NEW DRUG UPDATE 2014

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Presentation Objectives
Following completion of the presentation, participants should be able to:
1. Discuss the basic pharmacology of the new drugs presented and how the pharmacologic actions relate to both therapeutic and adverse effects.
2. Discuss clinically significant adverse effects and drug interactions, and the appropriate dosing and monitoring of the new drugs presented.
3. Discuss the therapeutic role of the new drugs presented as compared to agents already marketed.

Changing Drug Marketplace
• New drug development is skewed toward specialty drugs and orphan drugs
• Cost-savings from generic launches being offset by costs for specialty drugs
  – Oncology drugs
  – Orphan drugs
  • 2.6 times more expensive if no competition
• In 2013, over half of physician visits were with specialists

Audience Participation
Seven of the top 10 most expensive drugs in the U.S. are specialty drugs for rare diseases. The most expensive drug costs how much per patient per year?
A. $200,000
B. $300,000
C. $400,000
D. $500,000
E. $600,000

New Drug Update 2014 is accredited by ACPE for pharmacists, ACPE 0154-0000-14-012-L01-P, and technicians, ACPE 0154-0000-14-012-L01-T, for 1.5 contact hours.

Leroy Knodel has not disclosed any financial or conflicts of interest in relation to this program.

Eculizumab (Soliris®)
Humanized monoclonal antibody used in the treatment of paroxysmal nocturnal hemoglobinuria

$600,000
### Top 5 Most Expensive Drugs in U.S. (cost per patient per year)

<table>
<thead>
<tr>
<th>Drug</th>
<th>Indication</th>
<th>Cost</th>
</tr>
</thead>
<tbody>
<tr>
<td>Eculizumab (Soliris&lt;sup&gt;®&lt;/sup&gt;)</td>
<td>Paroxysmal nocturnal hemoglobinuria</td>
<td>$600,000</td>
</tr>
<tr>
<td>Idursulfase (Elaprase&lt;sup&gt;®&lt;/sup&gt;)</td>
<td>Hunter Syndrome</td>
<td>$375,000</td>
</tr>
<tr>
<td>Arylsulfatase B (Nagalzyme&lt;sup&gt;®&lt;/sup&gt;)</td>
<td>Mucopolysaccharidosis VI</td>
<td>$365,000</td>
</tr>
<tr>
<td>C1 esterase inhibitor [human] (Cinryze&lt;sup&gt;®&lt;/sup&gt;)</td>
<td>Hereditary angioedema</td>
<td>$350,000</td>
</tr>
<tr>
<td>Ivacaftor (Kalydeco&lt;sup&gt;®&lt;/sup&gt;)</td>
<td>Cystic fibrosis (G551D mutation)</td>
<td>$307,000</td>
</tr>
</tbody>
</table>

### Audience Participation

Which of the following drugs had the highest sales in the U.S. in 2013?

- A. Abilify<sup>®</sup> (aripiprazole)
- B. Nexium<sup>®</sup> (esomeprazole)
- C. Crestor<sup>®</sup> (rosuvastatin)
- D. Synthroid<sup>®</sup> (levothyroxine)
- E. Cymbalta<sup>®</sup> (duloxetine)

### Audience Participation

Which of the following drugs was the most widely prescribed drug in the United States in 2013?

- A. Abilify<sup>®</sup> (aripiprazole)
- B. Nexium<sup>®</sup> (esomeprazole)
- C. Crestor<sup>®</sup> (rosuvastatin)
- D. Synthroid<sup>®</sup> (levothyroxine)
- E. Cymbalta<sup>®</sup> (duloxetine)

### FDA Drug Approvals in 2013

#### New Molecular Entities – 28
- Pulmonary
  - Umeclidinium/vilanterol (Anoro Ellipta<sup>®</sup>) – COPD
  - Fluticasone/vilanterol (Breo Ellipta<sup>®</sup>) – COPD
  - Riociguat (Adempas<sup>®</sup>) – pulmonary hypertension
  - Macitentan (Opsumit<sup>®</sup>) – pulmonary hypertension
- Diabetes
  - Canagliflozin (Invokana<sup>®</sup>) – type 2 diabetes
  - Alogliptin (Nesina<sup>®</sup>) – type 2 diabetes
  - Alogliptin/metformin (Kazano<sup>®</sup>) – type 2 diabetes
  - Alogliptin/pioglitazone (Oseni<sup>®</sup>) – type 2 diabetes
- Oncology
  - Afatinib (Gilotrif<sup>®</sup>) – metastatic non-small cell lung CA
  - Ibrutinib (Imbruvica<sup>®</sup>) – mantle cell lymphoma
  - Trametinib (Mekinist<sup>®</sup>) – advanced melanoma
  - Pomalidomide (Pomalyst<sup>®</sup>) – multiple myeloma
  - Dabrafenib (Tafinlar<sup>®</sup>) – advanced melanoma
  - Radium Ra223 (Xofigo<sup>®</sup>) – advanced prostate cancer
- Infectious Diseases
  - Luliconazole (Luzu<sup>®</sup>) – antifungal
  - Simeprevir (Olysio<sup>®</sup>) – chronic hepatitis C
  - Sofosbuvir (Sovaldi<sup>®</sup>) – chronic hepatitis C
  - Dolутegravir (Tivicay<sup>®</sup>) – HIV-1 infection
- CNS
  - Vortioxetine (Brilinta®) – depression
  - Eslicarbazepine (Aptiom<sup>®</sup>) – partial-onset seizures
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FDA Drug Approvals in 2013 (cont)

