxidase B inhibitor
  - Similar to rasagiline and selegiline
  - Also inhibits glutamate
Safinamide (Xadago®)

- Pharmacokinetics
  - Peaks in 2-3 hours
  - $T_{\frac{1}{2}}$ 20-26 hours
  - Steady-state in 5-6 days
  - Metabolized by 3 oxidative pathways (not CYP450 mediated)
    - Levels increased in hepatic impairment (Child Pugh B)
  - Inactive metabolites excreted via kidneys
Safinamide (Xadago®)

- **Contraindications**
  - Hypersensitivity
  - Severe hepatic impairment (Child-Pugh C)
  - MAOI’s (including linezolid)
  - Meperidine, tramadol, methadone
  - SNRIs, TCAs, cyclobenzaprine, methylphenidate, amphetamine derivatives, St. John’s Wort
  - Dextromethorphan
Safinamide (Xadago®)

- Warnings/precautions
  - Hypertension
  - SSRI’s
  - Sleep attacks
  - Dyskinesia
  - Psychosis/hallucinations
  - Compulsive behaviors
  - Withdrawal
  - Retinal degeneration
Safinamide (Xadago®)

• Drug interactions
  • Increases levels of BCRP substrates (e.g. methotrexate, rosuvastatin)
  • Dopaminergic antagonists may decrease effectiveness
    • Antipsychotics
    • Metoclopramide
## Adverse Reactions from Placebo-controlled Phase III Trials

<table>
<thead>
<tr>
<th>Reaction</th>
<th>Safinamide 50 mg N = 223</th>
<th>Safinamide 100 mg N = 498</th>
<th>Placebo N = 497</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dyskinesia</td>
<td>21%</td>
<td>17%</td>
<td>9%</td>
</tr>
<tr>
<td>Fall</td>
<td>4%</td>
<td>6%</td>
<td>4%</td>
</tr>
<tr>
<td>Nausea</td>
<td>3%</td>
<td>6%</td>
<td>4%</td>
</tr>
<tr>
<td>Insomnia</td>
<td>1%</td>
<td>4%</td>
<td>2%</td>
</tr>
<tr>
<td>Orthostatic hypotension</td>
<td>2%</td>
<td>2%</td>
<td>1%</td>
</tr>
</tbody>
</table>

Xadago PI 2017
<table>
<thead>
<tr>
<th>Measurement (hours/day)</th>
<th>Safinamide 100 mg N = 274</th>
<th>Placebo N = 275</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline</td>
<td>9.3</td>
<td>9.06</td>
</tr>
<tr>
<td>24 weeks</td>
<td>10.73</td>
<td>9.63</td>
</tr>
<tr>
<td>Change</td>
<td>+1.42</td>
<td>+0.57</td>
</tr>
<tr>
<td>Mean Difference from Placebo (95% CI)</td>
<td>+0.96 (0.56-1.37)*</td>
<td>NA</td>
</tr>
</tbody>
</table>

* P < 0.001

JAMA Neurol. 2017;74(2):216-224
## "On" Time Without Troublesome Dyskinesia

<table>
<thead>
<tr>
<th>Measurement (hours/day)</th>
<th>Safinamide 50 mg N = 223</th>
<th>Safinamide 100 mg N = 224</th>
<th>Placebo N = 222</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline</td>
<td>9.4</td>
<td>9.5</td>
<td>9.3</td>
</tr>
<tr>
<td>24 weeks</td>
<td>10.9</td>
<td>11</td>
<td>10.3</td>
</tr>
<tr>
<td>Change</td>
<td>1.5</td>
<td>1.5</td>
<td>1</td>
</tr>
<tr>
<td>Mean Difference from Placebo (95% CI)</td>
<td>0.51 (0.07-0.94)*</td>
<td>0.55 (0.12-0.99) †</td>
<td>NA</td>
</tr>
</tbody>
</table>

