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

Gastrointestinal Disorders

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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.

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Learning Objectives

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.

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Chapter Outline

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

Viral Hepatitis

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Viral Hepatitis

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

Table 7. Estimated Viral Hepatitis Disease Burden in the United States in 2009*

	Acute Disease		Chronic Disease
	Reported New Cases	Estimated New Cases	No. of Individuals Living with Chronic Infection
Hepatitis A	1987	21,000	0
Hepatitis B	3371	38,000	800,000–1.4 million
Hepatitis C	781	16,000	2.7–3.9 million

*www.cdc.gov/hepatitis/PDFs/disease_burden.pdf.

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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

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Hepatitis A

- Prevention
  - Avoid exposure
  - Institute good handwashing techniques and personal hygeine practices
  - Prophylaxis
    - Pre-exposure
    - Post-exposure

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Hepatitis B (HBV)

- DNA virus; genotypes A-H
  - Genotype prevalence varies according to geographic region
  - Data suggestions disease progression maybe linked to genotype
- Transmission
  - Body fluids
  - Sexual contact, parenteral, perinatal

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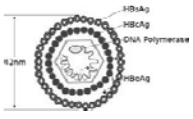
HBV: clinical presentation & assessment

- Symptoms
  - Many are asymptomatic
  - Abdominal pain, diarrhea, fever, jaundice, myalgia, nausea and vomiting
- History and physical exam
- Laboratory testing
- Serologic testing



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HBV: serologic testing

Table 11. HBV Serologic Markers

Serologic Marker	Abbreviation	Comments
Anticore antigen antibody (IgG)	Anti-HBc	Appears at symptom onset, denotes previous exposure to HBV
Anti-surface antigen antibody	Anti-HBs	Confers protective immunity; present after recovery from acute infection or after vaccination
Anti-E antibody	Anti-HBe	May indicate peak viral replication has resolved
Core antigen	HBcAg	Presents after cell damage during acute infection
E antigen	HBeAg	Indicates ongoing viral replication
Surface antigen	HBsAg	First detected; present during acute and chronic infections
HBV DNA	HBV DNA	Quantifies HBV; indicates active replication

HBcAg = hepatitis B core (antigen); HBeAg = hepatitis B e antigen; HBsAg = hepatitis B surface antigen; HBV = hepatitis B virus; IgG = immunoglobulin G.

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HBV: serologic testing

Table 12. Interpretation of HBV Serologic Test Results

	HBsAg	Anti-HBc	IgM anti-HBc	Anti-HBs
No infection, no immunization	–	–	–	–
Acute infection	+	+	+	–
Chronic infection	+	+	–	–
Recovered from infection; immune	–	+	–	+
Immune (immunization or natural)	–	–	–	+

HBc = hepatitis B core (antigen); HBsAg = hepatitis B surface antigen; HBV = hepatitis B virus; IgM = immunoglobulin M.

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HBV: phases

- Immune tolerant
- Immune active
- Inactive carrier

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HBV: phases

Table 10. Summary of Chronic Hepatitis B Phases

	Immune Tolerant	Chronic HBV (Immune Active)		Inactive HBsAg Carrier State
HBsAg	Positive	Positive	Positive	Positive
HBeAg	Positive	Positive	Negative	Negative
Anti-HBc	Negative	Negative	Positive	Positive
HBV DNA	Normal	> 20,000 IU/mL	2000–20,000 IU/mL	< 2000 IU/mL
AST/ALT	Normal	Elevated	Elevated	Normal
Liver biopsy	Confirms absence of significant hepatitis	Moderate or severe necroinflammation		Confirms absence of significant hepatitis

ALT = alanine aminotransferase; HBeAg = hepatitis B early antigen; HBsAg = hepatitis B surface antigen; HBV = hepatitis B virus.

Viral replication	Increasing	Very Active	Less Active
Liver Activity	Minimal	Increased	Minimal

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HBV: phases

- Shifts

  Immune tolerant → Immune active → Inactive carrier

  Immune active ← Inactive carrier

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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

Table 14. HBV Antiviral Therapy: Time of Assessment

Category of Response	Definition
On therapy	During therapy
Maintained	Persists throughout treatment
End of treatment	At the end of defined treatment course
Off therapy	After treatment is discontinued
Sustained (SR-6)	6 months after treatment is discontinued
Sustained (SR-12)	12 months after treatment is discontinued

HBV = hepatitis B virus.

HBV: Treatment

- 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

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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
- No Treatment indicated
  - **Immune tolerant**
  - **Inactive carrier**

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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)

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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

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HBV: Pharmacotherapy

Table 20. Comparison of Agents for Treatment of Adult Chronic HBV

	INF-α Peg-INF-α	Lamivudine (Epivir)	Adefovir (Hepsera)	Entecavir (Baraclude)	Telbivudine (Tyzeka)	Tenofovir (Viread)
Route of administration	Subcutaneous	Oral	Oral	Oral	Oral	Oral
Formulations		Tablet Solution	Tablet	Tablet Solution	Tablet	Tablet
Adverse events	Many	Minimal	Nephrotoxic potential	Minimal	Myopathy	Nephrotoxic potential
Mutations	None	YMDD	N236T A181V/T	M204V/I	M204I	
Incidence of resistance	N/A	20% 1 year 69% 5 years	0% 1 year 29% 5 years	0% 1 year 1.2% 5 years	5% 1 year 25% 2 years	0% 1 year
Costs	High	Low	Moderate	High	Moderate	Moderate
Therapy duration						
HBeAg positive Normal or elevated ALT	4–12 months	At least 12 months; continue at least 6 months after anti-HBe seroconversion				
HBeAg negative	1 year	Greater than 12 months				

ALT = alanine aminotransferase; HBeAg = hepatitis B early antigen; HBV = hepatitis B virus; INF = interferon alfa; N/A = not applicable.