- Miscellaneous
  - Conjugated estrogen/bazedoxifene (Duavee®) – menopausal symptoms/osteoporosis
  - Mipomersen (Kynamro®) – homozygous familial hypercholesterolemia
  - Glycerol phenylbutyrate (Ravicti®) – urea cycle disorders
  - Dimethylfumarate (Tecfidera®) – relapsing MS
  - Ospemifene (Osphena®) – painful sexual intercourse

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FDA Breakthrough Therapy Designation

- Breakthrough Therapy Designation
  - Legislation enacted July 9, 2012
  - Expedite development & review of drugs for serious or life-threatening conditions
  - Requires preliminary clinical evidence demonstrating substantial improvement on at least one clinically significant endpoint over available therapy
  - Fast-track review by FDA

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Dapagliflozin (Farxiga® - AstraZeneca/BMS)

Major Summary Points

- INDICATION – adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus
  - Monotherapy or combination therapy
- Second agent in this class for diabetes
  - Canagliflozin (Invokana®)

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Dapagliflozin Major Summary Points (cont)

- Sodium-glucose co-transporter 2 (SGLT2) inhibitor
  - SGLT2 is a carrier responsible for reabsorption of glucose filter by kidneys back into the bloodstream
  - A “glucuretic”
  - Osmotic diuresis results in ↓ blood pressure
- Possible secondary effects
  - Paradoxical ↑ endogenous glucose production
  - Improved beta-cell function & insulin sensitivity

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Dapagliflozin Major Summary Points (cont)

- Safety & efficacy demonstrated in > 9,000 pts

Monotherapy Results (24 wks)

<table>
<thead>
<tr>
<th></th>
<th>Adjusted Mean Change in A1C</th>
<th>Adjusted Mean Change in FBS*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Placebo</td>
<td>↓ 0.2%</td>
<td>↓ 4.1 mg/dL</td>
</tr>
<tr>
<td>Dap 5 mg</td>
<td>↓ 0.8%</td>
<td>↓ 24 mg/dL</td>
</tr>
<tr>
<td>Dap 10 mg</td>
<td>↓ 0.9%</td>
<td>↓ 29 mg/dL</td>
</tr>
</tbody>
</table>

* FBS – fasting blood sugar

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Dapagliflozin Major Summary Points (cont)

Combination Therapy with Metformin (24 wks)*

<table>
<thead>
<tr>
<th></th>
<th>Adjusted Mean Change in A1C</th>
<th>Adjusted Mean Change in FBS**</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dap 5 mg</td>
<td>↓ 1.2%</td>
<td>↓ 42.0 mg/dL</td>
</tr>
<tr>
<td>Dap 10 mg</td>
<td>↓ 1.5%</td>
<td>↓ 46.4 mg/dL</td>
</tr>
<tr>
<td>Metformin XR</td>
<td>↓ 1.4%</td>
<td>↓ 33.6-34.8 mg/dL</td>
</tr>
<tr>
<td>Dap 5 + Met XR</td>
<td>↓ 2.1%</td>
<td>↓ 61.0 mg/dL</td>
</tr>
<tr>
<td>Dap 10 + Met XR</td>
<td>↓ 2.0%</td>
<td>↓ 60.4 mg/dL</td>
</tr>
</tbody>
</table>

* Initial combination therapy (not add-on combination therapy)
** FBS – fasting blood sugar

Dapagliflozin Major Summary Points (cont)

• Adverse effects
  – Hypoglycemia is unlikely with monotherapy

<table>
<thead>
<tr>
<th></th>
<th>Placebo</th>
<th>Dap 5 mg</th>
<th>Dap 10 mg</th>
</tr>
</thead>
<tbody>
<tr>
<td>Female genital mycotic</td>
<td>1.5%</td>
<td>8.4%</td>
<td>6.9%</td>
</tr>
<tr>
<td>infection</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Urinary tract infection</td>
<td>3.7%</td>
<td>5.7%</td>
<td>4.3%</td>
</tr>
<tr>
<td>Increased urination</td>
<td>1.7%</td>
<td>2.9%</td>
<td>3.8%</td>
</tr>
<tr>
<td>Male genital mycotic</td>
<td>0.3%</td>
<td>2.8%</td>
<td>2.7%</td>
</tr>
<tr>
<td>infection</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Dapagliflozin Major Summary Points (cont)

• Drug Interactions
  – Metabolism of dapagliflozin is primarily via glucuronidation by UDP-glucuronosyl transferase (UGT) enzymes
    • UGT inducers (e.g., rifampin, phenytoin, phenobarbital, ritonavir) could ↓ AUC of dapagliflozin
  – No clinically significant interactions reported

Dapagliflozin Major Summary Points (cont)

• Warnings and Precautions
  – Symptomatic hypotension
  – Impaired renal function
  – Hypoglycemia when combined with insulin or an insulin secretagogue
  – ↑ in LDL-cholesterol
  – Bladder cancer

Dapagliflozin Major Summary Points (cont)

• Pregnancy Category C
  – No well-controlled studies in pregnant women
  – Problems with renal development and maturation in rat studies

• Contraindications
  – Severe renal impairment, end-stage renal disease, patients on dialysis
  – History of serious hypersensitivity reaction
Dapagliflozin Major Summary Points (cont)

- Concern - Impaired renal function
  - Common feature of diabetes, particularly long-standing diabetes
  - Appears less effective in patients with renal dysfunction; with long-term use, could it damage the kidneys further?