* p = 0.0223; † p = 0.013

Safinamide (Xadago®)

- Dosing
  - 50 mg daily for 2 weeks, then increase to 100 mg daily based on tolerability and response
  - Used with or without food
  - If stopping use 50 mg daily x 1 week
  - Max of 50 mg daily if moderate hepatic impairment

<table>
<thead>
<tr>
<th>MOA-B Inhibitors Monthly Cost Comparison</th>
</tr>
</thead>
<tbody>
<tr>
<td>Safinamide</td>
</tr>
<tr>
<td>$670</td>
</tr>
</tbody>
</table>

Xadago PI 2017; Pharmacists Letter; 2017
Safinamide (Xadago®)

- **Bottom line**
  - MAO-B inhibitor w/ glutaminate inhibition
  - Likely use when not tolerating rasagiline or selegiline—no direct comparator trials
  - Must be used in combination with carbidopa/levodopa

- **Additional Review**
What is the most common side effect associated with valbenazine?

A. Headache
B. Diarrhea
C. Somnolence
D. Dizziness
Valbenazine (Ingrezza™)

• Indication
  • Treatment of adults with tardive dyskinesia

• Pharmacology
  • Selectively inhibits vesicular monoamine transporter type 2 (VMAT-2)
  • VMAT is a protein in neurons that regulates storage of dopamine in neuronal vesicles
  • Inhibition of VMAT-2 results in reduction of synaptic dopamine levels
Valbenazine (Ingrezza™)

• Pharmacokinetics
  • Hydrolysis and CYP3A4 metabolism
    • Metabolite further metabolized by CYP2D6
  • Peaks in 0.5-1h (4-8 hours for active metabolite)
  • T½ 15-22 hours
  • Steady-state in 1 week
Valbenazine (Ingrezza™)

- Contraindications
  - None listed

- Precautions/warnings
  - Somnolence
  - QT prolongation
    - Concern if on a strong CYP3A4 or CYP2D6 inhibitor, poor CYP2D6 metabolizer, or baseline QT prolongation
    - 11.7 msec vs 6.7 msec in poor CYP2D6 metabolizers
  - Not recommended in severe renal impairment
    - CrCl < 30 ml/min

Ingrezza PI 2017
Valbenazine (Ingrezza™)

- Drug interactions
  - Monoamine oxidase inhibitors
    - Concomitant use not recommended
  - Strong CYP3A4 inhibitors (e.g. itraconazole) & CYP2D6 inhibitors (e.g. fluoxetine)
    - Reduce dose
  - Strong CYP3A4 inducers (e.g. phenytoin)
    - Avoid use
  - May increase digoxin levels due to P-glycoprotein inhibition
### Reactions from 6-week placebo controlled trials

<table>
<thead>
<tr>
<th>Reaction</th>
<th>Reaction Valbenazine N = 262</th>
<th>Reaction Placebo N = 183</th>
</tr>
</thead>
<tbody>
<tr>
<td>Somnolence</td>
<td>10.9%</td>
<td>4.2%</td>
</tr>
<tr>
<td>Anticholinergic effects</td>
<td>5.4%</td>
<td>4.9%</td>
</tr>
<tr>
<td>Falls/balance issues</td>
<td>4.1%</td>
<td>2.2%</td>
</tr>
<tr>
<td>Headache</td>
<td>3.4%</td>
<td>2.7%</td>
</tr>
<tr>
<td>Akathisia</td>
<td>2.7%</td>
<td>0.5%</td>
</tr>
<tr>
<td>Vomiting</td>
<td>2.6%</td>
<td>0.6%</td>
</tr>
<tr>
<td>Nausea</td>
<td>2.3%</td>
<td>2.1%</td>
</tr>
</tbody>
</table>