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HBV: Pharmacotherapy

Table 21. Comparison of HBV Treatment Strategies

	Advantages	Disadvantages
Interferon alfa	Defined therapy duration Minimal resistance	Subcutaneous administration Significant adverse event profile High cost
Nucleoside/nucleotide analogs	Oral administration Variable costs among agents Improved efficacy Better safety profile	Indefinite therapy duration Development of resistance High cost

HBV = hepatitis B virus.

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HBV: Pharmacotherapy

- Other points to consider
  - Combination therapy
  - Special populations
    - Decompensated cirrhotics
    - Individuals not responding to therapy
    - Individuals on NA therapy that develop viral breakthrough

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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

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HBV: Treatment summary

- Indication
  - Based on phase of disease
- Pharmacotherapy
  - Preferred agents: peg-INF-α (or) NA
  - Choice of therapy: patient specific

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HBV: Prevention

- Screening
  - Should include HBsAg and be performed on high-risk populations
  - Immunization should be offered to all seronegative individuals
- Prophylaxis
  - Pre-exposure
  - Postexposure

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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.

Chapter Page 391; Answer Page 395

Patient Case #7

- **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?**

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Patient Case #7

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

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HCV: Clinical presentation & assessment

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

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HCV: Testing

Table 23. Interpretation of HCV Laboratory Data

Anti-HCV	HCV RNA	Interpretation
+	+	Clinical assessment is necessary to differentiate between acute and chronic disease
+	–	Resolution of acute infection; acute infection during period of low viremia
–	+	Early acute infection Chronic in setting of immunosuppressed False-positive HCV RNA test
–	–	Absence of infection

HCV = hepatitis C virus.

HCV RNA = quantitative (IU/mL)

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HCV: Treatment

- Goals
  - Eradicate virus; achieve sustained virologic response (SVR)
  - Prevent liver disease progression (cirrhosis, HCC) and death
- Response
  - Classified as biochemical, virologic and/or histologic

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HCV: Virologic response

Table 24. HCV Virologic Response Definitions

Virologic Response	Assessment Point	Definition
Rapid virologic response (RVR)	Treatment week 4	HCV RNA undetectable
Partial early virologic response (partial EVR)	Treatment week 12	≥ 2-log reduction in HCV RNA compared with baseline
Complete early virologic response (complete EVR)	Treatment week 12	HCV RNA undetectable
End-of-treatment response (ETR)	End of treatment (treatment week 24 or 48)	HCV RNA undetectable
Sustained virologic response (SVR)	24 weeks after treatment completed	HCV RNA undetectable
Breakthrough	Anytime while on treatment	HCV RNA detectable after being undetectable
Relapse	Anytime once treatment has been discontinued	HCV RNA detectable in serum after treatment discontinued
Nonresponse	Treatment week 24	Remain HCV RNA positive after 24 weeks of treatment
Partial response	Treatment week 24	HCV RNA decline > 2 log from baseline at week 12 but HCV RNA detectable at weeks 12 and 24
Null response	Treatment week 24	HCV RNA decline < 2 log from baseline to week 12

Note: HCV RNA must be performed by a sensitive PCR-based quantitative assay.
EVR = early virologic response; HCV = hepatitis C virus; PCR = polymerase chain reaction.

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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 naïve
      - Genotype 1 (triple therapy): 67–75%
      - Genotype 4 (combination therapy): 45 – 50%
      - Genotype 2 and 3 (combination therapy): 80%

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HCV: Virologic response

Table 24. HCV Virologic Response Definitions

Virologic Response	Assessment Point	Definition
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Note: HCV RNA must be performed by a sensitive PCR-based quantitative assay.
EVR = early virologic response; HCV = hepatitis C virus; PCR = polymerase chain reaction.

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HCV: Predictors of response

- Pretreatment
  - HCV genotype
  - Viral load
  - Histologic stage
  - IL28B genotypes
    - CC, CT and TT
    - CC more likely to achieve SVR
- ~~Posttreatment~~
- On-treatment
  - EVR
  - RVR

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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)

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HCV: Pharmacotherapy

- Peg-INF-α
- Ribavirin
- Protease inhibitors

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HCV: Peg-INF-α

- Similar efficacy
- Dosing constant for ALL genotypes

Table 25. Comparison of Pegylated Interferon Alphas

	Pegylated Interferon Alpha-2a (Pegasys)	Pegylated Interferon Alpha-2b (PEG-Intron)
Dosing	180 mcg/week	1.5 mcg/kg/week
Route of administration	Subcutaneously	Subcutaneously
Metabolism	Liver	Liver
Excretion	Renal	Renal
Adverse event profile*	Fatigue Fever Headache Nausea Myalgia Anxiety Injection site reactions	Anorexia Arthralgia Musculoskeletal pain Insomnia Depression Rigors Alopecia

*Dose reduction or discontinuation may be necessary because of adverse events; follow manufacturer's recommendations.

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HCV: Ribavirin

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

Table 26. Ribavirin Weight-Based Dosing According to HCV Genotype

HCV Genotype	Ribavirin	Weight (kg)	Dose (mg/day) in 2 divided doses	Route of Administration
1 or 4	Copegus (with Pegasys)	< 75	1000	Orally
		≥ 75	1200	
	Rebetol (with PEG-Intron)	≤ 75	1000	
		> 75	1200	
2 or 3	Copegus (with Pegasys)	N/A	800	Orally
	Rebetol (with PEG-Intron)			

HCV = hepatitis C virus.