Dapagliflozin - Major Summary Points (cont)

- Dosage and Administration
  - Usual starting dose - 5 mg once daily in AM, before or after food
  - If inadequate response, ↑ dose to 10 mg
  - Do not use if eGFR is < 60 mL/min/1.73 m²
- FDA requiring studies to assess:
  - Bladder cancer risk
  - Risk of serious adverse effects (e.g., malignancies, cardiovascular problems, liver problems)
  - Safety and efficacy in children & during pregnancy

Comparison with Canagliflozin (Invokana®)

<table>
<thead>
<tr>
<th>A1C Reduction</th>
<th>Dapagliflozin</th>
<th>Canagliflozin</th>
</tr>
</thead>
<tbody>
<tr>
<td>Weight Loss, modest ↓ in blood pressure, modest ↑ LDL cholesterol</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Possible small ↑ risk of bladder cancer</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>Discontinue use if eGFR (per 1.73 m²)</td>
<td>&lt; 60 mL/min</td>
<td>&lt; 45 mL/min</td>
</tr>
</tbody>
</table>

Audience Response Time

When compared to gliptins such as sitagliptin & alogliptin, dapagliflozin is more likely to
A. Cause weight loss
B. Cause genital fungal infections
C. Increase serum creatinine
D. A and B only
E. A, B and C

Albiglutide (Tanzeum® - GlaxoSmithKline)

Major Summary Points

- INDICATION – adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus
  - Monotherapy or combination therapy
  - Not first-line therapy for patients inadequately controlled on diet and exercise

Albiglutide – Major Summary Points

- Glucagon-like peptide -1 (GLP-1) receptor agonist
  - Stimulates endogenous insulin production
  - Inhibits release of postprandial glucagons
  - Slows gastric emptying
  - Increases satiety
- Competition
  - Liraglutide (Victoza®) – daily injection
  - Exenatide extended-release (Bydureon®) – weekly injection (prefilled, single-use pen injector available later in 2014)
Albiglutide versus Liraglutide

- 32-week non-inferiority trial comparing daily liraglutide with weekly albiglutide
  - Albiglutide was NOT non-inferior
    - HbA1C decreased by 0.8% (A) vs. 1.0% (L)
  - Albiglutide was better tolerated
    - Adverse GI events overall – 35.9% (A) vs. 49% (L)
    - Nausea – 9.9% (A) vs. 29.2% (L)
    - Vomiting – 5% (A) vs. 9.3% (L)
  - Weight loss greater with liraglutide (2.19 kg vs. 0.64 kg)

Albiglutide – Major Summary Points

- Warning and precautions
  - Pancreatitis reported with all GLP-1 agonists
  - Hypoglycemia - can occur with insulin secretagogues (e.g., sulfonylureas) or insulin
  - Hypersensitivity reactions
  - Renal impairment
    - Especially important in patients experiencing GI adverse effects
  - Drug interactions – albiglutide delays gastric emptying

Albiglutide – Major Summary Points

- Initial dosage – 30 mg SC in abdomen, thigh or upper arm once weekly
  - ↑ dose to 50 mg as needed and tolerated
  - If dose is missed, administer within 3 days
  - Available as 30 mg & 50 mg single-dose pen

Role of GLP-1 Receptor Antagonists

- Some other therapies are more effective at ↓ A1C
- Considerations in use of GLP-1 receptor agonists
  - Circumstances where hypoglycemia can be serious
  - Patients experiencing frequent episodes of hypoglycemia
  - Adjunct in obese patients treated with metformin

Audience Response Time

In comparison to Liraglutide (Victoza®), albiglutide appears to be
A. Associated with fewer adverse GI effects
B. Associated with greater weight loss
C. More effective at lowering HbA1c
D. A and B only
E. A, B and C
Vorapaxar (Zontivity® - MSK)

**Major Summary Points**
- **INDICATION** – reduction of thrombotic cardiovascular events in patients (1) with a history of MI or (2) with peripheral arterial disease
  - not approved as monotherapy
  - use in combination with aspirin or clopidogrel (Plavix®)

Vorapaxar – Major Summary Points

- Protease-activated receptor-1 (PAR-1) reversible antagonist
  - Inhibits thrombin-induced and thrombin receptor agonist peptide (TRAP)-induced platelet aggregation
  - Does NOT inhibit ADP-, collagen- or thromboxane mimetic-induced platelet aggregation
- Effective half-life of 3-4 days; apparent terminal elimination half-life of 8 days

Vorapaxar – Major Summary Points (cont)

- Metabolized by CYP3A4 and CYP2J2; primary route of elimination is feces
- Drug interactions
  - Avoid strong CYP3A4 inhibitors (e.g., ketoconazole) and inducers (e.g., rifampin)
  - Avoid use with anticoagulants
- Contraindications
  - History of stroke, TIA, intracranial hemorrhage
  - Active pathological bleeding

Vorapaxar – Major Summary Points (cont)