*Ingrezza PI 2017*
# KINECT 3 Trial Data

<table>
<thead>
<tr>
<th>Measure</th>
<th>Valbenazine 40mg N = 70</th>
<th>Valbenazine 80mg N = 79</th>
<th>Placebo N = 76</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline AIMS score</td>
<td>9.8</td>
<td>10.4</td>
<td>9.9</td>
</tr>
<tr>
<td>AIMS mean change at 6 weeks</td>
<td>-1.9</td>
<td>-3.2</td>
<td>-0.1</td>
</tr>
<tr>
<td>Placebo difference (95% CI)</td>
<td>-1.8 (-3, -0.7) p &lt; 0.01</td>
<td>-3.1 (-4.2, -2.0) p &lt; 0.001</td>
<td>N/A</td>
</tr>
</tbody>
</table>

Valbenazine (Ingrezza™)

- **Dosing**
  - Initially 40 mg once daily with or without food
  - After 1 week increase to 80 mg once daily
  - **Dose adjustments**
    - Moderate to severe hepatic impairment (40mg daily)
    - CYP3A4 inhibitors (40 mg daily)
    - Poor CYP 2D6 metabolizers (“reduce dose”)
    - CYP2D6 inhibitors (“reduce dose”)

- **Cost**
  - #30, 40mg capsules = $6330
Valbenazine (Ingrezza™)

• Bottom line
  • First agent approved for tardive dyskinesia
  • Benefit seen as soon as 2 weeks
  • Limited data up to 48 weeks
  • Somnolence most common side effect

• Additional review
  • Citrome L. Int J Clin Pract 2017;e12964.
Delafloxacin is a broad-spectrum fluoroquinolone antibiotic currently approved for pneumonia.

A. True
B. False
Delafloxacin (Baxdela™)

- **Indication**
  - Acute bacterial skin and skin structure infections

- **Pharmacology**
  - Fluoroquinolone antimicrobial
  - Lacks strong basic group at the C-7 position
  - “anionic” vs. “zwitterionic”
  - Increased activity in acidic environment

Baxdela PI 2017.
Delafloxacin (Baxdela™)

- Spectrum of activity
  - Gram-positive organisms
    - MSSA, MRSA, *Streptococcus pyogenes*, *E. faecalis*
  - Gram-negative organisms
    - *E. coli*, *E. cloacae*, *K. pneumoniae*, *P. aeruginosa*
Delafloxacin (Baxdela™)

- Pharmacokinetics
  - $T\frac{1}{2} \sim 12$ hours
  - Oral bioavailability $\sim 59\%$
  - AUC of 450 mg PO similar to 300 mg IV
  - Metabolized primarily via glucuronidation
  - 65% renal elimination
    - Dose adjustments indicated
Delafloxacin (Baxdela™)

• Contraindications
  • Fluoroquinolone allergy

• Warnings and precautions
  • Similar to other fluoroquinolones
  • Tendon rupture, peripheral neuropathy, CNS effects
  • May exacerbate myasthenia gravis
  • *C. difficile*-associated diarrhea

• Drug interactions
  • Antacids, sucralfate, multivitamins

Baxdela PI 2017.
<table>
<thead>
<tr>
<th>Reaction</th>
<th>Delafloxacin N = 741</th>
<th>Vanco/aztreonam N = 751</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nausea</td>
<td>8%</td>
<td>6%</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>8%</td>
<td>3%</td>
</tr>
<tr>
<td>Headache</td>
<td>3%</td>
<td>6%</td>
</tr>
<tr>
<td>Increased transaminases</td>
<td>3%</td>
<td>4%</td>
</tr>
<tr>
<td>Vomiting</td>
<td>2%</td>
<td>2%</td>
</tr>
</tbody>
</table>

