Conflict of Interest Disclosures

- I have nothing to disclose

Learning Objectives

1. Evaluate guideline based treatment strategies for patients with gastrointestinal disorders.
2. Describe appropriate preventative strategies for patients with gastrointestinal disorders.
3. Compare and contrast the efficacy and adverse event profiles of medications used for treatment of gastrointestinal disorders.
4. Discuss the advantages and disadvantages of various diagnostic tests used for gastrointestinal disorders.
5. Formulate treatment plans for patients with newly diagnosed gastrointestinal disorders.
6. Review and understand treatment options for patients who are refractory to standard therapies and determine the best option on the basis of each patient's medication history and profile.
7. Educate patients, caregivers, and prescribers regarding appropriate use and toxicities of pharmacologic agents used for the management of gastrointestinal disorders.

Chapter Outline

- Gastroesophageal reflux disease (GERD)
- Peptic ulcer disease (PUD)
- Complications of cirrhosis
  - Ascites, spontaneous bacterial peritonitis (SBP), hepatorenal syndrome, hepatic encephalopathy, gastroesophageal varices
- Viral hepatitis

Viral Hepatitis
**Viral Hepatitis**
- Hepatitis A, B, C (D and E)
- Chronic: infection > 6 months

**Hepatitis A**
- RNA virus
- Transmission
  - Fecal-oral
  - Person-to-person, or ingestion of contaminated food or water
- Symptoms
  - Acute onset; fatigue, abdominal pain, anorexia, nausea, vomiting, jaundice, pruritus
- Diagnosis: liver test elevation, anti-HAV positive
- Treatment: no specific therapy, supportive

**Hepatitis B (HBV)**
- DNA virus; genotypes A-H
- Transmission
  - Body fluids
  - Sexual contact, parenteral, perinatal
- Data suggests disease progression may be linked to genotype

**Hepatitis B: clinical presentation & assessment**
- Symptoms
  - Many are asymptomatic
  - Abdominal pain, diarrhea, fever, jaundice, myalgia, nausea and vomiting
- History and physical exam
- Laboratory testing
- Serologic testing

**HBV: serologic testing**

---

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**HBV: serologic testing**

Table 12: Interpretation of HBV Serologic Test Results

<table>
<thead>
<tr>
<th>Condition</th>
<th>HBsAg</th>
<th>Anti-HBs</th>
<th>IgM anti-HBs</th>
<th>Anti-HBe</th>
</tr>
</thead>
<tbody>
<tr>
<td>No infection, no evidence</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Acute infection</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Chronic infection</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Recovered from acute illness</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Inactive (remission or Failure)</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
</tbody>
</table>

*HBs = hepatitis B surface antigen; HBcAg = hepatitis B core antigen; HBV = hepatitis B virus; IgM = immunoglobulin M.*

**HBV: phases**

- **Immune tolerant**
- **Immune active**
- **Inactive carrier**

**Shifts**

- Immune tolerant → Immune active → Inactive carrier
- Immune active ← Inactive carrier

**HBV: Treatment**

- **Goals**
  - Suppress HBV replication
  - Prevent liver disease progression (cirrhosis, HCC) and death
- **Response**
  - Classified as biochemical, virologic and/or histologic
  - Classified according to time of assessment

**Indication for therapy**

- When there is a likely risk of liver-related morbidity and mortality in the next 5-10 years AND when it is likely to achieve ongoing viral suppression during therapy
HBV: Treatment – guideline recommendations

- Consider treatment
  - Immune active
    - HBeAg positive
      - HBV DNA > 20,000 IU/mL
      - ALT 2x ULN
    - HBeAg negative
      - HBV DNA > 20,000 IU/mL
      - ALT 2x ULN
  - Immune tolerant
  - Inactive carrier

- No Treatment indicated
  - Immune tolerant
  - Inactive carrier

HBV: Treatment

- Treatment end points
  - Suppression of HBV DNA to undetectable levels
  - Loss of HBeAg and HBsAg

- Choice of therapy is patient specific
  - Selection based on patient profile, treatment history, contraindications, medication cost etc.

- Pharmacotherapy
  - Interferons
  - Nucleoside analogs (reverse transcriptase inhibitors)

HBV: Pharmacotherapy

- Interferons (INF-α, Peg-INF-α)
  - Comparable efficacy; Peg-INF-α is preferred

- Nucleoside analogs
  - First line: Entecavir, tenofovir

- Class effects
  - Lactic acidosis (box warning)
  - Rebound hepatitis
  - Antiviral resistance
    - Major concern with long term use
    - Virologic breakthrough → biochemical breakthrough

Table 20: Comparisons of Agents for Treatment of Adult Chronic HBV

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Entecavir (Baraclude)</th>
<th>Tenofovir (Viread)</th>
<th>Lamivudine (Epivir)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Efficacy</td>
<td>Plasma DNA undetectable</td>
<td>Plasma DNA undetectable</td>
<td>Plasma DNA undetectable</td>
</tr>
<tr>
<td>Resistance</td>
<td>Reduced</td>
<td>Reduced</td>
<td>Reduced</td>
</tr>
</tbody>
</table>

Other points to consider

- Combination therapy
- Special populations
  - Decompensated cirrhosis
  - Individuals not responding to therapy
  - Individuals on NA therapy that develop viral breakthrough
HBV: Pharmacotherapy

Guideline Recommendations

- **Lamivudine resistance**
  - Add adefovir or tenofovir
  - Discontinue lamivudine; add truvada (emtricitabine 200mg + tenofovir 200 mg)

- **Adefovir resistance**
  - Add lamivudine or entecavir
  - Discontinue adefovir, add truvada
  - Discontinue adefovir, add entecavir

- **Entecavir resistance**
  - Discontinue entecavir and change to tenofovir or truvada

- **Telbivudine resistance**
  - Add adefovir or tenofovir
  - Discontinue telbivudine and change to truvada

HBV: Treatment summary

- **Indication**
  - Based on phase of disease

- **Pharmacotherapy**
  - Preferred agents: peg-Inf-α (or) NA
  - Choice of therapy: patient specific

Patient Case #7

**HPI:** 57 year-old female with history of intravenous drug and alcohol abuse and depression. Diagnosed with chronic HBV 6 months ago presents with mild ascites. Patient reports naïve to anti-viral therapy.

**Vitals:** height 5’7”, T 98.7° F, HR 79 beats/min, RR 15 breaths/min, BP 130/80 mmHg

**Laboratory:** AST 478 IU/mL, ALT 780 IU/mL, albumin 3.3 g/dL, INR 1.1, SCr 1.3 mg/dL, HBsAg positive, HBeAg positive, HBV DNA 94,000 IU/mL

**Liver biopsy:** significant fibrosis (stage 3)

**Medications:** Citalopram 20mg daily

Which one of the following is the best option for this patient?

A. Initiate Peg-Inf-α at 180 mcg once weekly
B. Initiate lamivudine at 100 mg orally for the first dose; then 50 mg orally daily
C. Initiate tenofovir 300 mg orally once daily
D. Initiate tenofovir 300 mg orally every other day

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Hepatitis C (HCV)

- Major cause of death from liver disease and leading indication for liver transplantation
  - Acute infection develops into chronic infection in 55-85%
  - Chronic infection develops into HCV-related cirrhosis over a 25-30 period in 5-25% of patients
- RNA virus (6 genotypes, 50 subtypes)
- Transmission
  - Infectious blood
  - Sexual contact, parenteral, perinatal

HCV: Clinical presentation & assessment

- Symptoms (chronic disease)
  - Asymptomatic for years
  - Anorexia, abdominal pain, fever, jaundice, malaise, naussea
- History and physical exam
- Testing
  - Laboratory, serologic and genotype
- Liver biopsy
  - Grade: extent of necroinflammation; Stage: extent of fibrosis

HCV: Transmission

- Infectious blood
- Sexual contact, parenteral, perinatal

HCV: Testing

Table 35 Laboratory Data

<table>
<thead>
<tr>
<th>Antivirus</th>
<th>HCV RNA</th>
<th>Interpretation</th>
</tr>
</thead>
<tbody>
<tr>
<td>-</td>
<td>-</td>
<td>Chronic infection is necessary to differentiate between acute and chronic disease</td>
</tr>
<tr>
<td>-</td>
<td>+</td>
<td>Resolution of acute infection, acute infection during period of low virus</td>
</tr>
<tr>
<td>-</td>
<td>Early acute infection</td>
<td></td>
</tr>
<tr>
<td>-</td>
<td>Chronic virus; transmission suppressed</td>
<td></td>
</tr>
<tr>
<td>-</td>
<td>Disease of infection</td>
<td></td>
</tr>
</tbody>
</table>

HCV RNA = quantitative (IU/mL)

HCV: Virologic response

<table>
<thead>
<tr>
<th>Virologic Response</th>
<th>Assessment Period</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>Interferon</td>
<td>Treatment week 4</td>
<td>Initial RNA detectable</td>
</tr>
<tr>
<td>Partial response</td>
<td>Treatment week 12</td>
<td>SVR: &lt;50 IU/mL; no detectable virus at week 24</td>
</tr>
<tr>
<td>Complete response</td>
<td>Treatment week 24</td>
<td>SVR: &lt;50 IU/mL; no detectable virus at week 48</td>
</tr>
</tbody>
</table>

HCV: Treatment response

- SVR
  - Best predictor of response and is considered virologic cure
- Achieving SVR varies according to genotype, patient population and treatment regimen
  - Treatment naive
    - Genotype 1 (triple therapy): 67 – 75%
    - Genotype 4 (combination therapy): 45 – 50%
- Genotype 2 and 3 (combination therapy): 80%
**HCV: Virologic response**