- Clinical efficacy demonstrated in TRA 2°P - TIMI 50 trial (> 20,000 patients) over 3 years

<table>
<thead>
<tr>
<th></th>
<th>Vorapaxar</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>Composite of CV death, MI &amp; stroke (secondary endpoint)</td>
<td>7.9%</td>
<td>9.5%*</td>
</tr>
<tr>
<td>Composite of CV death, MI, stroke, &amp; UCR (primary endpoint)</td>
<td>10.1%</td>
<td>11.8%*</td>
</tr>
</tbody>
</table>

*P < .001
UCR – urgent coronary revascularization

Vorapaxar – Major Summary Points (cont)

- Bleeding in TRA 2°P - TIMI 50 trial

<table>
<thead>
<tr>
<th></th>
<th>Placebo</th>
<th>Vorapaxar</th>
</tr>
</thead>
<tbody>
<tr>
<td>Severe</td>
<td>1.0%</td>
<td>1.3%</td>
</tr>
<tr>
<td>Moderate or Severe</td>
<td>2.4%</td>
<td>3.7%*</td>
</tr>
<tr>
<td>Any Bleeding (Severe/Moderate/Mild)</td>
<td>19.8%</td>
<td>27.7%*</td>
</tr>
<tr>
<td>Fatal Bleeding</td>
<td>0.2%</td>
<td>0.2%</td>
</tr>
<tr>
<td>Intracranial Hemorrhage</td>
<td>0.4%</td>
<td>0.6%</td>
</tr>
<tr>
<td>Gastrointestinal Bleeding</td>
<td>3.5%</td>
<td>4.7%*</td>
</tr>
</tbody>
</table>

* p < .05

Omega-3-Carboxylic Acids (Epanova® - AZ)

**Major Summary Points**
- **INDICATION** – adjunct to diet to reduce triglyceride levels in adult patients with severe (≥ 500 mg/dL) hypertriglyceridemia
  - Effect on cardiovascular mortality and morbidity in patients with TGs ≥ 500 mg/dL is not known
- 4-5 million Americans have TGs ≥ 500 mg/dL
- Primary competition is Lovaza®
Epanova® - Major Summary Points (cont)

• Fish oil derived product
  – Concentrated mixture of EPA (50-60%) and DHA (15-25%) in free fatty acid form
• Third U.S. prescription omega-3 polyunsaturated fatty-acid product (Lovaza® & Vascepa®)
• Contraindication - patients with fish and/or shellfish hypersensitivity

Epanova® – Major Summary Points

• Warnings and Precautions
  – Monitor ALT and AST in patients with hepatic impairment
  – Monitor LDL-C levels periodically
• Drug Interactions
  – Anticoagulants and anti-platelet drugs
    • Omega-3 acids may prolong bleeding time

Epanova® - Major Summary Points (cont)

• ↑ bioavailability compared to ethyl ester forms found in Lovaza® and Vascepa®

Adult Patients with Severe Hypertriglyceridemia*

<table>
<thead>
<tr>
<th></th>
<th>Epanova® 2 g</th>
<th>Lovaza® 4 g</th>
<th>Vascepa® 4 g</th>
</tr>
</thead>
<tbody>
<tr>
<td>Triglycerides</td>
<td>-16% (2 g)</td>
<td>-31.6%</td>
<td>-33%</td>
</tr>
<tr>
<td>LDL-C (mg/dL)</td>
<td>+5 (2 g)</td>
<td>+4 (4 g)</td>
<td>+49.3</td>
</tr>
<tr>
<td>HDL-C (mg/dL)</td>
<td>+13 (2 g)</td>
<td>+15 (4 g)</td>
<td>+9.1</td>
</tr>
</tbody>
</table>

*Changes were calculated by taking the median % change for each drug and subtracting the placebo median % change. Based on data from approved product labeling.

Epanova® – Major Summary Points

• Most common adverse effects

<table>
<thead>
<tr>
<th></th>
<th>Placebo</th>
<th>Epanova® 2 g</th>
<th>Epanova® 4 g</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diarrhea</td>
<td>2%</td>
<td>7%</td>
<td>15%</td>
</tr>
<tr>
<td>Nausea</td>
<td>1%</td>
<td>4%</td>
<td>6%</td>
</tr>
<tr>
<td>Abdominal Pain</td>
<td>2%</td>
<td>3%</td>
<td>5%</td>
</tr>
<tr>
<td>Belching</td>
<td>&lt;1%</td>
<td>3%</td>
<td>3%</td>
</tr>
</tbody>
</table>

Epanova® - Major Summary Points (cont)

• Dosage and administration
  – Available as soft gelatin capsules (1 gram)
  – 2 or 4 grams once daily; based on patient response and tolerability
  – Administer without regard to meals
  – Swallow capsules whole

<table>
<thead>
<tr>
<th></th>
<th>Epanova® 2-4 caps/day</th>
<th>Lovaza® 4 g 4 caps/day</th>
<th>Vascepa® 4 g 2 caps BID with food</th>
</tr>
</thead>
</table>

Epanova® - Major Summary Points (cont)

• Additional research
  – Evaluation in patients with TGs > 200 mg/dL
  – Mixed dyslipidemia cardiovascular outcomes trial in combination with a statin (i.e., rosuvastatin - Crestor®)
$1000-a-Pill Sovaldi Jolts US Health Care System

For Patients, Costly Hepatitis C Cure is Priceless

$1000-A-Pill Sovaldi: Salvation or Rip-Off?

Insurers Worry That $84,000 Hepatitis C Drug Sovaldi Could Break the Bank

Fiercest Debate in Health Care Is about a $1000 Pill

Hepatitis C

• More than 3 million infected in the U.S.; majority have or will develop chronic disease
• Leading viral cause of cirrhosis, end-stage liver disease, & liver cancer
  – Over 10,000 deaths in U.S. annually; overtook HIV/AIDS in 2007
• Spreads primarily via contact with contaminated blood
  – transmission possible via a shared razor, toothbrush, or nail clippers

Hepatitis C

• Prevention
  – do not inject illicit drugs
  – avoid contact with infected blood
  – avoid high-risk sexual behavior such as multiple partners & anal contact (?)
• Acute infections are usually asymptomatic
• Most chronic infections asymptomatic
  – 15-20% will develop cirrhosis
    • End-stage liver disease requires transplantation
    • Inflammation and cirrhosis can lead to liver cancer

Hepatitis C

• Six primary genotypes of HCV; influences duration and success of treatment
  – Genotype 1 – most common in U.S. (70-80%)
    • Longer duration of treatment than genotypes 2 or 3
  – Genotypes 2 and 3 (20-25%)
  – Genotype 4 (common in Africa, the Middle East, and Eastern Europe), Genotype 5 (common in South Africa), and Genotype 6 (common in Southeast Asia) are less commonly seen in the U.S.

Sofosbuvir (Sovaldi® - Gilead)

Major Summary Points

• INDICATION – treatment of chronic hepatitis C (CHC) infection as a component of a combination antiviral treatment regimen
  – efficacy demonstrated in HCV genotype 1, 2, 3 & 4 infection, including those with
    • Hepatocellular carcinoma awaiting liver transplantation
    • HCV/HIV-1

Sofosbuvir - Major Summary Points (cont)

• Inhibitor of HCV RNA polymerase
  – Compared to protease inhibitors, development of resistance is less likely
• Prodrug - extensively metabolized in the liver to pharmacologically active nucleoside analog triphosphate GS-461203
**Sofosbuvir - Major Summary Points (cont)**

- 80% eliminated via the kidneys
- Half-life of GS-461203 – 27 hours
- No dosage adjustment required in mild/moderate renal impairment or hepatic disease

**Sofosbuvir - Major Summary Points (cont)**

- Efficacy in HCV genotype 1 infection
  - 327 patients (treatment naïve)
  - 12 weeks treatment with ribavirin (oral) AND peginterferon alfa (injection)
  - 89% sustained viral clearance (cure rate)
- Efficacy in HCV genotype 2 infection – 89-95% sustained viral clearing
- Efficacy in HCV genotype 3 infection – 61-63% sustained viral clearing

**Sofosbuvir - Major Summary Points (cont)**

- Patients with hepatocellular carcinoma awaiting liver transplantation
  - to prevent post-transplant HCV reinfection
  - Sofosbuvir + ribavirin is recommended
  - up to 48 weeks of treatment or until the time of liver transplantation, whichever occurs first

**Contraindications**

- Ribavirin may cause birth defects & fetal death; ribavirin is contraindicated in pregnant women and in men whose female partners are pregnant
- Interferons have abortifacient effects in animal models
- Avoid pregnancy in female patients and female partners of male patients

**Sofosbuvir - Major Summary Points (cont)**

<table>
<thead>
<tr>
<th>Adverse Effects</th>
<th>Placebo</th>
<th>Sofosbuvir Plus Ribavirin</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fatigue</td>
<td>24%</td>
<td>30-38%</td>
</tr>
<tr>
<td>Headache</td>
<td>20%</td>
<td>24-30%</td>
</tr>
<tr>
<td>Nausea</td>
<td>18%</td>
<td>13-20%</td>
</tr>
<tr>
<td>Insomnia</td>
<td>4%</td>
<td>15-16%</td>
</tr>
<tr>
<td>Pruritus</td>
<td>8%</td>
<td>11-27%</td>
</tr>
</tbody>
</table>

**Sofosbuvir - Major Summary Points (cont)**

<table>
<thead>
<tr>
<th>Adverse Effects</th>
<th>Peginterferon Plus Ribavirin</th>
<th>Sofosbuvir Plus Peginterferon Plus Ribavirin</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fatigue</td>
<td>55%</td>
<td>59%</td>
</tr>
<tr>
<td>Headache</td>
<td>44%</td>
<td>36%</td>
</tr>
<tr>
<td>Nausea</td>
<td>29%</td>
<td>34%</td>
</tr>
<tr>
<td>Insomnia</td>
<td>29%</td>
<td>25%</td>
</tr>
<tr>
<td>Anemia</td>
<td>12%</td>
<td>21%</td>
</tr>
</tbody>
</table>
Sofosbuvir – Drug Interactions

- A substrate of drug transporter P-gp
  - P-gp inducers MAY ↓ absorption and efficacy of Sofosbuvir
    - Should NOT be used with rifampin or St. John’s Wort
    - Co-administration of other inducers (e.g., carbamazepine, rifabutin, tipranavir/ritonavir) is NOT recommended
  - P-gp inhibitors do NOT affect absorption or efficacy of Sofosbuvir

Sofosbuvir - Major Summary Points (cont)

- Should NOT be used as monotherapy
- For patients who do NOT have severe liver disease (genotype 1), waiting is an option
- Advanced liver disease (genotype 1) options
  - Sofosbuvir/interferon/ribavirin is first choice
  - Sofosbuvir + simeprevir (Olysio®) ± ribavirin is an alternative option (off-label)

Sofosbuvir - Major Summary Points (cont)

- Dosage - one 400 mg tablet taken once daily with or without food

Regimens for Chronic Hepatitis C Infection

<table>
<thead>
<tr>
<th>Genotype</th>
<th>Treatment</th>
<th>Duration</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Sofosbuvir + Peginterferon alfa + Ribavirin</td>
<td>12 weeks</td>
</tr>
<tr>
<td>2</td>
<td>Sofosbuvir + Ribavirin</td>
<td>12 weeks</td>
</tr>
<tr>
<td>3</td>
<td>Sofosbuvir + Ribavirin</td>
<td>24 weeks</td>
</tr>
</tbody>
</table>

Sofosbuvir - Major Summary Points (cont)

- Should NOT look at just cost per pill ($1000)
  - Additional monitoring required for other therapies
  - More adverse effects/drug interactions with other therapies = higher cost
  - Protease inhibitor regimens (24-48 weeks)
    - $40,000-$73,000

Audience Response Time

The recommended treatment for the majority of patients with chronic hepatitis C infection in the U.S. is

A. Sofosbuvir for 24 weeks
B. Sofosbuvir + Ribavirin for 12 weeks
C. Sofosbuvir + Ribavirin for 24 weeks
D. Sofosbuvir + Peginterferon alfa + Ribavirin for 12 weeks
E. Sofosbuvir + Simeprevir (Olysio®) ± Ribavirin for 12 weeks

Lightning Rounds
Multiple Sclerosis

- Chronic, often disabling autoimmune disease
  - Damage to myelin sheaths around axons of the spinal cord and brain
  - Damaged myelin affects nerve transmission
- Onset typically in young adulthood; females > males
- 400,000 Americans affected; 2.4 million worldwide
- Prognosis – physical and cognitive disability

Dimethyl Fumarate (Tecfidera™) – Biogen

**Major Summary Points**

- INDICATION - treatment of patients with relapsing forms of multiple sclerosis
- Once used as a biocide against mold in furniture & shoes
- A dimethyl fumarate (DMF) formulation used in Germany since 1994 for treatment of psoriasis
- Exact MOA unknown
  - Immunomodulatory effects
  - Neuroprotective effects

Dimethyl Fumarate – Major Summary Points

- Rapidly converted by presystemic hydrolysis to its active metabolite, monomethyl fumarate (MMF)
- Primarily eliminated via CO2 exhalation
- Half-life = 1 hour
- Contraindications – none
- Drug interactions - none

Dimethyl Fumarate – Clinical Efficacy

- **Study 1** – 2-year, randomized, double-blind trial

<table>
<thead>
<tr>
<th></th>
<th>DMF</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>% Patients Relapsing</td>
<td>27%</td>
<td>49%</td>
</tr>
<tr>
<td>% Pts with Disability Progression</td>
<td>16%</td>
<td>27%</td>
</tr>
<tr>
<td>Mean Number of New Brain Lesions or Newly Enlarging Lesions</td>
<td>2.6</td>
<td>17</td>
</tr>
<tr>
<td>% with No New or Newly Enlarging Lesions</td>
<td>45%</td>
<td>27%</td>
</tr>
</tbody>
</table>

All differences statistically significant
**Teriflunomide (Aubagio®) – Sanofi Aventis**

**Major Summary Points**
- **INDICATION** - treatment of patients with relapsing forms of multiple sclerosis
- Active metabolite of leflunomide (Arava®)
- Exact MOA unknown
  - Immunomodulatory effects
  - Antiinflammatory effects
- Dosage – 7 or 14 mg tablet once daily, with or without food

**Teriflunomide – Major Summary Points**
- Clinical Efficacy (7 and 14 mg doses)
  - Placebo comparisons
  - relapses and disability progression reduced by approximately 1/3
  - Interferon beta 1a comparison (treatment failure rates over 2 years*)
  - Teriflunomide 7 mg – 48.6%
  - Teriflunomide 14 mg – 37.8%
  - Interferon beta 1a – 42.3%
- *Treatment failure – relapse or permanent drug d/c

**Teriflunomide – Major Summary Points**
- Phase III Study (TOPIC Trial) – teriflunomide versus placebo in preventing/delaying conversion from Clinically Isolated Syndrome (CIS) to definite MS
  - TFM 14 mg – 43% ↓ in risk of conversion
  - TFM 7 mg – 37% ↓ in risk of conversion
- Other agents demonstrating a reduction in risk of conversion
  - Interferons
  - Glatiramer acetate (Copaxone®)

**Teriflunomide – Median half-life**
- 18-19 days

**Teriflunomide – Drug Interactions**
- In vivo, teriflunomide is an inhibitor of CYP2C8
  - CYP2C8 substrates - repaglinide, paclitaxel, pioglitazone, rosiglitazone
- Warfarin
  - 25% ↓ in peak INR
- Oral contraceptives
  - Teriflunomide may ↑ exposure of ethinylestradiol and levonorgestrel
- In vivo, teriflunomide is a WEAK inducer of CYP1A2
  - CYP1A2 substrates – duloxetine, tizanidine

**Teriflunomide – Warnings & precautions**
- May ↓ WBC; may ↑ risk of infection
- Peripheral neuropathy
- Acute renal failure/hyperkalemia
- Severe skin reactions – d/c and initiate accelerated elimination procedure
- Blood pressure – measure at initiation & monitor
**Audience Response Time**

Flushing associated with dimethyl fumarate (Tecfidera™) can be minimized by which of the following?

A. Taking with food  
B. Taking concomitant aspirin  
C. Avoiding hot beverages and food  
D. A and B only  
E. A, B and C

**Paroxetine (Brisdelle™ – Noven)**

Major Summary Points

- **INDICATION** - treatment of moderate to severe vasomotor symptoms associated with menopause  
  — not indicated for the treatment of any psychiatric condition  
- Selective serotonin reuptake inhibitor  
- First non-hormonal therapy approved for the treatment of menopausal vasomotor symptoms

**Brisdelle™ – Efficacy**

- **Study 1**: 12-week, randomized, double-blind trial in 606 menopausal women  
  **Reduction in Episodes of VMS**

<table>
<thead>
<tr>
<th></th>
<th>Brisdelle™</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline Daily Episodes (median)</td>
<td>10.4</td>
<td>10.4</td>
</tr>
<tr>
<td>Change in Episodes (median)</td>
<td>-5.9*</td>
<td>-5.0*</td>
</tr>
</tbody>
</table>

* p<0.01

- **Study 2**: 24-week, randomized, double-blind trial in 568 menopausal women  
  **Reduction in Episodes of VMS**

<table>
<thead>
<tr>
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<th>Brisdelle™</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline Daily Episodes (median)</td>
<td>9.9</td>
<td>9.6</td>
</tr>
<tr>
<td>Change in Episodes (median)</td>
<td>-5.6*</td>
<td>-3.9*</td>
</tr>
</tbody>
</table>

* p<0.01

**Brisdelle™ – Major Summary Points**

- Contraindications  
  — Concurrent use with MOAs, thioridazine, or pimozide  
  — Pregnancy  
- Warnings & precautions  
  — Suicidality, serotonin syndrome, abnormal bleeding, bone fracture, seizures, akathisia, acute angle closure glaucoma, cognitive impairment

**Drug Interactions** - paroxetine is a strong CYP2D6 inhibitor  
— ↑ serum concentrations possible with
  - many TCAs (e.g., amitriptyline, desipramine)  
  - fluoxetine  
  - phenothiazines  
  - risperidone  
  - Type 1C antiarrhythmics (e.g., flecainide, encainide)
Brisdelle™ – Major Summary Points

- Most common adverse effects
  
<table>
<thead>
<tr>
<th></th>
<th>Brisdelle™</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>Headache</td>
<td>6.3%</td>
<td>4.8%</td>
</tr>
<tr>
<td>Fatigue/Lethargy</td>
<td>4.9%</td>
<td>2.8%</td>
</tr>
<tr>
<td>Nausea/Vomiting</td>
<td>4.3%</td>
<td>2.3%</td>
</tr>
</tbody>
</table>

- Dosage and administration
  - 7.5 mg capsule once daily at bedtime, with or without food
- Consideration – cost of Brisdelle™ 7.5 mg capsule vs. generic paroxetine tablet 10 mg

Sublingual Immunotherapies

- Oralair® - grass pollen-induced allergic rhinitis, with or without conjunctivitis, confirmed by positive skin test or in vitro testing for pollen-specific IgE antibodies for any of the following five grass species: sweet vernal, orchard, perennial ryegrass, Timothy, and Kentucky blue grass

- Grastek® - grass pollen-induced allergic rhinitis, with or without conjunctivitis, confirmed by positive skin test or in vitro testing for pollen-specific IgE antibodies for Timothy grass or cross-reactive grass pollens*
  
  * including sweet vernal, orchard, perennial ryegrass, Kentucky blue, & red top grasses

Sublingual Immunotherapies (cont)

<table>
<thead>
<tr>
<th></th>
<th>Oralair®</th>
<th>Grastek®</th>
<th>Ragwitek®</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ages</td>
<td>10-65 years</td>
<td>5-65 years</td>
<td>18-65 years</td>
</tr>
<tr>
<td>First Dose</td>
<td>MD office; observe 30 minutes</td>
<td>MD office; observe 30 minutes</td>
<td>MD office; observe 30 minutes</td>
</tr>
<tr>
<td>Directions</td>
<td>Allow at least 1 minute under tongue before swallowing</td>
<td>Allow at least 1 minute under tongue before swallowing</td>
<td>Allow at least 1 minute under tongue before swallowing</td>
</tr>
<tr>
<td>Initiation of Therapy</td>
<td>4 months before onset of pollen season</td>
<td>12 weeks before onset of pollen season</td>
<td>12 weeks before onset of pollen season</td>
</tr>
<tr>
<td>Duration of Therapy</td>
<td>Continue treatment throughout the season.</td>
<td>May be taken daily for three consecutive years</td>
<td>Continue treatment throughout the season.</td>
</tr>
</tbody>
</table>

Sublingual Immunotherapies (cont)

- Warnings
  - Immunotherapies can cause life-threatening allergic reactions
  - Prescribe and train patients on the use of auto-injectable epinephrine
  - May not be suitable for patients
    - with certain underlying medical conditions that may reduce their ability to survive a serious allergic reaction
    - who may be unresponsive to epinephrine or inhaled bronchodilators, such as those taking beta-blockers

Audience Response Time

In comparative trials, both Brisdelle™ and placebo have been shown to reduce vasomotor episodes in menopausal women. The difference in the number of daily vasomotor episodes between women treated with Brisdelle™ and those treated with placebo is approximately

- A. 1-2
- B. 3-4
- C. 5-6
- D. 7-8
- E. > 8
Sublingual Immunotherapies (cont)

• Contraindications
  – Severe, unstable or uncontrolled asthma
  – History of any severe systemic allergic reaction or any severe local reaction to sublingual allergen immunotherapy
  – A history of eosinophilic esophagitis
  – Hypersensitivity to any of the inactive ingredients contained in the products

• Oral inflammation or oral wounds – stop therapy until healing has occurred

Sublingual Immunotherapies (cont)

• Grastek® Adverse Effects

<table>
<thead>
<tr>
<th></th>
<th>Grastek®</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>Oral Pruritus</td>
<td>26.7%</td>
<td>3.5%</td>
</tr>
<tr>
<td>Throat Irritation</td>
<td>22.6%</td>
<td>2.8%</td>
</tr>
<tr>
<td>Ear Pruritus</td>
<td>12.5%</td>
<td>1.1%</td>
</tr>
<tr>
<td>Mouth Edema</td>
<td>11.1%</td>
<td>0.8%</td>
</tr>
</tbody>
</table>

Sublingual Immunotherapies (cont)

• Oralair® Adverse Effects

<table>
<thead>
<tr>
<th></th>
<th>Oralair®</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>Oral Pruritus</td>
<td>25.1%</td>
<td>5%</td>
</tr>
<tr>
<td>Throat Irritation</td>
<td>22%</td>
<td>3.7%</td>
</tr>
<tr>
<td>Ear Pruritus</td>
<td>8.4%</td>
<td>0.6%</td>
</tr>
<tr>
<td>Mouth Edema</td>
<td>8.2%</td>
<td>0.6%</td>
</tr>
<tr>
<td>Tongue Pruritus</td>
<td>7.9%</td>
<td>0.7%</td>
</tr>
</tbody>
</table>

Sublingual Immunotherapies (cont)

• Ragwitek® Adverse Effects

<table>
<thead>
<tr>
<th></th>
<th>Ragwitek®</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>Oral Pruritus</td>
<td>10.9%</td>
<td>2.0%</td>
</tr>
<tr>
<td>Throat Irritation</td>
<td>16.6%</td>
<td>3.3%</td>
</tr>
<tr>
<td>Ear Pruritus</td>
<td>10.4%</td>
<td>1.1%</td>
</tr>
<tr>
<td>Mouth Edema</td>
<td>6.1%</td>
<td>0.5%</td>
</tr>
<tr>
<td>Tongue Pruritus</td>
<td>5.1%</td>
<td>0.5%</td>
</tr>
</tbody>
</table>

Sublingual Immunotherapies (cont)

• Considerations
  – Option for persons declining allergy shots
  – Not for immediate relief of allergic symptoms
  – Persons with mild asthma & not taking daily medications were included in clinical trials
  – Efficacy demonstrated in reduce symptom scores and the need for supplemental medication (e.g., oral/ocular antihistamines, inhaled steroids)

Levomilnacipran (Fetzima™ – Forest)

Major Summary Points

• INDICATION - treatment of major depressive disorder
• An enantiomer of racemic milnacipran
• Interconversion between levomilnacipran and its stereoisomer does not occur in humans
• Approved in France in 1996
• Serotonin/norepinephrine reuptake inhibitor (SNRI)
Levomilnacipran – Major Summary Points

• Other SNRIs indicated in depression
  – Duloxetine (Cymbalta®)
  – Venlafaxine (Effexor XR®)
  – Desvenlafaxine (Pristiq®)

• In vitro, more potent than venlafaxine and duloxetine in inhibiting norepinephrine uptake compared to serotonin uptake

Levomilnacipran – Major Summary Points

• NOT approved for fibromyalgia
• SNRIs approved for fibromyalgia
  – Duloxetine (Cymbalta®)
  – Venlafaxine (Effexor XR®)
  – Milnacipran (Savella®)

Levomilnacipran – Major Summary Points

• Clinical efficacy demonstrated in placebo-controlled trials
• Contraindications, warnings/precautions, and adverse effects similar to other SSRIs & SNRIs
• Metabolized via CYP3A4
  – ↓ dose (maximum 80 mg/day) if administered with strong CYP3A4 inhibitors (e.g., ketoconazole)

Levomilnacipran – Major Summary Points

• Dosage and administration
  – Initial therapy: 20 mg once daily for 2 days
  – ↑ dosage to 40 mg once daily
  – Based on efficacy and tolerability, may ↑ dosage in increments of 40 mg every 2 or more days
  – Maximum recommended dose – 120 mg once daily

Audience Challenge

Will you be able to use the information included in this presentation to improve the care you provide to your patients?

• Yes
• No

Your Questions