Baxdela PI 2017.
# Clinical Trial Data for Skin Infections

<table>
<thead>
<tr>
<th>Trial</th>
<th>Delafloxacin N = 331</th>
<th>Vancomycin/aztreonam N = 329</th>
<th>Treatment Difference (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>PROCEED 1</strong></td>
<td><strong>Clinical Response rate</strong></td>
<td>78.2%</td>
<td>80.9%</td>
</tr>
<tr>
<td><strong>PROCEED 2</strong></td>
<td><strong>Clinical Response rate</strong></td>
<td>83.7%</td>
<td>80.6%</td>
</tr>
</tbody>
</table>
Delafloxacin (Baxdela™)

- **Dosing**
  - IV—300 mg every 12 hours over 60 minutes
  - PO—450 mg every 12 hours
  - Duration of 5-14 days
  - Give at least 2 hours before or 6 hours after antacids, sucralfate, metal cations
  - Give with or without food

- **Renal impairment (CrCl 15-29 ml/min)**
  - IV—200 mg every 12 hours
  - PO—No adjustment

- **Avoid in end stage renal disease and dialysis (CrCl < 15 ml/min)**

Baxdela PI 2017.
Delafloxacin (Baxdela™)

- Bottom line
  - Unique fluoroquinolone for skin infections
  - MRSA activity
  - Similar warnings as other fluoroquinolones
  - Available both IV & PO

- Additional review
Bezlotoxumab has a lower recurrence rate of Clostridium difficile infections compared to vancomycin.

A. True
B. False
Bezlotoxumab (Zinplava™)

- Indication
  - Reduce recurrence of *Clostridium difficile* infection (CDI)
  - Patients MUST be receiving treatment for *Clostridium difficile* and at high risk of recurrence
  - NOT indicated for the treatment of CDI
- Pharmacology
  - Human monoclonal antibody
  - Binds to *Clostridium difficile* toxin B
  - Not fully understood why it prevents recurrence
- Pharmacokinetics
  - T½ ~ 19 days

Zinplava PI 2016
Bezlotoxumab (Zinplava™)

- Contraindications
  - None

- Warnings and Precautions
  - Heart failure exacerbations
    - 12.7% (15/118) bezlotoxumab vs. 4.8% (5/104) placebo
  - Deaths in patients with a history of heart failure
    - 19.5% (23/118) bezlotoxumab vs. 12.5% (13/104) placebo
  - Risk vs. benefit

- Drug interactions
  - None identified
## Adverse Reactions from Modify I and II Trials

<table>
<thead>
<tr>
<th>Reaction</th>
<th>Bezlotoxumab N = 786</th>
<th>Placebo N = 781</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall infusion-related</td>
<td>10%</td>
<td>8%</td>
</tr>
<tr>
<td>Nausea</td>
<td>7%</td>
<td>5%</td>
</tr>
<tr>
<td>Pyrexia</td>
<td>5%</td>
<td>3%</td>
</tr>
<tr>
<td>Headache</td>
<td>4%</td>
<td>3%</td>
</tr>
<tr>
<td>Heart failure</td>
<td>2.3%</td>
<td>1%</td>
</tr>
</tbody>
</table>

Zinplava PI 2016
# MODIFY I and MODIFY II Efficacy Results

<table>
<thead>
<tr>
<th>Recurrent CDI</th>
<th>Bezlotoxumab N = 781</th>
<th>Placebo N = 781</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall*</td>
<td>16.5% (129/781)</td>
<td>26.6% (206/773)</td>
</tr>
<tr>
<td>Hx of CDI in past 6 month</td>
<td>25% (54/216)</td>
<td>41.1% (90/219)</td>
</tr>
<tr>
<td>Hypervirulent strain</td>
<td>22% (22/100)</td>
<td>32.1% (35/109)</td>
</tr>
<tr>
<td>Age ≥ 65 years</td>
<td>15.4% (60/390)</td>
<td>31.4% (127/405)</td>
</tr>
</tbody>
</table>

*primary endpoint; NNT = 10; p-value < 0.0001

All subjects received vancomycin, metronidazole or fidaxomicin for 10-14 days

http://ofid.oxfordjournals.org/content/2/suppl_1/67.full.pdf+html
Bezlotoxumab (Zinplava™)