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HCV: Protease Inhibitors

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

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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

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HCV: Telaprevir

- 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

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HCV: Telaprevir

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

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HCV: Telaprevir

- Anemia

Hemoglobin	Triple Therapy	Combination Therapy
≤ 10 g/dL	36%	17%
< 8.5 g/dL	14%	5%
RBV dose modification [1]	32%	12%

[1]Dose reduction, interruption or discontinuation

  - 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

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HCV: Telaprevir

- Anorectal symptoms
  - Hemmorrhoids, 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)

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HCV: Telaprevir

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

Table 30. Drugs Contraindicated with Telaprevir Administration According to FDA Prescribing Information

Alfuzosin	Midazolam (oral)
Atrovastatin	Pimozide
Cisapride	Rifampin
Dihydroergotamine	St. John's wort
Ergonovine	Sildenafil
Ergotamine	Simvastatin
Lovastatin	Tadalfil
Methylergonovine	Triazolam (oral)

Note: These medications are contraindicated; however, other drugs metabolized by similar enzyme systems also may have significant drug interactions requiring dose adjustments and additional monitoring (refer to prescribing guidelines for additional information).

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HCV: Telaprevir

- Triple therapy
  - Must ALSO consider Peg-INF-α and ribavirin's
    - Adverse events
    - Drug interactions
    - Contraindications

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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.

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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

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HCV: Boceprevir

- Adverse events
  - Most common
    - Fatigue, anemia, nausea, headache and dysgeusia

	Triple Therapy	Combination Therapy
Anemia	45-50%	20-30%
Dysguesia	44-35%	11-16%

HCV: Boceprevir

- 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)

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HCV: Boceprevir

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

Table 34. Drugs Contraindicated with Boceprevir Administration According to FDA Prescribing Information

Alfuzosin	Midazolam (oral)
Carbamazepine	Phenobarbital
Cisapride	Phenytoin
Dihydroergotamine	Pimozide
Drospirenone	Rifampin
Ergonovine	Sildenafil
Ergotamine	Simvastatin
Lovastatin	Tadalfil
Methylergonovine	

Note: These medications are contraindicated; however, other drugs metabolized by similar enzyme systems also may have significant drug interactions requiring dose adjustments and additional monitoring (refer to prescribing guidelines for additional information).

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HCV: Boceprevir

- Triple therapy
  - Must ALSO consider Peg-INF-α and ribavirin's
    - Adverse events
    - Drug interactions
    - Contraindications

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HCV: Protease inhibitors summary

	Telaprevir	Boceprevir
Dose	750mg po tid *12 weeks*	800mg po tid *Lead in phase*
Administration	With food (non lowfat)	With food
Most common adverse events	rash, fatigue nausea, diarrhea anemia, dysgeusia anorectal symptoms	fatigue, anemia nausea, headache dysgeusia
Contraindications	Hypersensitivity Pregnancy Medications (Table 30)	Hypersensitivity Pregnancy Medications (Table 34)
Drug interactions	CYP3A4	CYP3A4

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HCV: Treatment – guideline recommendations

- Pharmacotherapy
  - **Combination therapy**
    - Genotypes 2-6
  - **Triple therapy**
    - Genotype 1
- Duration

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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 undectable, consider extending duration to 72 weeks

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HCV: Treatment duration

- Triple therapy
  - Genotype 1 — response guided
    - Differs for each triple therapy regimen
      - Peg-INF-α + ribavirin + telaprevir
      - Peg-INF-α + ribavirin + boceprevir
    - Varies by patient population

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HCV: Treatment duration

- 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

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HCV: Treatment duration

Table 27. Telaprevir Triple Therapy: Treatment Naive and Relapsers*

HCV RNA			Total Length of Therapy (weeks)	Type of Therapy According to Week of Treatment
Week 4	Week 12	Week 24		
Undetectable (with level ≤ 10–15 IU/mL) at BOTH weeks 4 and 12			24	Weeks 1–12: P + RBV + TVR Weeks 13–24: P + RBV
Detectable (with level ≤ 1000 IU/mL) at week 4 and/or week 12		Undetectable (with level ≤ 10–15 IU/mL)	48	Weeks 1–12: P + RBV + TVR Weeks 13–48: P + RBV
Detectable (with level ≤ 1000 IU/mL) at week 4 and/or week 12		Detectable (with level > 10–15 IU/mL)	24	Weeks 1–12: P + RBV + TVR Weeks 13–24: P + RBV
Detectable (with level > 1000 IU/mL) at week 4 and/or week 12		—	12	Weeks 1–12: P + RBV + TVR

P = Peg-INF-α, RBV = ribavirin, TVR = telaprevir.
*Relapse includes patients with an undetectable HCV RNA upon completion of non-telaprevir-based treatment but with a detectable HCV RNA during the follow-up period.

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HCV: Treatment duration

- 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

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HCV: Treatment duration

- Triple therapy with telaprevir
  - Discontinue therapy based on the <u>futility rules</u>
    - HCV RNA detectable (> 1000 IU/mL) at treatment week #4 or #12
    - HCV RNA detectable at treatment week #24

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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 cirrhotics
    - Table 33 – partial responders and relapsers

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HCV: Treatment duration

Table 31. Boceprevir Triple Therapy: Treatment Naive – Interferon Responsive

HCV RNA			Total Length of Therapy (weeks)	Type of Therapy According to Week of Treatment
Week 8	Week 12	Week 24		
Undetectable	—	Undetectable	28	Weeks 1–4: P + RBV Weeks 5–8: P + RBV + BOC Weeks 9–24: P + RBV + BOC Weeks 25–28: P + RBV + BOC
Detectable	Undetectable	Undetectable	48	Weeks 1–4: P + RBV Weeks 5–8: P + RBV + BOC Weeks 9–24: P + RBV + BOC Weeks 25–36: P + RBV + BOC Weeks 37–48: P + RBV
Detectable	Undetectable	Detectable	24	Weeks 1–4: P + RBV Weeks 5–8: P + RBV + BOC Weeks 9–24: P + RBV + BOC
Detectable	Detectable	—	12	Weeks 1–4: P + RBV Weeks 5–8: P + RBV + BOC Weeks 9–12: P + RBV + BOC

BOC = boceprevir; detectable = HCV RNA greater than 100 IU/mL; P = Peg-INF-α; RBV = ribavirin.