<table>
<thead>
<tr>
<th>Virologic Response</th>
<th>Assessment Point</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rapid virologic response (RVR)</td>
<td>Treatment week 4</td>
<td>HCV RNA undetectable</td>
</tr>
<tr>
<td>Early virologic response (pRVR)</td>
<td>Treatment week 2</td>
<td>HCV RNA &lt; 400 IU/mL by HCVRNA assay</td>
</tr>
<tr>
<td>Complete virologic response (cRVR)</td>
<td>Treatment week 12</td>
<td>HCV RNA undetectable</td>
</tr>
<tr>
<td>Undetectable viral load (ULN)</td>
<td>12 weeks after start of treatment</td>
<td>HCV RNA &lt; 400 IU/mL</td>
</tr>
<tr>
<td>Sustained virologic response (SVR)</td>
<td>24 weeks after end of treatment</td>
<td>HCV RNA undetectable</td>
</tr>
</tbody>
</table>

**HCV: Predictors of response**

- **Pretreatment**
  - HCV genotype
  - Viral load
  - Histologic stage
  - IL28B genotypes
    - CC, CT and TT
    - CC more likely to achieve SVR

- **Posttreatment**
  - EVR
  - RVR

**HCV: Treatment – guideline recommendations**

- Recommendations based on genotype
  - **Pharmacotherapy**
    - **Genotype 1**: triple therapy
      - Peg-INF-α + ribavirin + protease inhibitor
    - **Genotypes 2-6**: combination therapy
      - Peg-INF-α + ribavirin
  - **Guidelines**
    - Hepatology 2009:49:1335-74
    - Hepatology 2011;54:1433-44 (genotype 1 only)

**HCV: Pharmacotherapy**

- Peg-INF-α
- Ribavirin
- Protease inhibitors

**HCV: Peg-INF-α**

- **Similar efficacy**
- **Dosing constant for ALL genotypes**

**HCV: Ribavirin**

- **Dosing**
  - Varies according to genotype, weight and Peg-INF-α
  - Reduction necessary for renal impairment and adverse events

**HCV: Peg-INF-α**

<table>
<thead>
<tr>
<th>Dosing</th>
<th>Peg-INF-α</th>
<th>Weight (kg)</th>
<th>Dose (mg/kg) to 2 divided doses</th>
<th>Route of Administration</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 or 2</td>
<td>75</td>
<td>≤ 75</td>
<td>1200</td>
<td>Oral</td>
</tr>
<tr>
<td>2 or 3</td>
<td>&gt; 75</td>
<td>1200</td>
<td></td>
<td>Oral</td>
</tr>
<tr>
<td>4</td>
<td>≤ 75</td>
<td>1000</td>
<td></td>
<td>Oral</td>
</tr>
<tr>
<td>5</td>
<td>&gt; 75</td>
<td>1200</td>
<td></td>
<td>Oral</td>
</tr>
</tbody>
</table>

**HCV: Ribavirin**

- **Dosing**
  - Varies according to genotype, weight and Peg-INF-α
  - Reduction necessary for renal impairment and adverse events

**HCV: Ribavirin**

<table>
<thead>
<tr>
<th>Dosing</th>
<th>Ribavirin</th>
<th>Weight (kg)</th>
<th>Dose (mg/kg) to 2 divided doses</th>
<th>Route of Administration</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 or 2</td>
<td>75</td>
<td>≤ 75</td>
<td>1200</td>
<td>Oral</td>
</tr>
<tr>
<td>2 or 3</td>
<td>&gt; 75</td>
<td>1200</td>
<td></td>
<td>Oral</td>
</tr>
<tr>
<td>4</td>
<td>≤ 75</td>
<td>1000</td>
<td></td>
<td>Oral</td>
</tr>
<tr>
<td>5</td>
<td>&gt; 75</td>
<td>1200</td>
<td></td>
<td>Oral</td>
</tr>
</tbody>
</table>

**Updates in Therapeutics® 2012: Ambulatory Care Pharmacy Preparatory Review and Recertification Course**

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HCV: Protease Inhibitors

- Agents
  - Telaprevir (Incivek®)
  - Boceprevir (Victrelis®)
- Mechanism of action
  - NS3/4A protease enzyme inhibition

HCV: Telaprevir

- FDA Indication
  - Treatment of chronic HCV genotype 1 (in combination with Peg-INF-α and ribavirin) in adult patients with compensated liver disease (including cirrhosis) who are treatment naïve or who have received previous interferon based treatment, including null and partial responders and treatment relapsers.

- Dose and administration
  - 750 mg by mouth 3 times daily for 12 weeks
  - No dose adjustments in renal or hepatic impairment
  - Not studied in patients with CrCl < 50 mL/min, hemodialysis or moderate to severe (Child-Pugh B and C)
  - Administer with non low-fat meal
  - Discontinue if either or both Peg-INF-α and ribavirin discontinued

HCV: Telaprevir

- Adverse events
  - Most common
    - Rash, fatigue, pruritus, nausea, anemia, diarrhea, anorectal symptoms, dysgeusia

- Anemia

<table>
<thead>
<tr>
<th>Hemoglobin</th>
<th>Triple Therapy</th>
<th>Combination Therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; 10 g/dL</td>
<td>36%</td>
<td>17%</td>
</tr>
<tr>
<td>&lt; 8.5 g/dL</td>
<td>14%</td>
<td>3%</td>
</tr>
<tr>
<td>RBV dose modification</td>
<td>32%</td>
<td>12%</td>
</tr>
</tbody>
</table>

- Refer to prescribing guidelines for evaluation and management

HCV: Telaprevir

- Rash
  - Developed in 56% receiving triple therapy
    - 4% severe; 6% discontinued therapy

- Prescribing guidelines
  - Mild rash
    - Continue ALL drugs
  - Moderate rash
    - Continue ALL drugs
  - Severe rash
    - Discontinue; continue Peg-INF-α and ribavirin

- Consider:
  - Good skin care practices
  - Oral antihistamines
  - Topical corticosteroids
**HCV: Telaprevir**

- **Anorectal symptoms**
  - Hemorrhoids, anorectal discomfort, anal pruritus and rectal burning
  - Developed in 29% receiving triple therapy
    - Mild to moderate in severity; <1% discontinued therapy

- **Prescribing guidelines**
  Consider:
  - Short-term use of topical corticosteroids or topical “caines”
  - Antihistamines
  - Control bowel movements (i.e. loperamide, adding fiber to diet etc.)

---

**HCV: Telaprevir**

- **Drug interactions**
  - Telaprevir is inhibitor and substrate of CYP3A4 and p-glycoprotein
  - SIGNIFICANT
    - Some medications contraindicated (Table 30)
    - Some medications require dose adjustments (prescribing guidelines)

---

**HCV: Telaprevir**

- **Contraindications**
  - Hypersensitivity
  - Pregnant females and males with pregnant partners
  - Coadministration with certain CYP3A4 substrate or inducer

---

**HCV: Boceprevir**

- **FDA Indication**
  - Treatment of chronic HCV genotype 1 (in combination with Peg-INF-α and ribavirin) in adult patients with compensated liver disease (including cirrhosis) who were previously untreated or whose previous therapy with Peg-INF-α and ribavirin failed.

---

**HCV: Boceprevir**

- **Dose and administration**
  - Lead in phase (treatment weeks 1–4)
    - Peg-INF-α and ribavirin only
    - Assessed to determine if interferon responsive or nonresponsive
  - 800 mg by mouth 3 times/day (starting on treatment week #5)
    - No dose adjustments required for renal impairment (not removed by HD)
    - No dose adjustment required for mild - severe hepatic impairment (not studied in decompensated cirrhosis)
  - Administer with food
HCV: Boceprevir

■ Adverse events
  ▪ Most common
    • Fatigue, anemia, nausea, headache and dysgeusia

<table>
<thead>
<tr>
<th></th>
<th>Triple Therapy</th>
<th>Combination Therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anemia</td>
<td>45-50%</td>
<td>20-30%</td>
</tr>
<tr>
<td>Dysgeusia</td>
<td>44-35%</td>
<td>11-16%</td>
</tr>
</tbody>
</table>

■ Drug interactions
  ▪ Boceprevir is inhibitor and substrate of CYP3A4 and p-glycoprotein
  ▪ SIGNIFICANT
    • Some medications contraindicated (Table 34)
    • Some medications require dose adjustments (prescribing guidelines)

HCV: Boceprevir

■ Contraindications
  ▪ Hypersensitivity
  ▪ Pregnant females and males with pregnant partners
  ▪ Co-administration with certain CYP3A4 substrate or inducer

HCV: Protease inhibitors summary

<table>
<thead>
<tr>
<th></th>
<th>Telaprevir</th>
<th>Boceprevir</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dose</td>
<td>750mg po tid</td>
<td>800mg po tid</td>
</tr>
<tr>
<td>Administration</td>
<td>With food (non-low fat)</td>
<td>With food</td>
</tr>
<tr>
<td>Most common adverse events</td>
<td>rash, fatigue, nausea, diarrhea</td>
<td>fatigue, anemia, headache</td>
</tr>
<tr>
<td></td>
<td>anemia, dysgeusia</td>
<td>dysgeusia</td>
</tr>
<tr>
<td>Contraindications</td>
<td>Hypersensitivity</td>
<td>Hypersensitivity</td>
</tr>
<tr>
<td></td>
<td>Pregnancy</td>
<td>Pregnancy</td>
</tr>
<tr>
<td></td>
<td>Medications (Table 30)</td>
<td>Medications (Table 34)</td>
</tr>
<tr>
<td>Drug interactions</td>
<td>CYP3A4</td>
<td>CYP3A4</td>
</tr>
</tbody>
</table>

HCV: Treatment – guideline recommendations

■ Pharmacotherapy
  ▪ Duration
    ▪ Combination therapy
      • Genotypes 2-6
    ▪ Triple therapy
      • Genotype 1
**HCV: Treatment duration**

- **Combination therapy**
  - Genotypes 2 and 3: 24 weeks
  - Genotype 4: response guided
  - Genotype 5-6: not specified