• Dosing
  • Administer during treatment for CDI
  • Single dose, 10 mg/kg IV infusion over 1 hour

• Availability/storage
  • 1000mg/40ml (25mg/ml) vial stored in refrigerator
  • Dilute in NS or D5 to 1 mg/ml to 10 mg/ml prior to infusion
  • Allow bag to come to room temp prior to use (stable x 16 hours)
  • AWP: $4560 per vial
Bezlotoxumab (Zinplava™)

• Bottom line
  • Reduced rate of recurrent CDI vs. placebo
  • Only in conjunction with antibiotic treatment
  • Consider for high risk populations
  • Well-tolerated in trials
  • Caution in heart failure

• Additional review
Which of the following is an approved duration of betrixaban?

A. Duration of hospitalization
B. 6 weeks
C. 3 months
D. 6 months
Betrixaban (Bevyxxa®)

• Indication
  • Prophylaxis of venous thromboembolism in hospitalized medical patients

• Pharmacology
  • Factor Xa inhibitor
Betrixaban (Bevyxxa®)

- Pharmacokinetics
  - Peaks in 3-4 hours
  - Food decreases absorption for up to 6 hours after a meal
  - $T\frac{1}{2}$ 19-27 hours
  - 85% GI, 11% renal elimination
  - Minimal metabolism
  - Renal impairment increases AUC 2-3x
Betrixaban (Bevyxxa®)

- Contraindications
  - Active bleeding

- Warnings/precautions
  - Spinal/epidural anesthesia
    - Wait 72 hours after last dose to remove epidural catheters
    - Wait 5 hours after catheter removal before giving next dose
  - Severe renal impairment (CrCl 15-29 ml/min)
  - Hepatic impairment
Betrixaban (Bevyxxa®)

- Drug interactions
  - P-glycoprotein inhibitors
    - Amiodarone, azithromycin, verapamil
    - Requires a dose reduction
  - Other anticoagulants/antiplatelets
### APEX Trial Cohort 1

<table>
<thead>
<tr>
<th></th>
<th>Betrixaban N = 1914</th>
<th>Enoxaparin N = 1956</th>
<th>RR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Composite</strong></td>
<td>6.9%</td>
<td>8.5%</td>
<td>0.81 (0.65-1.00) p = 0.054</td>
</tr>
<tr>
<td><strong>Asymptomatic DVT</strong></td>
<td>5.5%</td>
<td>6.6%</td>
<td>NR</td>
</tr>
<tr>
<td><strong>Symptomatic DVT</strong></td>
<td>0.7%</td>
<td>0.1%</td>
<td>NR</td>
</tr>
<tr>
<td><strong>Non-fatal PE</strong></td>
<td>0.3%</td>
<td>0.9%</td>
<td>NR</td>
</tr>
<tr>
<td><strong>VTE-related death</strong></td>
<td>0.6%</td>
<td>0.6%</td>
<td>NR</td>
</tr>
<tr>
<td><strong>Symptomatic events</strong></td>
<td>1.3%</td>
<td>1.9%</td>
<td>0.67 (0.42-1.07) p = 0.09</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Overall Population</th>
<th>Betrixaban N = 3112</th>
<th>Enoxaparin N = 3174</th>
<th>RR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Composite</td>
<td>5.3%</td>
<td>7%</td>
<td>0.76 (0.63-0.92) p = 0.006</td>
</tr>
<tr>
<td>Asymptomatic DVT</td>
<td>4.2%</td>
<td>5.5%</td>
<td>NR</td>
</tr>
<tr>
<td>Symptomatic DVT</td>
<td>0.4%</td>
<td>0.7%</td>
<td>NR</td>
</tr>
<tr>
<td>Non-fatal PE</td>
<td>0.3%</td>
<td>0.6%</td>
<td>NR</td>
</tr>
<tr>
<td>VTE-related death</td>
<td>0.4%</td>
<td>0.5%</td>
<td>NR</td>
</tr>
<tr>
<td>Symptomatic events</td>
<td>0.9%</td>
<td>1.5%</td>
<td>0.64 (0.42-0.98) p = 0.04</td>
</tr>
<tr>
<td>Ischemic stroke</td>
<td>0.48%</td>
<td>0.91%</td>
<td>0.53 (0.3-0.94) p = 0.026</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Overall Safety Outcomes</th>
<th>Betrixaban N = 3716</th>
<th>Enoxaparin N = 3716</th>
<th>RR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Major Bleeding</td>
<td>0.67%</td>
<td>0.57%</td>
<td>1.19 (0.67-2.12) p = 0.55</td>
</tr>
<tr>
<td>Gastrointestinal</td>
<td>0.51%</td>
<td>0.24%</td>
<td>NR</td>
</tr>
<tr>
<td>Intracranial hemorrhage</td>
<td>0.05%</td>
<td>0.19%</td>
<td>NR</td>
</tr>
<tr>
<td>Fatal bleeding</td>
<td>0.03%</td>
<td>0.03%</td>
<td>NR</td>
</tr>
<tr>
<td>Major or CRNM Bleeding</td>
<td>3.1%</td>
<td>1.6%</td>
<td>1.97 (1.44-2.68) p &lt; 0.001</td>
</tr>
</tbody>
</table>