Chapter Page 387 - 88

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 cirrhotics
    - Table 33 – partial responders and relapsers

Chapter Page 387 - 88

HCV: Treatment duration

- Triple therapy with boceprevir
  - Discontinue therapy based on the futility rules
    - HCV RNA detectable (≥ 100 IU/mL) at treatment week #12
    - HCV RNA detectable at treatment week #24

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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

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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

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HCV: Prevention

- No vaccine available

Chapter Page 390

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

Chapter Page 391; Answer Page 395

Patient Case #8

Which one of the following is the best option for initiating HCV therapy and monitoring HCV RNA to make the appropriate decision regarding response guided therapy?

	Peg-INF-α	RBV	TEL	HCV RNA
A	180mg weekly	600mg 2 times/day	750mg 3 times/day	4, 12
B	180mg weekly	600mg 2 times/day	750mg 3 times/day	4, 12, 24
C	180mg weekly	600mg 2 times/day	750mg 2 times/day	4, 12
D	180mg weekly	600mg 2 times/day	750mg 2 times/day	4, 12, 24

Chapter Page 391; Answer Page 395

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 Page 335; Answer Page 397

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 Page 335; Answer Page 397

Chapter Outline

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

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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

Chapter Page 351

Complications of Cirrhosis

- Clinical Presentation

Table 4 Cirrhosis: Clinical Presentation

Signs and symptoms	Hepatomegaly Palmar erythema Spider angiomata Gynecomastia Encephalopathy Edema Malaise Anorexia	Splenomegaly Pruritus Jaundice Hyperpigmentation Ascites Pleural effusion Respiratory difficulties Weight loss
Laboratory abnormalities	↑ AST, ALT, GGT Hypoalbuminemia	↑ Alkaline phosphatase, ↑ PT/INR Thrombocytopenia

ALT = alanine aminotransferase; AST = aspartate aminotransferase; GGT = γ-glutamyl transferase; INR = international normalized ratio; PT = prothrombin time.

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

Chapter Page 351

Complications of Cirrhosis

- Disease severity (scoring systems)
  - Child-Pugh

Table 5. Child-Pugh Classification

	Score		
	1 point	2 points	3 points
Encephalopathy	Absent	Mild-moderate	Severe-Coma
Ascites	Absent	slight	Moderate
Bilirubin (mg/dL)	< 2	2–3	> 3
Albumin (mg/dL)	> 3.5	2.8–3.5	< 2.8
Prothrombin time (seconds prolonged)	1–4	4–6	> 6

  - Grade A: < 7 points - compensated liver disease
  - Grade B: 7-9 points - significantly functional compromised liver disease
  - Grade C: 10-15 points - decompensated liver disease

Chapter Page 351

Complications of Cirrhosis

- 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 x log(SCr) + 3.78 x log (total bilirubin) + 11.2 x log (INR) = 6.43
    - Maximum score is 40

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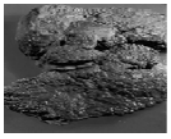
Complications of Cirrhosis



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

Chapter Page 351

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 buldging 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

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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

Chapter Page 354; Answer Page 1-165

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

Chapter Page 352 - 54

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)

Chapter Page 352 - 54

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

Chapter Page 352 - 54

Ascites: Treatment

- Refractory
  - Paracentesis
  - Transjugular intrahepatic portasystemic stent-shunt (TIPS)
  - Liver transplant

Chapter Page 352 - 54

Spontaneous Bacterial Peritonitis (SBP)

- Occurs in 15-26% of hospitalized patients with ascities
- Bacterial infection of ascitic fluid
  - Source of infection is unclear, thought to be from GI tract
  - Common pathogens: Escherichia coli, Klebsiella pneumoniae, pneumococci

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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

Chapter Page 354 – 56

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 antibiotic
  - Secondary: ANY patient with history of SBP
    - Therapy: Norfloxacin, ciprofloxacin, trimethorprim/sulfamethoxazole DS

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Complications of Cirrhosis

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

Chapter Page 351

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

Chapter Page 356 - 59

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

Chapter Page 356 - 59

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 $\geq$ 1
  - Acute or Chronic

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HE: staging

- West Haven criteria and Glasgow Coma Scale

Table 6. West Haven Criteria

Stage	Definition
0 (minimal)	Lack of detectable changes in personality or behavior Asterixis absent
1	Trivial lack of awareness Shortened attention span Impaired addition or subtraction Hypersomnia, insomnia, or inversion of sleep pattern Euphoria or depression Asterixis can be detected
2	Lethargy or apathy Disorientation Inappropriate behavior Slurred speech Obvious asterixis
3	Gross disorientation Bizarre behavior Semi-stupor to stupor Asterixis generally absent
4	Coma

Chapter Page 356 - 59

HE: Treatment

- Goals
  - Identify and eliminate precipitating factors
  - Reduce nitrogenous load
  - Supportive care
- Options
  - Nutritional management
  - Pharmacologic therapy
  - Manipulation of splanchnic circulation (invasive)

Chapter Page 356 - 59

HE: Pharmacologic Therapy

- Lactulose
  - Nonabsorbable disaccharide; degrade colonic bacteria
  - Standard of care according to practice guidelines
  - Challenges
- Antibiotics
  - Alternate to nonabsorbable disaccharide; reduce bacterial production of ammonia
  - Neomycin, rifaxamin
  - May work in synergy with lactulose

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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.

Chapter Page 359; Answer Page 394

Patient Case #5

- **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

Chapter Page 359; Answer Page 394

Patient Case #5

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

- A. Rifaxamin 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.**

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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

Chapter Page 361; Answer Page 395

Patient Case #6

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

Chapter Page 361; Answer Page 395

Gastroesophageal Varices

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

Chapter Page 359 - 61

Gastroesophageal Varices: Treatment

- Goals
  - Prompt diagnosis
  - Control bleeding
  - Prevent complications
- Acute management (hospitalized)
  - Volume expansion and hemodynamic stabilization
  - Endoscopic intervention
    - Band ligation / sclerotherapy
  - Pharmacotherapy

Chapter Page 359 – 61

Gastroesophageal Varices: Treatment

- Pharmacotherapy
  - Used to cause splanchnic vasoconstriction, subsequently decreasing portal blood flow
- Options
  - Octreotide or somatostatin
  - Vasopressin
  - Antibiotics

Chapter Page 359 – 61

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 varies, 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

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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 varies, 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 Page 359 - 61

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

Chapter Page 359 - 61

Patient Case #6

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

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Chapter Outline

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

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

Chapter Page 344

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

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PUD: Diagnosis of *H. pylori*

- *H. pylori* is a carcinogen; so 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

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PUD: Diagnosis *H. pylori*

Type of Test	Invasive	↓ sensitivity with medications reducing urease activity[1]	Provides accurate posttreatment testing
RUT	X	X	
Histology	X	X	
Culture	X		
Antibody			
UBT		X	X
FAT		X	X

[1] Medications that reduce urease activity: bismuth containing, antibiotics and PPIs

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PUD: Treatment of *H. pylori*

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

Chapter Page 346

PUD: Treatment of *H. pylori*

- Strategies
  - Nonpharmacologic
    - Smoking cessation, avoid NSAIDs, avoid foods that exacerbate symptoms, and reduce/eliminate physiologic stress
  - Pharmacologic

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PUD: Treatment of *H. pylori*

- 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

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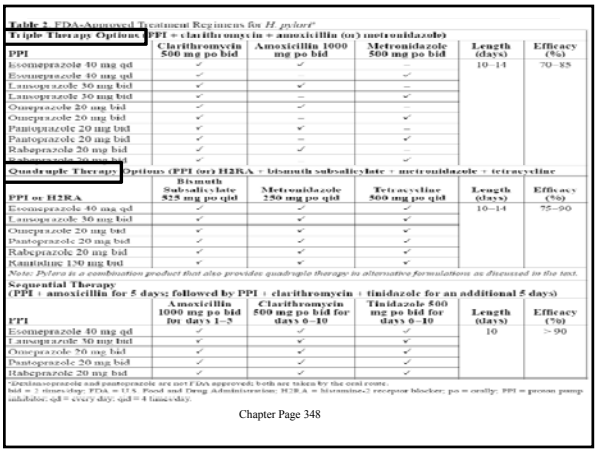

Table 2. FDA-Approved Treatment Regimens for *H. pylori*[a]

Triple Therapy Options (PPI + clarithromycin + amoxicillin (or) metronidazole)

PPI	Clarithromycin 500 mg po bid	Amoxicillin 1000 mg po bid	Metronidazole 500 mg po bid	Length (days)	Efficacy (%)
Esomeprazole 40 mg qd	✓	✓	–	10–14	70–85
Esomeprazole 40 mg qd	✓	–	✓		
Lansoprazole 30 mg bid	✓	✓	–		
Lansoprazole 30 mg bid	✓	–	✓		
Omeprazole 20 mg bid	✓	✓	–		
Omeprazole 20 mg bid	✓	–	✓		
Pantoprazole 20 mg bid	✓	✓	–		
Pantoprazole 20 mg bid	✓	–	✓		
Rabeprazole 20 mg bid	✓	✓	–		
Rabeprazole 20 mg bid	✓	–	✓		

Quadruple Therapy Options (PPI (or) H2RA + bismuth subsalicylate + metronidazole + tetracycline

PPI or H2RA	Bismuth Subsalicylate 525 mg po qid	Metronidazole 250 mg po qid	Tetracycline 500 mg po qid	Length (days)	Efficacy (%)
Esomeprazole 40 mg qd	✓	✓	✓	10–14	75–90
Lansoprazole 30 mg bid	✓	✓	✓		
Omeprazole 20 mg bid	✓	✓	✓		
Pantoprazole 20 mg bid	✓	✓	✓		
Rabeprazole 20 mg bid	✓	✓	✓		
Ranitidine 150 mg bid	✓	✓	✓		

Note: Pylera is a combination product that also provides quadruple therapy in alternative formulations as discussed in the text.

Sequential Therapy (PPI + amoxicillin for 5 days; followed by PPI + clarithromycin + tinidazole for an additional 5 days)

PPI	Amoxicillin 1000 mg po bid for days 1–5	Clarithromycin 500 mg po bid for days 6–10	Tinidazole 500 mg po bid for days 6–10	Length (days)	Efficacy (%)
Esomeprazole 40 mg qd	✓	✓	✓	10	>90
Lansoprazole 30 mg bid	✓	✓	✓		
Omeprazole 20 mg bid	✓	✓	✓		
Pantoprazole 20 mg bid	✓	✓	✓		
Rabeprazole 20 mg bid	✓	✓	✓		

[a]Esomeprazole and pantoprazole are not FDA approved; both are taken by the oral route.
bid = 2 times/day; FDA = U.S. Food and Drug Administration; H2RA = histamine-2 receptor blocker; po = orally; PPI = proton pump inhibitor; qd = every day; qid = 4 times/day.

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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

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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:** antacids as needed, 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?**

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Patient Case #2

- A. Amoxicillin 1g twice daily + clarithromycin 500 mg twice daily + esomeprazole 40 mg once daily for 7 days.
- B. Amoxicillin 1 g twice daily + clarithromycin 500 mg twice daiily + esomeprazole 40 mg twice daily for 14 days
- 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
- **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**

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Patient Case #3

Which one of the following options is best to perform when JP returns to the clinic after her *H. pylori* treatment is complete to confirm *H. pylori* eradication?

- A. Tissue culture — • Invasive; cannot test for eradication
- **B. UBT** — • Noninvasive; can test for eradication
- C. RUT — • Invasive; cannot test for eradication
- D. Serum antibody test — • Noninvasive: cannot test for eradication

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PUD: NSAID ulcers

- NSAID therapy is associated with mucosal injury to upper GI tract and potential cardiovascular hazards
  - Use must be combined with ulcer prevention strategies
    - Cotherapy
    - Replacement therapy
    - Risk factor assessment

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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

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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

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PUD: NSAID ulcers

Table 3. Therapy Recommendations for Ulcer Prevention According to GI and CV risk

GI Risk	CV Risk	
	Low	High
Low	NSAID alone	Naproxen + PPI (or) misoprostol
Moderate	NSAID + PPI (or) misoprostol	Naproxen + PPI (or) misoprostol
High	Alternative therapy if possible (or) COX-2 inhibitor + PPI/misoprostol	Avoid NSAID (or) COX-2 inhibitors

COX-2 = cyclooxygenase-2; CV = cardiovascular; GI = gastrointestinal; NSAID = nonsteroidal anti-inflammatory drug; PPI = proton pump inhibitor.

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

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PUD: NSAID ulcers

Table 3. Therapy Recommendations for Ulcer Prevention According to GI and CV risk

GI Risk	CV Risk	
	Low	High
Low	NSAID alone	Naproxen + PPI (or) misoprostol
Moderate	NSAID + PPI (or) misoprostol	Naproxen + PPI (or) misoprostol
High	Alternative therapy if possible (or) COX-2 inhibitor + PPI/misoprostol	Avoid NSAID (or) COX-2 inhibitors

COX-2 = cyclooxygenase-2; CV = cardiovascular; GI = gastrointestinal; NSAID = nonsteroidal anti-inflammatory drug; PPI = proton pump inhibitor.

CV Risk
- High: arbitrarily defined as requirement for low-dose aspirin

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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

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Self Assessment Question #2

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

Chapter Page 334; Answer Page 396

PUD: NSAID ulcers

- 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

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PUD: NSAID ulcers

- Other considerations
  - Concurrent use of NSAIDs and antiplatelet therapy

	Ischemic Risk	Bleeding Risk
Antiplatelet	↓	↑
NSAIDs		↑

Chapter Page 349 - 50

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

Chapter Page 336

Gastroesophageal Reflux Disease (GERD)

- Normal: parietal cells secrete acid into gut lumen in coordinated fashion
- Impaired:
  - Reflux: disruption of signal
  - Mucosal damage: inflammation due to repeated acid exposure for prolonged periods

Chapter Page 336

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

Chapter Page 336 - 37

GERD CLASSIFICATION

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

Chapter Page 336 – 37

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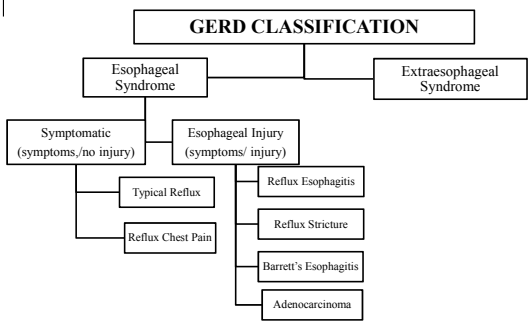

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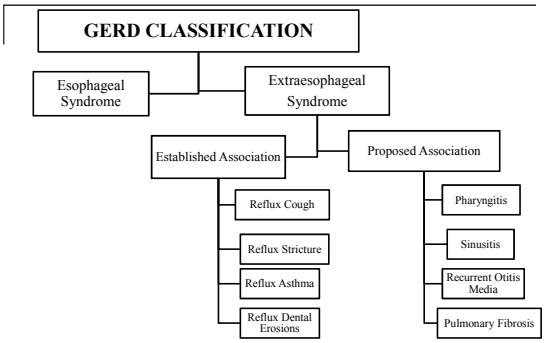

Chapter Page 336 – 37

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

Chapter Page 337

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

Chapter Page 337 – 38

GERD: Treatment

- Approaches
  - Step-up approach: Add on in stepwise manner until symptom improvement
  - Step-down approach: Start aggressive and decrease in stepwise manner
- Select approach based on:
  - Patient's condition
  - Symptom intensity
  - Degree of inflammation
  - Presence of complications

Chapter Page 338

GERD: Treatment

- 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

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GERD: Treatment

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

Chapter Page 339 - 42

GERD: Treatment

- 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

Chapter Page 339 - 40

GERD: Treatment

- Proton pump inhibitors
  - Most effective to treat symptoms and mucosal healing
  - Maintenance therapy often indicated
  - Similar efficacy for all agents

Chapter Page 339 - 40

GERD: PPIs

Table 1. Comparison of Proton Pump Inhibitors Used to Treat Typical Reflux Syndrome

Agent	Typical Dose Range	Available as OTC
Esomeprazole (Nexium)	20 mg/day for 4–8 weeks	No
Omeprazole (Prilosec)	20 mg/day for up to 4 weeks	Yes
Omeprazole + sodium bicarbonate (Zegerid)	20 mg/day for up to 4 weeks	Yes
Lansoprazole (Prevacid)	15 mg/day for up to 8 weeks	Yes
Rabeprazole (AcipHex)	20 mg/day for 4–8 weeks	No
Pantoprazole (Protonix)	20 mg/day, duration not specified	Yes
Dexlansoprazole (Dexilant)	30 mg/day for 4 weeks	No

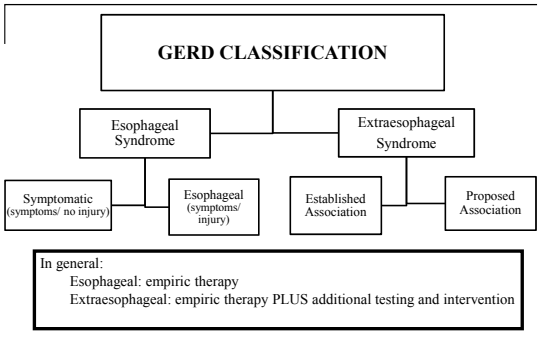
OTC = over the counter.

Chapter Page 339 - 42

GERD: PPIs

- Dosing
  - Daily versus twice daily
    - Disconnect between trial data and clinical practice
    - Guidelines recommend twice daily dosing in patients with unsatisfactory response to once daily dosing
- Administration

Chapter Page 339 - 42



Chapter Page 338

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

Chapter Page 338 - 39

GERD: Treatment recommendations

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

Chapter Page 338 - 39

GERD: Treatment

- 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

- Improper administration
- Adherence to regimen
- Esophageal hypersensitivity
- Nocturnal breakthrough
- Agent specific
- H. pylori status
- Delayed esophageal healing
- Residual reflux
- Bile acid reflux
- Comorbid conditions.

Chapter Page 342

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

Chapter Page 343; Answer Page 394

Patient Case #1

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 famotidine10mg, 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)

Chapter Page 343; Answer Page 394

Gastrointestinal Disorders

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

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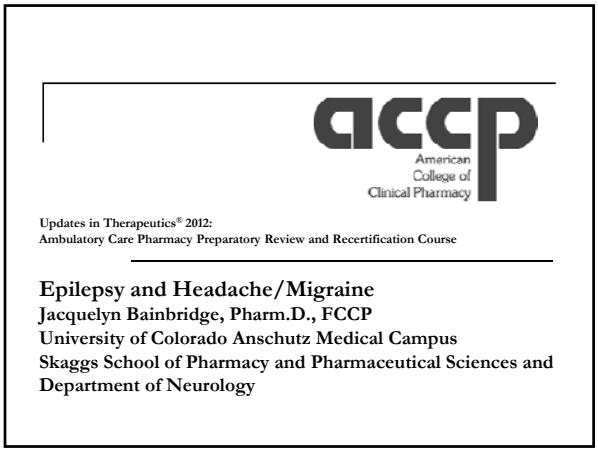

Conflict of Interest Disclosures

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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.

Learning Objectives

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.

Learning Objectives

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.

Learning Objectives

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.

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Learning Objectives

14. List common migraine triggers.

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

Handout Page 1-419

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

Handout Page 1-402

Clinical Presentation of Epilepsy

- Partial Seizures
  - Simple partial
  - Complex partial
  - Secondary generalized
- Generalized Seizures
  - Absence
  - Atonic
  - Clonic
  - Myoclonic
  - Tonic
  - Tonic-clonic
  - Infantile spasms

Handout Page 1-403

Treatment Options for Epilepsy

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

How do you choose therapy?

Handout Page 1-405 & 1-420

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, Carbatrol) (CBZ) – **1974**
- Valproate (Depakote, Depakene) (VPA) – **1978**

Newer or 2nd Generation AEDs

- 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**
- Lacosamide (Vimpat) (LCM) – **2009**
- Rufinamide (Banzel) (RFN) – **2009**
- Vigabatrin (Sabril) (VGB) – **2009**
- Ezogabine (Potiga) (EZG) – **2011**
- Clobazam (Onfi) (CLB) - **2011**

Handout Page 1-405

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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

Drug	F %	Binding %	Cl	t ½ (hrs)	Cause PK Interaction?
CBZ	80	75-85	100% H*	6-15	yes
PB	100	50	75% H	72-124	yes
PHT	95	90	100% H**	12-60	yes
VPA	100	75-95**	100% H	6-18	yes

Problems:
Poor water solubility
Extensive protein binding
Extensive oxidative metabolism
Multiple drug-drug interactions

CBZ= carbamazepine, PB= phenobarbital PHT= phenytoin, VPA= valproate

* autoinduction
** non-linear
Schedule IV: Phenobarbital

Pharmacokinetics of Newer AEDs

Drug	Absorption	Binding	Elimination[a,b]	T ½ (hrs)	Interactions?
GBP	≤ 60%[c]	0%	100% renal	5-9	No
PGB	90%	0%	90% renal	6	No
LTG	100%	55%	100% hepatic	18-30	No
LEV	~100%	<10%	66% renal	4-8	No
TGB	~100%	96%	100% hepatic	5-13	No
TPM	≥80%	15%	30-55% renal	20-30	Yes/No
ZNS	80-100%	40-60%	50-70% hepatic	50-80	No
OXC/MHD[d]	100%	40%	100% hepatic	5-11	Yes/No
VGB	50%	None	~70% renal	5-7	Yes
LCM	100%	< 15%	95% renal	13	No
RFN	85%	34%	85% renal	6-10	Yes
EZG	60%	80%	85% renal	7-11	No
CLB	87%	80-90%	82% renal	36-42	Yes

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

Schedule V: Pregabalin and Lacosamide
Adapted from Pellock JM

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

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

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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

Handout Page 1-419

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 arrhythmias
    - Fosphenytoin: NTE 150 mg/min, any solution
      - Repeat at ½ of dose if no results

Handout Page 1-222-223

1. Patient Case # 3

What would you communicate to the physician regarding the most appropriate dosing recommendation for phenytoin?

- A. Phenytoin can be given intramuscular (IM)
- B. The infusion rate of IV phenytoin cannot exceed 50 mg/minute
- C. IV phenytoin should be diluted prior to reaching the patient
- D. IV phenytoin can cause tissue necrosis upon extravasation

Handout Page 1-419; Answer Page 1-417-418, I-437

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

Handout Page 1-429

Types of Headaches

	Tension	Migraine with Aura	Migraine without Aura	Cluster
Epidemiology	a. Self-reported in 69% of males and 88% of females b. Most common of the primary headache disorders, with a lifetime prevalence of 30%–78% c. Often begins in the early 20s	a. Less common than migraine without aura	a. 28 million Americans i. 21 million women ii. 7 million men b. In around 50% of patients, the problem is severe and disabling. c. Often not diagnosed or treated appropriately	a. Affects about 200 individuals in 100,000 b. Occurs predominantly in patients older than 30 years c. Affects males more than females 6:1 d. Associated with cluster pattern
Clinical presentation	a. Attacks on 15 days/month or more (180 days/year) b. Dull and bandlike c. Bilateral d. No nausea/vomiting, photophobia, or phonophobia	a. At least one fully reversible aura symptom b. At least one aura symptom developing gradually over 4 minutes or two symptoms in succession c.. No aura symptom lasting more than 60 minutes d. Migraine headache follows aura within 60 minutes.	Headache has two of the following: (a) Unilateral location (b) Pulsating quality (c) Moderate or severe intensity (d) Aggravated by routine physical activity During headache, at least one of the following: (a) Nausea and/or vomiting (b) Photophobia (c) Phonophobia	a. Sudden onset, excruciating, stabbing quality b. Unilateral location with facial pain c. Restlessness d. Often, an attack occurs within 90 minutes of falling asleep. e. Can occur up to eight times within a 24-hour period f. Typically, no long-term consequences
Duration	Varies	4-72 hours	4-72 hours	1-4 hours

Handout Page 1-425-429

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

Handout Page 1-429; Answer Page 1-425-427, 437

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Treatment of Cluster Headache

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

Handout Page 1-426-427

1. 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

Handout Page 1-429; Answer Page 1-426, 437

Patient Case # 4

Which of the following triptans would be the best therapy to recommend to R.L.?

- A. Almotriptan oral
- B. Rizatriptan oral
- C. Sumatriptan subcutaneous injection
- D. Zolmitriptan oral disintegrating tablet

Handout Page 1-429; Answer Page 1-426, 437-438

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

Handout Page 1-433

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

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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
  - Cyproheptadine
  - Methysergide (only compounded)

Handout Page 1-433-434

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 /d decreases by 50 %)
  - Acupuncture

Handout Page 1-434

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

Handout Page 1-433; Answer Page 1-433-435, 438

Characteristics of Triptans (Abortive)

Drug	Route	Onset	Duration	Half-Life	Metabolism
Amerge (naratriptan)	Oral	1-3 hours	Long	6 hours	Renal, 70% CYP
Axert (almotriptan)	Oral	30-120 minutes	Short	3-4 hours	CYP and MAO
Frova (frovatriptan)	Oral	2-3 hours	Long	26 hours	Renal, 50%
Imitrex (sumatriptan)	Oral/nasal spray/SQ injection/needle-free delivery system/auto-injector	20-30 minutes/15 minutes/10-15 minutes/~ 10 minutes	Short	2.5 hours/2 hours/115 minutes	MAO
Relpax (eletriptan)	Oral	30 minutes	Short	4 Hours	CYP3A4
Treximet (sumatriptan/naproxen)	Oral	20-30 minutes	Short	2 hours	
Zomig/Zomig-ZMT –orange (zolmitriptan)	Oral/nasal spray/ODT	Oral = 45 minutes/nasal =15 minutes	Short	3 hours	CYP and MAO
Maxalt/Maxalt-MLT-Mint (rizatriptan)	Oral/ODT	30-120 minutes	Short	2-3 hours	MAO

Handout Page 1-432

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

Handout Page 1-433; Answer Page 1-432, 438

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

Handout Page 1-433; Answer Page 1-432, 438

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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

Handout Page 1-421 and 1-434

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

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

Neurology: Alzhemier Disease and Parkinson Disease

J. Mark Ruscin, Pharm.D., BCPS
SIU-Edwardsville School of Pharmacy

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

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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

Drug-induced Cognitive Impairment

- Table 1 (page 1-447)
  - Anticholinergic effects
    - Amitriptyline
    - Oxybutynin
    - Diphenhydramine
  - Benzodiazepines
  - CNS active agents

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

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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

Handout Page 1-451; Answer Page 1-466

Relevant Case Points

- Initiating treatment
- Titration of cholinesterase inhibitors
- Interruption of therapy
- Cost of treatment

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

Handout Page 1-454; Answer Page 1-466

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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

Handout Page 1-452 & 453

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

Handout Page 1-454; Answer Page 1-466

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
  - Typicals 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)

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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

Table 3 – Pages 1-459, 460

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

Handout Page 1-456; Answer Page 1-466

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

Handout Page 1-457; Answer Page 1-467

Relevant Case Points

- Titrating PD medications
- Adverse effects of PD treatments

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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

Handout Page 1-459; Answer Page 1-467

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 3months, 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

Handout Page 1-463; Answer Page 1-467

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 rasagaline
D. Initiate amantadine

Handout Page 1-463; Answer Page 1-467

Relevant Case Points

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

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?Questions?

- Feel free to email me if you have questions
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