**Genotype 4: response guided**

(a) EVR, continue therapy for 48 weeks
(b) No EVR, retest HCV RNA at 24 weeks
  - If detectable, discontinue
  - If undetectable, consider extending duration to 72 weeks

- **Triple therapy**
  - Genotype 1: response guided
    - Differs for each triple therapy regimen
  - Genotype 4: response guided
  - Genotype 5-6: not specified

**Triple therapy with telaprevir**

- Response guided
- Varies by patient population
  - Table 27 – naïve and relapsers
  - Table 28 – naïve (compensated cirrhosis)
  - Table 29 – partial and null responders

**Table 27: Telaprevir Triple Therapy**

<table>
<thead>
<tr>
<th>HIVRNA</th>
<th>Duration</th>
<th>Type of Therapy According to Weeks of Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Undetectable (HIVRNA ≤ 100 IU/mL) OR Undetectable (HIVRNA ≤ 10 IU/mL)</td>
<td>24</td>
<td>Weeks 1-24 or 1B14 + TVR</td>
</tr>
<tr>
<td>Detectable (HIVRNA &gt; 1000 IU/mL)</td>
<td>48</td>
<td>Weeks 1-12 or 1B28 + TVR</td>
</tr>
<tr>
<td>Detectable (HIVRNA &gt; 1000 IU/mL)</td>
<td>24</td>
<td>Weeks 1-12 or 1B28 + TVR</td>
</tr>
<tr>
<td>Detectable (HIVRNA &gt; 1000 IU/mL)</td>
<td>12</td>
<td>Weeks 1-24 or 1B28 or TVR</td>
</tr>
</tbody>
</table>

- Discontinue therapy based on the futility rules
  - HCV RNA detectable (> 1000 IU/mL) at treatment week #4 or #12
  - HCV RNA detectable at treatment week #24
HCV: Treatment duration

- Triple therapy with boceprevir
  - Response guided
  - Varies by patient population
    - Table 31 - naïve (interferon responsive)
    - Table 32 - naïve (interferon nonresponsive), null responders, compensated cirrhosis
    - Table 33 - partial responders and relapsers

<table>
<thead>
<tr>
<th>HCV: Treatment duration</th>
<th>HCV: Treatment duration</th>
</tr>
</thead>
<tbody>
<tr>
<td>Triple therapy with boceprevir</td>
<td>Triple therapy with boceprevir</td>
</tr>
<tr>
<td>Response guided</td>
<td>Discontinue therapy based on the futility rules</td>
</tr>
<tr>
<td>Varies by patient population</td>
<td>HCV RNA detectable (≥ 100 IU/mL) at treatment week #12</td>
</tr>
<tr>
<td>Table 31 - naïve (interferon responsive)</td>
<td>HCV RNA detectable at treatment week #24</td>
</tr>
<tr>
<td>Table 32 - naïve (interferon nonresponsive), null responders, compensated cirrhosis</td>
<td></td>
</tr>
<tr>
<td>Table 33 - partial responders and relapsers</td>
<td></td>
</tr>
</tbody>
</table>

HCV: Treatment – candidate selection

- Candidates
  - > 18 years of age
  - HCV RNA positive
  - Biopsy: moderate to severe fibrosis
  - Compensated liver disease
  - Willingness to be treated and adhere to guidelines

- Not candidates
  - Major uncontrolled depressive disorder
  - Severe concurrent disease
  - Pregnant females and males with pregnant partners
  - CI: Peg-INF-α, RBV, or PI
  - Treatment experienced: history of poorly tolerating or experiencing serious adverse events leading to premature therapy discontinuation

HCV: Treatment – candidate selection

- Special populations (according to 2009 guidelines): require an individualized approach to therapy
  - Advanced liver disease (e.g. decompensated, bridging fibrosis)
  - Lack of advanced disease on biopsy (no or minimal fibrosis)
  - Solid-organ transplant recipients
  - HIV coinfection
  - Chronic kidney disease
**HCV: Prevention**
- No vaccine available

**Patient Case #8**
- **HPI:** 49 year-old female with history of chronic HCV (genotype 1) presents to the hepatology clinic for her anti-viral therapy initiation visit. Weight 91 kg
- **Laboratory:** AST 157 IU/mL, ALT 321 IU/mL, total bilirubin 1.3 g/dL, INR 1.1, albumin 3.3 g/dL, SCr 1.1 mg/dL, TSH 1.8 mIU/L and HCV RNA 387,000 IU/mL
- **PMH:** GERD
- **Liver biopsy:** moderate fibrosis

**Self Assessment Question #8**
Which one of the following is the best course of action for a patient with HCV (genotype 4) being treated with PEG-INF-α and ribavirin that is HCV RNA positive at 12 weeks and HCV RNA negative at 24 weeks?

- A. Discontinue therapy and monitor for symptoms
- B. Double the dose of Peg-INF-α
- C. Continue treatment for a total of 72 weeks
- D. No changes are recommended at this time

**Chapter Outline**
- Gastroesophageal reflux disease (GERD)
- Peptic ulcer disease (PUD)
- Complications of cirrhosis
  - Ascites, spontaneous bacterial peritonitis (SBP), hepatorenal syndrome, hepatic encephalopathy, gastroesophageal varices
- Viral hepatitis
Complications of Cirrhosis

Liver cirrhosis
- Results from destroyed hepatocytes replaced by fibrous tissue, resulting in a liver with reduced function, which causes several pathophysiologic abnormalities (complications):
  - Ascites
  - Spontaneous bacterial peritonitis
  - Hepatorenal syndrome
  - Hepatic encephalopathy
  - Gastroesophageal varices

Etiologies
- Infectious, metabolic, immune mediated, biliary obstruction, cardiovascular, drugs and toxins, other and cryptogenic

Disease severity (scoring systems)
- Child-Pugh
- Model for End Stage Liver Disease (MELD)
  - Currently used to accurately rank patients with cirrhosis awaiting transplantation according to their mortality risk
  - Incorporates INR, SCr and total bilirubin
  - \[9.57 \times \log(\text{SCr}) + 3.78 \times \log(\text{total bilirubin}) + 11.2 \times \log(\text{INR}) = 6.43\]
  - Maximum score is 40

Patient Case #4
- HPI: 57 year-old women with cirrhosis (Child Pugh class B) due to autoimmune hepatitis presents with new onset abdominal pain and shortness of breath.
- Physical exam: Afebrile, abdominal tenderness, flank bulging and shifting dullness, pulmonary congestion
- PMH: Hypothyroid, chronic back pain
- Medications: Levothyroxine 75 mcg daily, oxycodone 10 mg every 8 hours as needed for pain
- Laboratory: values are within normal limits
Patient Case #4
Which one of the following is the best recommendation to treat her new-onset ascites?

- A. Spironolactone 100mg daily + furosemide 40 mg daily
- B. Spironolactone 100mg daily
- C. Spironolactone 40mg daily + furosemide 100 mg daily
- D. Furosemide 40 mg daily

Ascites
- Accumulation of fluid in peritoneal cavity
- Cirrhosis (portal hypertension) is most common cause
  - 50-60% of cirrhotics develop ascites within 10 years
- Portal hypertension
  - Raises capillary hydrostatic pressure within splanchnic beds, increasing hepatic lymph production
    - Initially: body can compensate with increased outflow
    - Over time: hepatic lymph production exceeds the ability to return and lymph spills over into the peritoneal cavity causing ascites

Ascites: clinical presentation & assessment
- Symptoms
  - Progressive abdominal heaviness, pressure, pain, SOB
- Assessment
  - Physical exam: shifting dullness, bulging flanks, fluid wave
  - Abdominal ultrasound
    - Classification: grade 1-3
  - Paracentesis with ascitic fluid analysis (SAAG)

Ascites: Treatment
- First Line
  - Dietary sodium restriction (+ fluid restriction)
  - Diuretics
    - Spironolactone / furosemide combination (typical ratio 100:40)
    - Titrate every 3-5 days; max ratio 400:160
    - Max weight loss goal 0.5 kg/day
  - Paracentesis (tense ascites)

Discontinue medications potentially interfering with sodium and water retention

Spontaneous Bacterial Peritonitis (SBP)
- Occurs in 15-26% of hospitalized patients with ascites
- Bacterial infection of ascitic fluid
  - Source of infection is unclear, thought to be from GI tract
  - Common pathogens: Escherichia coli, Klebsiella pneumoniae, pneumococci
**SBP: clinical presentation & assessment**

- **Symptoms**
  - Abdominal tenderness/pain, vomiting, diarrhea
  - Chills, tachycardia, tachypnea
  - Worsening liver function → shock / renal failure
- **Diagnosis**
  - Paracentesis with ascitic fluid analysis and culture

**SBP: Treatment & Prevention**

- **Treatment**
  - Hospital Management
    - Broad spectrum antibiotics
    - Albumin administration
  - Up to 70% of patients have recurrent episodes
    - Risk Factors
      - Ascitic fluid protein concentration < 1.0 g/dL
      - Variceal bleed
      - Previous SBP episode
- **Prevention**
  - Primary: hospitalized patients
    - Cirrhosis with GI bleed
    - Cirrhosis with ascites with ascitic protein < 1.5 g/dL, plus other characteristics
  - Therapy: broad spectrum antibiotics
  - Secondary: ANY patient with history of SBP
    - Therapy: Norfloxacin, ciprofloxacin, trimethoprim/sulfamethoxazole DS

**Complications of Cirrhosis**

- Ascites
- Spontaneous bacterial peritonitis
- Hepatorenal syndrome
- Hepatic encephalopathy
- Gastroesophageal varices

**Hepatic Encephalopathy (HE)**

- Complex central nervous system disturbance with a broad spectrum of neurological impairments secondary to hepatic insufficiency
- Exact mechanism unknown
  - Accumulation of nitrogenous substances are key factors

**HE: clinical presentation & assessment**

- **Symptoms**
  - Wide range (minimal dysfunction to coma)
  - Confusion, disorientation, asterixis, decreased energy level, impaired sleep-wake cycles, abnormal speech patterns and cognitive deficits
- **Diagnosis**
  - Of exclusion; rule out other causes of diminished mental function

**HE: subtypes**

- **2001 guidelines**
  - 4 subtypes: acute, recurrent, persistent and minimal
- **Current practice**
  - Minimal or Overt
    - Minimal: west haven criteria grade ≥ 0
    - Overt: west haven criteria grade ≥ 1
  - Acute or Chronic
HE: staging

- West Haven criteria and Glasgow Coma Scale

<table>
<thead>
<tr>
<th>Stage</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>Lack of sleep, change in personality or behavior, Acute onset</td>
</tr>
<tr>
<td>1</td>
<td>Irritable, lack of awareness, Disoriented, confusion, Disorientation, Memory loss, New deficit</td>
</tr>
<tr>
<td>2</td>
<td>Lethargy, sedation, Disorientation, Disorganized behavior, Drowsiness, Delirium</td>
</tr>
<tr>
<td>3</td>
<td>Coma, Unresponsive, Fixed or dilated pupils</td>
</tr>
</tbody>
</table>

Table 6, West Haven Criteria

HE: Treatment

- Goals
  - Identify and eliminate precipitating factors
  - Reduce nitrogenous load
  - Supportive care

- Options
  - Nutritional management
  - Pharmacologic therapy
  - Manipulation of splanchnic circulation (invasive)

- Options
  - Nutritional management
  - Pharmacologic therapy
  - Manipulation of splanchnic circulation (invasive)

- Options
  - Nutritional management
  - Pharmacologic therapy
  - Manipulation of splanchnic circulation (invasive)

HE: Pharmacologic Therapy

- Lactulose
  - Nonabsorbable disaccharide; degrade colonic bacteria
  - Standard of care according to practice guidelines
  - Challenges

- Antibiotics
  - Alternates to nonabsorbable disaccharide; reduce bacterial production of ammonia
  - Neomycin, rifaximin
  - May work in synergy with lactulose

HE: Pharmacologic Therapy

- Lactulose
  - Nonabsorbable disaccharide; degrade colonic bacteria
  - Standard of care according to practice guidelines
  - Challenges

- Antibiotics
  - Alternates to nonabsorbable disaccharide; reduce bacterial production of ammonia
  - Neomycin, rifaximin
  - May work in synergy with lactulose

Patient Case #5

- HPI: 53 year-old man with cirrhosis (Child Pugh class B) due to alcohol abuse presents for a routine appointment. He appears to be more confused than usual with slurred speech and asterixis. He is unable to provide details so you interview his wife. She states his confusion and disorientation are worse, and that last week while driving home from the supermarket, he made a wrong turn and could not find the home where they have lived for more than 30 years.

- Vitals: T 98.7°F, HR 91 beats/min, RR 18 breaths/min, BP 126/87 mmHg
- Laboratory: within normal limits except AST 120 IU/mL, ALT 187 IU/mL, SCR 1.6 ng/mL
- PMH: Chronic renal insufficiency, gout
- Medications: Spironolactone 100 mg daily, furosemide 40 mg day, multivitamin 1 tab daily

Patient Case #5

Which one of the following therapeutic choices for HE treatment would be best at this time?

- A. Rifaximin 550 mg by mouth twice daily and lactulose by mouth as needed.
- B. Neomycin 1000 mg by mouth every 6 hours.
- C. Lactulose 45 mL by mouth 3 times/day
- D. Lactulose 45 mL/hour by mouth until evacuation occurs; then titrate dose as needed to achieve three bowel movements a day.
Patient Case #6

- **HPI:** 62 year-old man with cirrhosis (Child Pugh class C) secondary to HCV is seen today for a follow up appointment. A routine EGD performed 2 weeks ago revealed a few small varices. He has no history of GI bleed.
- **PMH:** HE, hepatocellular carcinoma, diabetes
- **Medications:** Rifaxamin 550 mg twice daily, famotidine 20 mg twice daily, zolpidem 10 mg as needed, MVI daily and calcium when he remembers

Which one of the following is the best recommendation for prophylaxis against variceal bleed?

- A. Propranolol
- B. Atenolol
- C. Prophylaxis is not recommended
- D. Isosorbide mononitrate

Gastroesophageal Varices

- Varices or alternate routes of bloodflow, develop to overcome increased resistance secondary to portal hypertension
- Bleeding risk
  - 50% of cirrhatics
  - Correlates with severity of disease (40% CPT-A, 85% CPT-C)
- Rate of recurrence: 60-70%
- Mortality: 25-30% per episode

Gastroesophageal Varices: Treatment

- **Goals**
  - Prompt diagnosis
  - Control bleeding
  - Prevent complications
- **Acute management (hospitalized)**
  - Volume expansion and hemodynamic stabilization
  - Endoscopic intervention
    - Band ligation / sclerotherapy
    - Pharmacotherapy
- **Pharmacotherapy**
  - Used to cause splanchnic vasoconstriction, subsequently decreasing portal blood flow
  - **Options**
    - Octreotide or somatostatin
    - Vasopressin
    - Antibiotics

Gastroesophageal Varices: Prophylaxis

- **Primary**
  - Recommended once varices develop in those at high risk for bleed
    - Cirrhotics (Child Pugh B or C)
    - Large varices
    - Those with small varices, no history of bleed with other high risk criteria
  - Recommendation
    - Nonselective β-blockers
  - **Nonselective β-blockers**
    - Propranolol, nadolol
    - HR target
      - HR 55-60 bpm (or) 25% reduction
    - Adverse events
    - Contraindications
### Gastroesophageal Varices: Prophylaxis

- **Primary**
  - Recommended once varices develop in those at high risk for bleed
  - Cirrhotics (Child Pugh B or C)
  - Large varices
  - Those with small varices, no history of bleed with other high risk criteria
  - Recommendation
    - Nonselective β-blockers

- **Secondary**
  - All patients with bleed history
  - Recommendation
    - Nonselective β-blockers
    - Endoscopic (band ligation)

---

### Chapter Outline

- Gastroesophageal reflux disease (GERD)
- Peptic ulcer disease (PUD)
- Complications of cirrhosis
  - Ascites, spontaneous bacterial peritonitis (SBP), hepatorenal syndrome, hepatic encephalopathy, gastroesophageal varices
- Viral hepatitis

---

### Patient Case #6

**HPI:** 62 year-old man with cirrhosis (Child Pugh class C) secondary to HCV
- EGD: a few small varices
- No history of GI bleed

---

### Peptic Ulcer Disease (PUD)

- **Definition**
  - Disease of the upper GI tract characterized by mucosal damage due to pepsin and gastric acid secretion
- **Pathophysiology**
  - Normal mucosal defense and healing mechanisms are disrupted in the presence of gastric acid and pepsin
- **Etiologies**
  - Most common: *H. pylori* and NSAID use

---

### PUD

- **Symptoms**
  - Heartburn, abdominal fullness, cramping, epigastric pain, anorexia and weight loss
- **Complications**
  - Upper GI bleed (melena or hematemesis), perforation and/or penetration, gastric outlet obstruction
PUD: Diagnosis of H. pylori

- H. pylori is a carcinogen; if testing, must treat!

- Diagnostic tests
  - Invasive (endoscopic)
    - Rapid urease testing (RUT)
    - Histology
    - Culture
  - Noninvasive (nonendoscopic)
    - Antibody (IgG) testing
    - Urea breath test (UBT)
    - Fecal antigen test (FAT)

Test selection depends on:
- Whether endoscopy is required
- Understanding of the strengths and weaknesses of each test

PUD: Treatment of H. pylori

- Goals
  - Pain relief
  - Ulcer healing
  - H. pylori eradication
  - Reduction of ulcer related complications
  - Prevention of ulcer recurrence

- Pharmacologic strategies
  - Triple therapy
    - PPI + amoxicillin (or) metronidazole + clarithromycin
    - Length of therapy: 10-14 days
    - First line for those that have not previously been treated
    - Similar efficacy regardless of which PPI is used in regimen
  - Quadruple therapy
    - PPI + bismuth + metronidazole + tetracycline
    - Length of therapy: 10-14 days
    - Consider in patients with penicillin allergy, previous exposure to macrolide or failed triple therapy

PUD: Diagnosis H. pylori

<table>
<thead>
<tr>
<th>Type of Test</th>
<th>Invasive</th>
<th>Posttreatment testing</th>
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</thead>
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<tr>
<td>RUT</td>
<td>X</td>
<td>X</td>
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<tr>
<td>Histology</td>
<td>X</td>
<td>X</td>
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<tr>
<td>Culture</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Antibody</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>UBT</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>FAT</td>
<td>X</td>
<td>X</td>
</tr>
</tbody>
</table>

Medications that reduce urease activity: bismuth containing, antibiotics and PPIs
### PUD: Treatment of *H. pylori*

**Predictors of treatment outcomes**

- **Success**
  - Eradication testing
  - Universal testing is not practical or cost effective
  - Guidelines indicate groups of individuals in which it should be performed
- **Failure**
  - Lack of adherence
  - Antibiotic resistance

### Patient Case #2

**HPI:** 47 year old female with sharp epigastric pain for 8 weeks. Pain is worse after meals and is present at least every other day. Additionally, she feels continuously bloated and experiences uncontrollable belches.

**PMH:** unremarkable; penicillin allergy

**Medications:**
- citalopram 20 mg daily
- loratidine 10 mg daily
- multivitamin 1 tab daily.

**Diagnostics:** UBT positive

Which one of the following treatments for *H. pylori* is best?

<table>
<thead>
<tr>
<th>Option</th>
</tr>
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<tbody>
<tr>
<td>A. Amoxicillin 1g twice daily + clarithromycin 500 mg twice daily + esomeprazole 40 mg once daily for 7 days.</td>
</tr>
<tr>
<td>B. Amoxicillin 1 g twice daily + clarithromycin 500 mg twice daily + esomeprazole 40 mg twice daily for 14 days</td>
</tr>
<tr>
<td>C. Bismuth subsalicylate 525 mg 4 times/day + metronidazole 250 mg 4 times/day + tetracycline 500mg 4 times/day + esomeprazole 40 mg once daily for 7 days</td>
</tr>
<tr>
<td>D. Bismuth subsalicylate 525 mg 4 times/day + metronidazole 250 mg 4 times/day + tetracycline 500mg 4 times/day + esomeprazole 40 mg once daily for 14 days</td>
</tr>
</tbody>
</table>

### PUD: NSAID ulcers

**Primary prevention**

- Cotherapy (NSAID plus another agent)
  - PPI
  - High dose H2RA’s (double dose)
  - Misoprostol
- Replace therapy (NSAID with another agent)
  - NSAID with COX-2 inhibitor
- PPI is preferred agent for prevention

- Use MUST be evaluated by a GI and CV risk assessment
PUD: NSAID ulcers

**GI Risk Factors**
- Previous GI event (especially if complicated)
- Age (older than 65)
- Concomitant medications
  - Anticoagulants, corticosteroids, other NSAIDS (including low dose aspirin)
- Chronic debilitating disorders (especially CV disease)
- *H. pylori*

**CV Risk Factors**
- Requirement for low dose aspirin
  - Such as: individuals with a prior CV event, diabetes, hypertension, hyperlipidemia, obesity

**CV Risk**
- Low: 0 risk factors
- Moderate: 1-2 risk factors
- High: > 2 risk factors; history of complicated ulcer (especially recent)

---

**Self Assessment Question #2**

**HPI:** 67 year-old women with rheumatoid arthritis

**Medications:** Naproxen 500 mg daily, metoprolol 25 mg twice daily, aspirin 81 mg daily, alendronate 70 mcg once weekly

**Which one is best gastroprotective therapy?**

A. Lansoprazole 30 mg daily
B. No gastroprotective therapy necessary
C. Misoprostol 200 mcg twice daily
D. Esomeprazole 40 mg twice daily

---

**Treatment (secondary prevention)**
- Risk factor modification (when possible)
- Reduce or eliminate NSAID therapy
- Test for *H. pylori* – if present, initiate eradication therapy
- First Line: PPI
  - Similar benefits for all agents
PUD: NSAID ulcers

- Other considerations
  - Concurrent use of NSAIDs and antiplatelet therapy

<table>
<thead>
<tr>
<th></th>
<th>Ischemic Risk</th>
<th>Bleeding Risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>Antiplatelet</td>
<td>↓</td>
<td>↑</td>
</tr>
<tr>
<td>NSAIDs</td>
<td>↑</td>
<td></td>
</tr>
</tbody>
</table>

GERD

Gastroesophageal Reflux Disease (GERD)

- Definition (Montreal consensus panel)
  - “A condition which develops when reflux of stomach contents causes troublesome symptoms and/or complications”
  - Troublesome are those symptoms which adversely affect an individual’s well-being.
  - Note: asymptomatic episodic heartburn is NOT included in the definition

GERD: Clinical presentation

- Symptoms
  - Nonspecific, highly variable
  - Hallmark: pyrosis, regurgitation and acidic taste
  - Usually do not correlate with duration of reflux
- Classified as set of syndromes
  - Esophageal
  - Extraesophageal

GERD CLASSIFICATION

- Esophageal Syndrome
  - Troublesome esophageal symptoms
  - With or without esophageal injury
- Extraesophageal Syndrome
  - Troublesome esophageal symptoms
  - GERD likely contributing etiology but seldom sole cause
**GERD CLASSIFICATION**

- **Esophageal Syndrome**
  - Symptomatic (symptoms/no injury)
  - Reflux Esophagitis
  - Reflux Stricture
  - Barrett’s Esophagitis
  - Adenocarcinoma

- **Extraesophageal Syndrome**
  - Established Association
    - Reflux Cough
    - Reflux Sinusitis
    - Reflux Asthma
  - Proposed Association
    - Pharyngitis
    - Sinusitis
    - Recurrent Otitis Media
    - Pulmonary Fibrosis

**GERD: esophageal diagnostic testing**
- Performed to:
  - Avert misdiagnoses
  - Identify complications of reflux
  - Evaluate empiric treatment failures
- Options:
  - Endoscopy (with or without biopsy)
  - Esophageal pH monitoring
  - Manometry

**GERD: Treatment**
- **Goals**
  - Reduce frequency and duration of reflux
  - Symptom reduction and/or elimination
  - Prevention of disease progression and developing complications
  - Promote healing of injured mucosa
- **Strategies:** usually based on duration of use
  - On demand or self directed
  - Intermittent / short term
  - Indefinite

**GERD: Nonpharmacologic: lifestyle modifications**
- **AIM:** to lessen incidence of reflux and enhance clearance
- Insufficient to advocate for all patients, targeted groups may benefit
- May include
  - Avoid reflux-inducing foods/beverages
  - Smoking cessation
  - Avoid tight fitting garments
  - Head of bed elevation
  - Weight loss
  - Promotion of salivation
GERD: Treatment

- Nonpharmacologic: lifestyle modifications
- Pharmacologic
  - Acid suppression
    - Antacids
    - Histamine2-Receptor Antagonists (H2RAs)
    - Proton Pump Inhibitors (PPIs)
  - Efficacy
    - PPI > H2RAs > placebo

- Antacids
  - Mild intermittent (less than 2 times/week)
  - Breakthrough
  - Not appropriate for chronic symptoms or healing damaged mucosa

- Histamine-2 receptor antagonists
  - Mild intermittent
  - Meal/exercise provoked symptoms
  - Less effective than PPIs in healing

GERD: PPIs

<table>
<thead>
<tr>
<th>Drug</th>
<th>Typical Dose Range</th>
<th>Available in OTC</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rabeprazole</td>
<td>20 mg/day for 1-8 weeks</td>
<td>Yes</td>
</tr>
<tr>
<td>Esomeprazole</td>
<td>20 mg/day for up to 8 weeks</td>
<td>Yes</td>
</tr>
<tr>
<td>Pantoprazole</td>
<td>20 mg/day for up to 16 weeks</td>
<td>Yes</td>
</tr>
<tr>
<td>Esomeprazole + omeprazole (Espradol)</td>
<td>20 mg/day for up to 4 weeks</td>
<td>Yes</td>
</tr>
<tr>
<td>Omeprazole</td>
<td>20 mg/day for up to 8 weeks</td>
<td>Yes</td>
</tr>
<tr>
<td>Rabeprazole (Acidil)</td>
<td>20 mg/day for 1-8 weeks</td>
<td>Yes</td>
</tr>
<tr>
<td>Pantoprazole (Proton)</td>
<td>20 mg/day, duration not specified</td>
<td>Yes</td>
</tr>
<tr>
<td>Esomeprazole (Decurar)</td>
<td>30 mg/day for 4 weeks</td>
<td>Yes</td>
</tr>
</tbody>
</table>

GERD CLASSIFICATION

- Esophageal Syndrome
  - Symptomatic (symptoms in situ)
    - Established Association
      - In general: Empiric therapy
    - Established: Empiric therapy PLUS additional testing and intervention

- Extraesophageal Syndrome
  - Symptomatic (symptoms away from site)
    - Established Association
      - Proposal Association
GERD: Treatment recommendations

- **Symptomatic**
  - Typical Reflux
    - Standard dose PPI twice daily
    - Maintenance therapy unclear
  - Reflux Chest Pain
    - Rule out ischemic heart disease
    - PPI twice daily
    - Consider additional tests for persistent symptoms

- **Esophageal injury**
  - Standard dose PPI twice daily
  - Maintenance is recommended to maintain healed mucosa
  - Avoid on demand therapy

**Established & Proposed Association**
- Standard dose PPI twice daily for 2 months
- Maintenance therapy?
- Use based on presence of symptoms

**Approach to refractory GERD**
- 10–40% do not respond to standard dose PPI
- Evaluate reason(s) for PPI failure
- Options
  - Optimize antisecretory therapy
  - Add-on therapy
  - Life style modifications
  - Perform esophageal testing
  - Treat delayed gastric emptying (promotility agents)
  - Treat bile acid reflux
  - Antireflux surgery

**Patient Case #1**
- HPI: 43 year old male with a 6-week history of intermittent (every other day) regurgitation and acidic taste in his mouth despite non-pharmacologic treatment (avoiding certain foods and sleeping with his head elevated) and as needed famotidine therapy. He reports his symptoms are so bad he has been unable to sleep and has missed 2 days of work.
- PMH: Type 2 diabetes mellitus, hypertension
- Medications: Metoprolol 100mg once daily, famotidine 10 mg as needed

**Which one of the following is the best course of action to address his symptoms?**
- A. Administer metoclopramide 10 mg four times daily
- B. Administer esomeprazole 20 mg daily
- C. Continue famotidine 10mg, but take on a scheduled frequency (3 – 4 times daily)
- D. Continue famotidine, but increase dose to 20 mg on a scheduled frequency (3 – 4 times daily)

**Gastrointestinal Disorders**
- Viral hepatitis
- Complications of cirrhosis
  - Ascites, spontaneous bacterial peritonitis (SBP), hepatorenal syndrome, hepatic encephalopathy, gastroesophageal varices
- Peptic ulcer disease (PUD)
- Gastroesophageal reflux disease (GERD)
Epilepsy and Headache/Migraine
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University of Colorado Anschutz Medical Campus
Skaggs School of Pharmacy and Pharmaceutical Sciences and Department of Neurology

Conflict of Interest Disclosures
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  - Grant support from the National Institutes of Health (NIH)
  - Research support from UCB Pharma
  - Advisory Boards: UCB Pharma and TEVA Neurosciences

Learning Objectives
1. Identify the seizure type and devise a treatment plan for a patient with new onset and refractory epilepsy.
2. Describe the mechanisms of action of recommended antiepileptic drugs (AEDs).
3. Select an appropriate AED regimen for a patient with epilepsy.
4. Discuss the role of ambulatory care clinical pharmacy services as it pertains to patients with a neurologic disorder.
5. Identify ways in which the ambulatory care pharmacy practitioner can track and reconcile medication errors.
6. Identify common adverse effects and drug interactions for first and second-generation AEDs, focusing on the cytochrome P450 system.
7. Formulate a monitoring plan for a given patient on AED therapy.
8. Discuss pertinent patient education counseling points together with patient assistance programs.
9. Choose an appropriate AED for a special population patient (e.g. pregnant, status epilepticus).
10. Distinguish between the signs and symptoms of headache types.
11. Recommend an appropriate pharmacologic therapy for a patient with an acute migraine headache.
12. Choose an appropriate prophylaxis regimen for a patient with a migraine headache.
13. Identify agents that have been implicated in causing medication overuse headache.
Learning Objectives


15. Provide patient education regarding pharmacologic and lifestyle interventions for migraine headache.

Patient Case # 1

- HPI: K.L. is a 65 year old male with a new diagnosis of complex partial seizures. An EEG was performed that showed epileptiform abnormalities, confirming a diagnosis of epilepsy. His renal function is stable.
- PMH: Complex partial seizures, diabetic peripheral neuropathy
- Diagnostics: EEG, complete neurologic exam, patient history

Epilepsy

- Clinical definition
  - Propensity to have unprovoked seizures repeatedly. A diagnosis can be made after one episode.
  - Idiopathic – 68%
  - CVD – 8-12%

- Epidemiology
  - 3rd most common neurologic disorder
  - 1-2% of the population has a diagnosis of epilepsy
  - 2.3 million persons in the United States have a diagnosis of epilepsy
  - 1/100 adults and 1/50 children

Clinical Presentation of Epilepsy

- Partial Seizures
  - Simple partial
  - Complex partial
  - Secondary generalized

- Generalized Seizures
  - Absence
  - Atonic
  - Clonic
  - Myoclonic
  - Tonic
  - Tonic-clonic
  - Infantile spasms

Treatment Options for Epilepsy

- Pharmacologic
- Non-pharmacologic
  - Surgical intervention
  - Vagus nerve stimulation (VNS)
  - Ketogenic diet
  - Responsive neurostimulator system

Pharmacologic Therapy for Epilepsy

Traditional or 1st Generation AEDs

- Phenobarbital (PB) – 1912
- Primidone (Mysoline) (PRM) – 1938
- Phenytoin (Dilantin) (PHT) – 1938
- Ethosuximide (Zarontin) (ESX) – 1960
- Carbamazepine (Tegretol, Tegretol CR) – 1974
- Valproate (Depakote, Depakene) (VPA) – 1975

- Felbamate (Felbatol) (FBM) – 1993
- Lamotrigine (Lamictal) (LTG) – 1993
- Gabapentin (Neurontin) (GBP) – 1994
- Topiramate (Topamax) (TPM) – 1996
- Tiagabine (Gabitril) (TGB) – 1997
- Oxcarbazepine (Trileptal) (OXC) – 1999
- Levetiracetam (Keppra) (LEV) – 2000
- Zonisamide (Zonegran) (ZNS) – 2000
- Pregabalin (Lyrica) (PGB) – 2006
- Rufinamide (Banzel) (RFN) – 2009
- Vigabatrin (Sabril) (VGB) – 2009
- Lacosamide (Vimpat) (LCM) – 2009
- Ezogabine (Potiga) (EZG) – 2011
- Clobazam (Onfi) (CLB) – 2011

- Gabapentin (Neurontin) (GBP) – 1994
- Topiramate (Topamax) (TPM) – 1996
- Tiagabine (Gabitril) (TGB) – 1997
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- Clobazam (Onfi) (CLB) – 2011

Newer or 2nd Generation AEDs

How do you choose therapy?
Patient Case #1
Which one of the following drugs would be the most appropriate for K.L.?

A. Felbamate
B. Gabapentin
C. Lamotrigine
D. Phenytoin

Handout Page 1-419; Answer Page 1-406/407, 1-437

Patient Case #1
Through the progression of K.L.’s diabetes, his renal function becomes severely compromised. Based on this information, recommend one of the following drugs to treat his epilepsy?

A. Lacosamide
B. Lamotrigine
C. Pregabalin
D. Vigabatrin

Handout Page 1-419, Answer Page 1-409-411, 437

Patient Case #2

- **HPI:** T.H. is a 70-year-old man that presents to the clinic today for a follow-up visit after his routine serum laboratory levels were obtained four weeks ago. His LFTs were 10 times the upper limit of normal. Results of the CT and liver biopsy confirmed severe liver disease.

- **PMI:** Long standing history of GTCS

- **Medication History:** Valproate, phenobarbital

Handout Page 1-419

Pharmacokinetics of Traditional AEDs

<table>
<thead>
<tr>
<th>Drug</th>
<th>F %</th>
<th>Binding %</th>
<th>CI</th>
<th>t½ (hrs)</th>
<th>Cause PK Interaction?</th>
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<tbody>
<tr>
<td>CBZ</td>
<td>80</td>
<td>75-85</td>
<td>100% H*</td>
<td>6-15</td>
<td>yes</td>
</tr>
<tr>
<td>PB</td>
<td>100</td>
<td>50</td>
<td>75% H</td>
<td>72-124</td>
<td>yes</td>
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<tr>
<td>PHT</td>
<td>95</td>
<td>90</td>
<td>100% H^</td>
<td>12-60</td>
<td>yes</td>
</tr>
<tr>
<td>VPA</td>
<td>100</td>
<td>75-95**</td>
<td>100% H</td>
<td>6-18</td>
<td>yes</td>
</tr>
</tbody>
</table>

* autoinduction
^ non-linear

Potential Advantages: Schedule V: Pregabalin and Lacosamide
- Improved water solubility → predictable bioavailability
- Negligible protein binding → no need to worry about hypoalbuminemia
- Less reliance on CYP metabolism → perhaps less variability over time

GBP = Gabapentin; PGB = Pregabalin; LTG = Lamotrigine; LEV = Levetiracetam; TGB = Tiagabine; TPM = Topiramate; ZNS = Zonisamide; OXC = Oxcarbazepine; VGB = Vigabatrin; LCM = Lacosamide; RUF = Rufinamide; EZG = Ezogabine; CLB = Clobazam

Handout Page 1-419; Answer Page 1-409-411, 437

1. Patient Case #2
Given his new diagnosis of liver disease, what is the best recommendation for treatment?

A. Continue phenobarbital and valproate; no change is needed
B. Continue phenobarbital and replace valproate with levetiracetam
C. Replace phenobarbital with levetiracetam and continue valproate
D. Replace both phenobarbital and valproate with levetiracetam and pregabalin

Handout Page 1-419; Answer Page 1-409-411, 437
**Patient Case # 3**

- HPI: J.D. is a 68-year-old seen in your clinic and upon leaving he began having multiple seizures lasting greater than 10 minutes. He is not regaining consciousness between episodes. He is taken to the ED and the physician requests information regarding IV phenytoin.
- PMI: Formal diagnosis of epilepsy
- Medication History: IV phenytoin initiated in the ED

**Status Epilepticus**

- First Line Therapy
  - Benzodiazepines
    - Lorazepam 4 mg or Diazepam 0.25 mg/kg or midazolam 200 mcg/kg
    - Slow IV push or IV drip
    - Rectal suppositories
- Second Line Therapy
  - Phenytoin or Fosphenytoin
    - Load with 18 to 20 mg or mg PE/kg
    - Phenytoin: NTE 50 mg/min, only NS, final filter
    - Tissue necrosis, hypotension, cardiac arrhythmia
    - Fosphenytoin: NTE 150 mg/min, any solution
    - Repeat at 1/3 of dose if no results

**Patient Case # 4**

- HPI: R.L. is a 32-year-old male that presents to the clinic today complaining of a unilateral headache. The headache started one hour ago. R.L. describes the headache as “an ice pick through my eye.” He denies nausea; however, has nasal congestion. R.L. is up and moving about constantly.
- PMI: He has experienced four of the same headaches over the past two years.
- FH: Father has the same headaches.
- Medication History: None

**Types of Headaches**

<table>
<thead>
<tr>
<th>Types of Headaches</th>
<th>Epilepsy</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Status Epilepticus</td>
</tr>
<tr>
<td></td>
<td>First Line Therapy</td>
</tr>
<tr>
<td></td>
<td>Benzodiazepines</td>
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<td>Load with 18 to 20 mg or mg PE/kg</td>
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<td></td>
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<td></td>
<td>Tissue necrosis, hypotension, cardiac arrhythmia</td>
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<tr>
<td></td>
<td>Fosphenytoin: NTE 150 mg/min, any solution</td>
</tr>
<tr>
<td></td>
<td>Repeat at 1/3 of dose if no results</td>
</tr>
</tbody>
</table>

**Patient Case # 4**

- R.L. is experiencing what type of headache?
  - A. Cluster headache
  - B. Tension headache
  - C. Migraine with aura
  - D. Migraine without aura

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Treatment of Cluster Headache

- Non-pharmacological
  - Avoid triggers
    - Alcohol
    - Vasodilators
    - Noxious smells
- Pharmacological
  - Oxygen
  - Triptans
  - Ergotamines
  - Intranasal lidocaine

Patient Case # 4
Which of the following is the best acute treatment of R.L.’s headache?

- A. Sumatriptan oral
- B. Methylsergide
- C. NSAIDs
- D. Oxygen therapy

Patient Case # 5
- HPI: R.P. is a 35-year-old woman that presents to the clinic today complaining of a headache. It started unilateral and pulsating in nature, on going for 24 hours accompanied by nausea. It is aggravated by bright lights and physical activity. She is interested in a prescription medication for her migraines. She has been treating the headaches with OTC Excedrin® for migraine.
- PMI: Same headache episodes twice monthly accompanied by nausea.
- Medication History: OTC Excedrin® for migraine

Migraine Triggers

- Increased or decreased sleep
- Dehydration
- Stress
- Emotional letdown
- Skipping meals
- Alcohol
- Medications
- Weather changes
- Smoking
- Strong perfumes
- Chocolate
- Caffeine
- Cheeses
- Hormone changes
- Loud noise
- Physical activity

Medication Overuse Headache

- Caused by frequent use of headache medications
- Withdrawal symptoms upon discontinuation of offending drug
- Escalating use of medications, increasing quantity or severity of headaches…
- Offending agents
  - Analgesics especially combination products with caffeine
  - Ergotamines
  - Caffeine
  - Opioids
  - Triptans
  - Barbiturates
- Limit use to 2 to 3 times per week for abortive therapy
Preventive Therapy for Migraine Headache

- Most commonly used agents
  - Beta-blockers (propranolol, timolol are FDA-approved)
  - Calcium channel blockers
  - Antidepressants
  - Antiepileptic drugs (AEDs) (divalproex sodium and topiramate are FDA-approved)
  - Botox (FDA-approved)
  - NSAIDS
  - Cox-2 Inhibitors
    - Celecoxib (Celebrex®) 200 mg daily
  - Riboflavin (400 mg/d)
  - Coenzyme Q-10 (100 mg TID)

- Also effective
  - Angiotension receptor blockers (Candesartan)
  - Feverfew (50 to 100 mg/d)
  - Magnesium (300mg/d)
  - Riboflavin (400 mg/d)
  - Coenzyme Q-10 (100 mg TID)
  - Butterbur (Petadolex 150 mg/d decreases by 50%)
  - Acupuncture

Characteristics of Triptans (Abortive)

<table>
<thead>
<tr>
<th>Drug</th>
<th>Route</th>
<th>Onset</th>
<th>Duration</th>
<th>Half-Life</th>
<th>Metabolism</th>
</tr>
</thead>
<tbody>
<tr>
<td>Amerge</td>
<td>Oral</td>
<td>1-3 hours</td>
<td>Long</td>
<td>6 hours</td>
<td>Renal, 70%</td>
</tr>
<tr>
<td>Axert</td>
<td>Oral</td>
<td>30-120 minutes</td>
<td>Short</td>
<td>3-4 hours</td>
<td>CYP and MAO</td>
</tr>
<tr>
<td>Frova</td>
<td>Oral</td>
<td>2-3 hours</td>
<td>Long</td>
<td>26 hours</td>
<td>Renal, 30%</td>
</tr>
<tr>
<td>Imitrex</td>
<td>Oral/nasal spray/ODT</td>
<td>20-30 minutes</td>
<td>Short</td>
<td>2.5 hours/2 hours</td>
<td>MAO</td>
</tr>
<tr>
<td>Zomig/Zomig-ZMT</td>
<td>Oral/nasal spray/ODT</td>
<td>45 minutes/nasal = 15 minutes</td>
<td>Short</td>
<td>3 hours</td>
<td>CYP and MAO</td>
</tr>
<tr>
<td>Relpax</td>
<td>Oral</td>
<td>30 minutes</td>
<td>Short</td>
<td>4 hours</td>
<td>CYP and MAO</td>
</tr>
<tr>
<td>Treximet</td>
<td>Oral</td>
<td>20-30 minutes</td>
<td>Short</td>
<td>2 hours</td>
<td>CYP and MAO</td>
</tr>
<tr>
<td>Maxalt/Maxalt-MLT-MINT</td>
<td>Oral/ODT</td>
<td>30-120 minutes</td>
<td>Short</td>
<td>3 hours</td>
<td>CYP and MAO</td>
</tr>
<tr>
<td>Sumatriptan</td>
<td>Oral</td>
<td>20 minutes</td>
<td>Short</td>
<td>4 hours</td>
<td>CYP and MAO</td>
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<tr>
<td>Almotriptan</td>
<td>Oral</td>
<td>30 minutes</td>
<td>Short</td>
<td>2 hours</td>
<td>CYP and MAO</td>
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<tr>
<td>Naratriptan</td>
<td>Oral/nasal spray/ODT</td>
<td>45 minutes/nasal = 15 minutes</td>
<td>Short</td>
<td>3 hours</td>
<td>CYP and MAO</td>
</tr>
<tr>
<td>Rizatriptan</td>
<td>Oral/ODT</td>
<td>30-120 minutes</td>
<td>Short</td>
<td>3 hours</td>
<td>CYP and MAO</td>
</tr>
<tr>
<td>Sumatriptan</td>
<td>Oral/nasal spray/ODT</td>
<td>45 minutes/nasal = 15 minutes</td>
<td>Short</td>
<td>3 hours</td>
<td>CYP and MAO</td>
</tr>
</tbody>
</table>

Patient Case #5
What would you recommend for migraine prophylaxis in R.P.?
- A. Excedrine Migraine
- B. Topiramate 25 mg PO daily
- C. Sumatriptan 50 mg PO daily
- D. Propranolol 20 mg PO TID

Patient Case #5
R.P. states that due to the nausea she would prefer not to have to swallow a tablet. Which of the following would be an best abortive therapy for R.P.?
- A. Almotriptan
- B. Frovatriptan
- C. Naratriptan
- D. Rizatriptan

Preventive Therapy for Migraine Headache continued…
- Also effective
  - Angiotension receptor blockers (Candesartan)
  - Feverfew (50 to 100 mg/d)
  - Magnesium (300mg/d)
  - Riboflavin (400 mg/d)
  - Coenzyme Q-10 (100 mg TID)
  - Butterbur (Petadolex 150 mg/d decreases by 50%)
  - Acupuncture

Patient Case #5
R.P. was prescribed eletriptan 20 mg at the onset of migraine. R.P. flies out of the country for business and notices her eletriptan does not last long enough for the migraine to be fully aborted. Which agent would be the most appropriate choice for R.P. on long flights?
- A. Almotriptan
- B. Frovatriptan
- C. Rizatriptan
- D. Sumatriptan
### Useful Resources

- **Epilepsy**
  - Epilepsy.com
  - AESNET.org
  - EpilepsyFoundation.org
  - Drugstore.com for prices
- **Headache/Migraine**
  - ACHENET.org
  - Drugstore.com for price
- **Adverse Event Monitoring**
  - www.MedWatch.com

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### Ambulatory Care & Clinical Pharmacists

- **Tracking and reconciling medication errors**
  - Working with inpatient team
  - Working with the ED
  - Working with other pharmacies
  - Use of family members as resources
- **Role of ambulatory care pharmacist**
  - Identify drugs with complex drug-drug interactions
  - Provide recommendations on averting adverse events and drug-drug interactions
  - Identify patient assistance programs to acquire medications for the appropriate patient

---

**THE END**
Conflict of Interest Disclosures

No conflicts of interest to disclose

Learning Objectives

- Identify signs or symptoms associated with Alzheimer’s (AD) or Parkinson’s disease (PD) that may be drug-induced.
- Describe reasonable expectations and limitations of available therapies for the treatment of patients with Alzheimer’s or Parkinson’s disease.
- Recommend an appropriate plan for the initiation, titration, monitoring, and altering of pharmacotherapy for cognitive/functional symptoms in patients with AD or PD.
- Recommend appropriate strategies for the management of patients with psychiatric or behavioral symptoms related to AD or PD.
- Recognize the impact of cognitive and functional impairment on the risk for medication discrepancies during transitions of care.

Alzheimer Disease

- Most common neurological problem among older adults
  - 10% of adults 60-70 years
  - 50% of adults ≥ 85 years
- Clinical presentation:
  - Cognitive loss
  - Loss of self-care activities (ADLs, IADLs)
  - Behavioral symptoms

Goals of Treatment

- Improve quality of life
- Maximize functional status/independence
- Maintain/ enhance cognitive status
- Minimize mood and behavioral problems
- Minimize safety hazards

AD Treatment Guidelines

- American Association for Geriatric Psychiatry
- NIA & Alzheimer’s Association
  - Updated NINCDS-ADRDA Criteria - May 2011
- American Geriatrics Society 2010 – A Guide to Dementia Diagnosis and Treatment
  - Evaluation and diagnosis
  - Initiating therapy
  - Treatment of behavioral symptoms
  - Discontinuing therapy
  - Evaluation tools
Evaluation Tools

- Cognition
  - MMSE
  - ADAS; ADAS-cog
- Depression
  - GDS
- Function
  - ADLs; IADLs
- Many others
  - CIBIC, SIB, NPI, etc

Details on Page 1-448

Patient Case 1 - AD

DT is a 76 year old widowed female who is in clinic today, accompanied by her daughter, for evaluation of cognitive complaints. DT has a history of osteoarthritis, hypertension, and atrial fibrillation. The daughter states that DT has had difficulties with her memory for almost a year. Initially, the symptoms were minor; DT would forget names or recent events, but more recently the memory complaints have been more severe and DT is becoming unable to manage at home alone, according to the daughter. DT states that she does not think she has memory problems. There is no known history of Alzheimer’s disease in their family. DT’s father died of a stroke, and her mother died of colon cancer. There is no recent history of falls, head trauma, or substance abuse. On exam today, the neurological exam is normal. A MMSE is performed, and DT scores 22/30. She has a 12th grade education. Her score on the GDS is found to be 2/30. Blood is drawn for laboratory testing, and DT is scheduled for a CT scan. Which of the following best describes the findings observed in this case?

A. Pseudodementia
B. Alzheimer Disease
C. Multi-infarct dementia
D. Cognitive impairment

Handout Page 1-445; Answer Page 1-466

Relevant Case Points

- Symptom onset and progression
- History
- MMSE
- GDS
- Differential diagnosis

Causes of cognitive impairment

- Vascular disease/stroke
- Depression
- Thyroid disease
- Vitamin deficiencies (B12, folate)
- Lewy body disease
- Parkinson disease
- Drug-induced causes

Patient Case 2 – AD

The daughter of an 81 year old woman with Alzheimer’s disease is asking the physician to start the patient on a medication for her memory. She was diagnosed with probable Alzheimer’s four years ago and is now in a nursing home and can perform some of her Activities of Daily Living (ADLs), but only with assistance. Her most recent MMSE was 14/30. She has been admitted to the emergency room twice in the last 6 months for bradycardia secondary to sick sinus syndrome. Which of the following would be the most appropriate treatment to recommend for this pt?

A. Donepezil
B. Memantine
C. Rivastigmine
D. Galantamine

Handout Page 1-449; Answer Page 1-466

Drug-induced Cognitive Impairment

- Table 1 (page 1-447)
  - Anticholinergic effects
    - Amantadine
    - Oxybutynin
    - Diphenhydramine
  - Benzodiazipines
  - CNS active agents
Relevant Case Points

- Severity of disease
- Concomitant medical problems
- Expectations of treatment

Medications to treat AD

- Cognitive enhancing medications (Table 2 – Handout page 1-450)
  - Cholinesterase inhibitors
    - Donepezil
    - Galantamine
    - Rivastigmine
  - NMDA receptor modulators
    - Memantine
  - Others
    - Gingko, Vitamin E, medical foods

Adverse Effects

- Cholinesterase inhibitors
  - GI (Nausea, Vomiting, Diarrhea)
  - Wt loss
  - Bradycardia
  - Exacerbation of pulmonary disease
- Memantine
  - Constipation
  - Dizziness
  - Headache

Patient Case 3 - AD

BL is a 72 year old male diagnosed with probable Alzheimer’s disease 1 year ago. He was started on galantamine ER 8mg daily shortly after his initial diagnosis, and was titrated up to galantamine ER 24 mg approximately 8 months ago. His most recent MMSE score was 23/30. He has tolerated this medication well to this point. His insurance coverage for medication is Medicare Part D, and 2 months ago he entered the ‘donut hole’, and was not able to afford to pay out of pocket to continue the galantamine ER. He is in clinic today, after the first of the year, and his physician is going to have BL restart galantamine. Which of the following is the most appropriate recommendation for BL to restart the galantamine?

A. Restart at 8mg daily x 4 weeks, since he has been off longer than several days
B. Restart at 16mg daily x 4 weeks, since it has been < 3 months since stopping
C. Restart at 24mg daily, since he has tolerated this dose
D. Restart at 8mg daily, but it may be titrated after 1 week

Patient Case 4 - AD

An 87 year old woman with severe Alzheimer’s disease is in the nursing home and is having disturbing visual hallucinations at night that keep her awake and she is frequently disruptive to other residents on the unit. She has gotten out of bed on multiple occasions, as though she is trying to get away, and has fallen on two occasions. She has been on lorazepam 0.5 mg at bedtime for 1 week, which has not improved her sleep or hallucinations. Which of the following would be the most appropriate recommendation for this patient at this time?

A. Stop lorazepam and begin zolpidem 5mg at HS
B. Stop lorazepam and begin trazodone 50 mg at HS
C. Stop lorazepam and begin risperidone 0.25 mg at HS
D. Stop lorazepam and begin temazepam 15 mg at HS

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Relevant Case Points

- Behavioral symptoms in AD
  - Types of symptoms
  - Target behaviors
  - Look for underlying causes
  - Non-pharm
  - Risks of psychotropics
  - Pharmacotherapy

Patient Case 5 - AD

BD is a 74 year old woman with Alzheimer’s disease who has been taking galantamine 24 mg daily for 1 year. She was seen 2 months ago and had been stable and doing well on this medication. She is in clinic today with her daughter who states that her mother’s memory and daily functioning have been noticeably worse over the past 2-3 weeks. Also new since the last visit, BD was not sleeping well at night, so her daughter started giving her an over-the-counter sleep medication, which has helped. Her MMSE score today is found to be 18/30. Two months ago it was 21/30. Which of the following would most likely explain this recent change with BD’s symptoms?

A. This represents normal progression of the disease
B. She is experiencing adverse effects of galantamine
C. The sleep medication likely contains an antihistamine
D. This represents the effects of sleep deprivation

Relevant Case Points

- Disease progression/MMSE decline
- New symptoms
- Drug interactions
- Combination therapy

Parkinson Disease (PD)

- Affects 2-3% of adults over 60 years
- Clinical presentation
  - Resting tremor
  - Rigidity
  - Bradykinesia
  - Motor symptoms
  - Autonomic symptoms
  - Cognitive and psychiatric symptoms

Drug-induced PD

- Antipsychotics
  - Typical vs atypicals
- Antiemetics
  - Metoclopramide, prochlorperazine
- Toxic substances
  - MPTP, manganese dust, carbon monoxide

Goals of Treatment

- Minimize motor and non-motor symptoms
- Maximize functional status and QOL
- Minimize medication-related adverse effects
- Maximize safety (fall risk)
PD Treatment Guidelines

- American Academy of Neurology
  - Initial treatment
  - Neuroprotection
  - Motor complications
  - Non-motor complications
  - Depression, psychosis, dementia

PD Pharmacotherapy

- Levodopa
- Dopamine agonists
- MAO-B inhibitors
- COMT inhibitors
- Anticholinergics
- Amantadine

Patient Case 6 - PD

A 72 year old female patient is in clinic for evaluation following a fall 1 week ago. She was seen in the emergency room at that time, but no significant injuries were noted. She states that she was dizzy prior to her fall. She has a history of hypertension, Parkinson’s disease, and osteoarthritis. Her current medications include: HCTZ 25mg daily, metoprolol XL 50mg daily, lisinopril 10mg daily, tramadol 50mg TID as needed for pain, levodopa/carbidopa CR 200/50mg BID, and pramipexole 0.125mg BID. She states that her PD symptoms are much better controlled since adding the pramipexole and decreasing the levodopa/carbidopa 1 month ago. On physical exam, her blood pressure is 136/72 sitting, and 118/60 standing. Her gait looks good, and her strength is good. Which of the following would be the most appropriate recommendation at this time to reduce her risk for future falls?

A. Discontinue the pramipexole
B. Decrease her blood pressure medications
C. Add midodrine
D. Add fludrocortisone

Relevant Case Points

- Autonomic symptoms
- Falls
- Concomitant medical problems
- Adverse effects of PD treatments
- Combination PD treatments

Patient Case 7 - PD

A 68 year old woman with PD has been on levodopa/carbidopa 100/25 mg QID for two weeks. Previously, she was taking levodopa/carbidopa 100/25 mg TID. She is calling your clinic to see what she can do about symptoms she describes including nausea, lightheadedness, and involuntary movements that sound like dyskinesias. Her PD symptoms were fairly well controlled on the TID schedule, but her physician increased the dose to QID to achieve additional benefit. Which of the following would be the best recommendation to address this woman’s symptoms?

A. Add rasagiline
B. Decrease levodopa/carbidopa to 100/25 mg TID
C. Add ropinirole
D. Change levodopa/carbidopa to 100/10 mg QID

Relevant Case Points

- Titrating PD medications
- Adverse effects of PD treatments
Patient Case 8 - PD

TB is a 63 year old gentleman who was diagnosed with early PD approximately 6 months ago, but is otherwise healthy. He was not initiated on any medications when first diagnosed, but was started on selegiline 5mg BID by his physician about 4 weeks ago. He is in clinic today with complaints of difficulty sleeping and with his memory. He states that most days he feels tired, but just cannot fall asleep. He states his wife has a prescription for lorazepam 0.5mg, and he has taken 1 tablet on occasion when he has had difficulty sleeping. He is asking for a prescription for lorazepam to help him sleep. Which of the following would be the best recommendation for this man at this time?

A. Give him a prescription for lorazepam 0.5mg HS
B. Have him take diphenhydramine 50mg HS
C. Change the selegiline dosing from BID to AM & Noon
D. Add levodopa/carbidopa to the selegiline

Relevant Case Points

- Initial therapy
- Adverse effects of PD treatments
- Non-motor symptoms of PD
- Behavioral/psychiatric symptoms and treatments

Patient Case 9 - PD

A 66 year old male diagnosed with PD is being evaluated today in clinic. He has been on levodopa/carbidopa for 6 years. His current levodopa/carbidopa dose is 100/25mg, 1 ½ tablets AM, 1 tablet 11am, 1 tablet 2pm, 1 tablet 5pm, ½ tablet at 8pm. He has been experiencing motor complications for approximately 3 months, including on-off symptoms and freezing episodes. On physical examination, he has some weakness, gait and balance abnormalities, and rigidity. His ability to ambulate and perform self-care activities over the past 3 months has continued to decline. Which of the following would be the most appropriate recommendation for this man’s symptoms?

A. Add benztropine to levodopa/carbidopa
B. Decrease levodopa/carbidopa dose to 4 tablets daily
C. Switch to levodopa/carbidopa CR
D. Add entacapone to levodopa/carbidopa

Relevant Case Points

- Long-term levodopa therapy
- Motor complications
- Combination therapy/add-on therapy

Patient Case 10 - PD

The 66 year old pt in the previous question returns to clinic 2 weeks after your recommendation above. He states that overall he thinks he is doing better, but that he frequently feels nauseated and occasionally feels light headed or dizzy. He also describes some abnormal movements, which are identified as dyskinesias on physical exam. The most appropriate recommendation for this man at this time would be:

A. Add prochlorperazine for nausea
B. Decrease the daily dose of levodopa/carbidopa
C. Initiate rasagiline
D. Initiate amantadine

Relevant Case Points

- Excessive dopaminergic signs/symptoms
- Adverse effects of PD treatments
- Managing adverse effects
Questions?

- Feel free to email me if you have questions
  - jruscin@siue.edu