CRNM = clinically relevant non-major bleeding

Bevxxa PI 2017
Betrixaban (Bevyxxa®)

- **Dosing**
  - 160 mg x 1 then 80 mg once daily
  - Give with food
  - Duration of 35-42 days
  - If CrCl 15-29 ml/min
    - 80 mg x 1 then 40 mg once daily
  - Concomitant P-gp inhibitor
    - 80mg x 1 then 40 mg once daily
Betrixaban (Bevyxxa®)

• Availability & Cost
  • 40 mg and 80 mg capsules
  • ? Release date
Betrixaban (Bevyxxa®)

- Bottom line
  - First agent approved for extended prophylaxis in hospitalized medically ill patients
  - Use for 35-42 days
  - Watch for renal impairment and P-gp inhibitors
  - Potential to reduce ischemic stroke post hospitalization

- Additional review
**Aspirin/Omeprazole (Yosprala™)**

- **Indication**
  - Secondary prevention of cardiovascular and cerebrovascular events in patients at risk for aspirin-associated ulcers

- **Dosage form**
  - Intelli-COAT system
  - Immediate release omeprazole 40mg
  - Delayed-release, enteric-coated aspirin (dissolves at pH > 5.5)
## Cumulative Incidence of Gastric Ulcers

<table>
<thead>
<tr>
<th>Months</th>
<th>Study 1</th>
<th>Study 2</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>ASA + OME N = 265</td>
<td>EC ASA N = 265</td>
</tr>
<tr>
<td>0-1</td>
<td>1.1%</td>
<td>3.8%</td>
</tr>
<tr>
<td>0-3</td>
<td>3%</td>
<td>6.8%</td>
</tr>
<tr>
<td>0-6</td>
<td>3.8%*</td>
<td>8.7%</td>
</tr>
</tbody>
</table>

ASA = aspirin; OME = omeprazole; EC = enteric coated
Yosprala PI 2016.

* p-value = 0.02; ** p-value 0.005
Aspirin/Omeprazole (Yosprala™)

• Dosing
  • 81/40 mg
  • 325/40 mg

• Price
  • ~$140 per month
  • ~ $40 for a month of omeprazole 40mg + ASA E.C. 325 mg

• Compliance vs. Cost

Yosprala PI 2016.
www.cardinal.com
Final Exam

- Get out your wireless device
- Go to kahoot.it
- Enter the game code: