Goals and Objectives

- Review new medications recently approved by the FDA
- Describe their clinical indications, dosages, and adverse effects
- Discuss safety and monitoring information

2011 New Drug Update
Jacqueline P. Jackson
PGY-1 Pharmacy Resident
Miami VA HealthCare System

Acute Coronary Syndrome (ACS)

Class/Indication
- Antiplatelet
- prevention of cardiovascular events for patients with ACS (combined with aspirin)

Brilinta® (ticagrelor)¹,²,³

| Dosage | Loading dose of 180 mg with maintenance dose of 90 mg twice daily
|        | Aspirin loading dose (usually 325 mg) with maintenance aspirin dose of 75-100 mg daily (maximum)
| Special Considerations | PLATO study: for every 1000 patients treated for up to one year, it prevents 11 more CV deaths, 11 more heart attacks, and at least six more stent thromboses compared to Plavix¹
|        | Faster onset but short duration of action
|        | Discontinue 5 days before surgery

PlATO: Study of Platelet Inhibition and Patient Outcomes

Brilinta® (ticagrelor)¹,²,³,⁵

- Metabolized mainly by CYP3A; avoid use with strong CYP3A4 inhibitors/inducers
- Avoid use of more than 40 mg of simvastatin or lovastatin daily
- Weak inhibitor of p-glycoprotein
- Monitor digoxin levels

Monitor Reduced thrombotic CV events

Anticoagulation

Class/Indication
- Anticoagulant
- Prevention of DVT and PE following hip or knee replacement surgery; reduce risk of stroke/systemic embolism in nonvalvular atrial fibrillation
**Xarelto® (rivaroxaban)**

**Formulation Adjustments**
- 10 mg, 15 mg, 20 mg tablets
- DVT prophylaxis:
  - 10 mg daily starting six to ten hours post-op; continued for 12 days for knee replacement
  - 10 mg daily starting six to ten hours post-op; continued for 35 days for hip replacement
  - Caution advised in CrCl 30-50 mL/min
  - CrCl <30 mL/min: avoid use
- Stroke/thromboembolism prophylaxis:
  - 20 mg daily with evening meal
  - CrCl 15-50 mL/min: 15 mg daily with evening meal
  - CrCl <15 mL/min: avoid use

**AEs**
- Bleeding (5.8%), epidural/spinal hematoma, thrombocytopenia, hypersensitivity reaction

---

**Ar Luca Neohaler® (indacaterol)**

**Class/Indication**
- Beta-2 adrenergic agonist
- Maintenance treatment of airflow obstruction in patients with COPD to include chronic bronchitis and/or emphysema

---

**Daliresp® (roflumilast)**

**Class/Indication**
- Phosphodiesterase inhibitor
- Reduce risk of COPD exacerbations in severe COPD associated with chronic bronchitis

**MOA**
- Exact mechanism unknown, selectively inhibits PDE4 leading to increased intracellular cAMP in lung cells
Daliresp® (roflumilast)5,8,9,10

**DIs**
- Concomitant use with strong CYP450 inducers is not recommended (e.g. rifampin, phenobarbital, carbamazepine, phenytoin).
- Metabolized by CYP3A4 and 1A2; use caution with these enzyme inhibitors

**Monitor** Weight, new or worsening depressive symptoms

**Special Considerations**
- Should not be used to treat acute bronchospasms
- Maximize bronchodilators before trying roflumilast

---

**Viibryd® (vilazodone)5,22**

| Formulation Dosage | - 10 mg, 20 mg, 40 mg tablets
|                   | - 10 mg daily X 7 days, then 20 mg daily X 7 days,
|                   | then 40 mg once daily with food

**AEs**
- diarrhea (28%), nausea (23%), dizziness (9%), dry mouth (8%), insomnia (6%), vomiting (5%), and decreased libido (male 5%, female 3%)

---

**Tradjenta® (linagliptin)5,11**

**Class/Indication**
- Dipeptidyl peptidase-4 (DPP-4) inhibitor
- Type 2 diabetes mellitus in adults as an adjunct to diet and exercise

**Dosage** 5 mg once daily

**AEs**
- Hypoglycemia (monotherapy 7.6%, combination therapy 22.9%), nasopharyngitis (4.3%-5.8%), pancreatitis, hypersensitivity reaction

---

**Depression**

**Class/Indication**
- Antidepressant
- treatment of major depressive disorder

**BBW**
- Increases suicidality risk in children, adolescents, and young adults with major depressive or psychiatric disorders

**CIs**
- Do not use with or within 14 days of MAOIs

**Cost** $150 for a 30 day supply
Tradjenta® (linagliptin)<sup>5,11</sup>

**Cls**
- Hypersensitivity to linagliptin

**Cost**
- $8 per tablet

---

Head Lice

**Class/Indication**
- Pediculicide
- Treatment of head lice (pediculosis capitis) infestation in patients > 4 years

---

Natroba® (spinosad)<sup>12</sup>

**Formulation**
- 0.9% topical suspension

**Dosage**
- Apply sufficient amount (max of 120 mL); may repeat application in seven days if live lice are present

**AEs**
- Application site erythema (3%), ocular erythema (2%), irritation (1%)

---

Natroba® (spinosad)<sup>12</sup>

**Cls**
- None identified

**Special Considerations**
- Continue to recommend over the counter products of permethrin or pyrethrins as first-line agents; they are typically effective and inexpensive
- Ovicidal activity, allows for single application in most cases
- Recommend spinosad in areas where resistance is problematic
- Disadvantages: requires prescription, no generic formulation, only approved for children four years and older

---

Hepatitis C

**Class/Indication**
- Protease inhibitor
- Chronic hepatitis C, genotype 1 and compensated liver disease in combination with peginterferon-alfa and ribavirin

---

Incivek® (telaprevir)<sup>5,13,14</sup>

**Formulation**
- 375 mg tablets

**Dosage**
- 750 mg three times daily (every 7-9 hours)
- With food for 12 weeks
- Plus peginterferon-alfa and ribavirin
- Discontinue if HCV RNA levels >1000 units/mL at week 4 or 12
- Avoid use in Child Pugh B or C hepatic impairment

**AEs**
- Increased uric acid levels (73%), rash (56%), fatigue (56%), pruritis (47%), nausea (39%), anemia (36%)
Incivek® (telaprevir)\textsuperscript{5,13,14}

**Dis**
- CYP3A substrate and strong inhibitor, p-glycoprotein substrate and inhibitor
- Contraindicated: alfuzosin, atorvastatin, simvastatin, cisapride, ergots, lovastatin, oral midazolam, pimozide, rifampin, sildenafil (Revatio), St. John’s wort, taludafil (Adcirca), triazolam

**Monitor**
Hgb at baseline; CBC w/ diff, Cr, LFTs, TSH, electrolytes, and uric acid at weeks 2, 4, 8, and 12

**Special Considerations**
Recommended by AASLD (combined w/ peginterferon alfa and ribavirin) as optimal therapy for HCV infection genotype 1

AASLD: American Association for the Study of Liver Diseases

---

Vicrelis® (boceprevir)\textsuperscript{5,15}

**Formulation/Dosage**
- 200 mg capsules
- 800 mg three times daily (every 7-9 hours) w/ food starting on week five of peginterferon plus ribavirin
- Cirrhosis patients: treatment is continued for 44 more weeks (48 weeks total treatment duration)
- Non-cirrhosis patients: total treatment duration is 28 - 48 weeks, depending on viral response and response history

**Dis**
- CYP3A substrate and strong inhibitor, P-gp substrate/inhibitor
- Contraindicated: alfuzosin, carbamazepine, cisapride, drospirenone, ergots, lovastatin, oral midazolam, pimozide, phenobarbital, phenytion, rifampin, sildenafil (Revatio), simvastatin, St. John’s wort, taludafil (Adcirca), triazolam

---

Human Immunodeficiency Virus (HIV)

**Class/Indication**
- Antiviral agent
- HIV (treatment naive patients)

---

Edurant® (rilpivirine)\textsuperscript{5,19}

**Dosage**
25 mg once daily w/ a meal

**Moderate intensity (\geq 2) AEs**
- Nausea, abdominal pain, vomiting, fatigue, headache, dizziness, depressive disorders, insomnia, rash, increased LFTs, increased LDL and serum cholesterol levels

---

Edurant® (rilpivirine)\textsuperscript{5,19}

**Ch**
- Concomitant administration w/ anticonvulsants: carbamazepine, oxcarbazepine, phenobarbital, phenytion; antimycobacterials: rifabutin, rifampin, rifapentine; proton pump inhibitors; more than a single dose of systemic dexamethasone; and St. John’s wort

**Cost**
$24 per tablet

---

Hypertension

**Class/Indication**
- Angiotensin Receptor Blocker (ARB)
- HTN
**Edarbi® (azilsartan)**<sup>5,16</sup>

<table>
<thead>
<tr>
<th>Formulation</th>
<th>Dosage</th>
<th>Dose adjustment</th>
</tr>
</thead>
<tbody>
<tr>
<td>- 40 mg, 80 mg tablets</td>
<td>- 80 mg once daily</td>
<td>- 40 mg once daily if on high dose diuretics</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Dis</th>
<th>AEs</th>
</tr>
</thead>
<tbody>
<tr>
<td>NSAIDs</td>
<td>Somnolence (20%-27%), dizziness (13%-22%), headache (12%-15%), suicidal thoughts</td>
</tr>
</tbody>
</table>

**Horizant® (gabapentin enacarbil)**<sup>5,17</sup>

**Indication**
Treatment of moderate to severe restless leg syndrome (RLS)

**Dosage**
- 600 mg extended release tablet once daily with food at 5 pm

**Dose adjustment**
- CrCl 30-59 mL/min: 600 mg x1 on day 1 and 3, then 600 mg daily
- CrCl <30 mL/min: do not administer

**AEs**
- Somnolence (20%-27%), dizziness (13%-22%), headache (12%-15%), suicidal thoughts

**Onfi® (clobazam)**<sup>5,20</sup>

**Class/Indication**
Benzodiazepine/adjunctive treatment of seizures associated with Lennox-Gastaut syndrome (LGS) in patients 2 years of age or older

**MOA**
Not fully understood, may bind to GABA<sub>α</sub> receptor and potentiate neurotransmission
### Onfi® (clobazam) 5,20

| AEs | Somnolence (16%-25%), fever (10%-17%) drooling (up to 14%), constipation (2%-10%), sedation (2%-9%), cough (3%-7%), urinary tract infection (2%-5%), aggression (3%-14%), insomnia (2%-7%), dysarthria (2%-5%) |
| Monitor | CNS depression, unusual mood or behavior changes, suicidality |
| Special Considerations | Doses > 5 mg/day should be administered in two divided doses safe and effective in reducing frequency of weekly drop seizures |

### Potiga® (ezogabine) 5,21

| Class/Indication | Anticonvulsant/adjunctive treatment of partial-onset seizures in patients aged 18 years and older |
| MOA | Potassium channel opener, stabilize the resting membrane potential and reduce brain excitability |

### Case Studies

- **Case 1:** 75 yo female describes to the pharmacist her home medications for reconciliation. She describes that she takes a 15 mg pill with her evening meals for “heart problems.” She has a calculated CrCl of 40ml/min
- **Case 2:** A doctor might write for this drug in a 65 yo male patient in addition to Lamictal 250 mg bid, unless the patient has BPH...
- **Case 3:** 55 yo male w/1 PMH of CAD, Hyperlipidemia and HTN who smokes 3pd/d has a poorly written order for ______ 90mg po bid and Aspirin 81mg po daily

**Answer Choices:**
- a. Onfi (clobazam)
- b. Karelto (vivaroxaban)
- c. Potiga (ezogabine)
- d. Brilinta (ticagrelor)

### True/False Test Questions

1. Horizant (gabapentin enacarbil) is an **immediate** release form of gabapentin  
   Answer: False; Horizant is an **extended release** form of gabapentin
2. Tradjenta (linagliptin) does not require renal dose adjustment  
   Answer: True
3. Onfi (clobazam) is an oral benzodiazepine use to treat patients with Lennox-Gastaut syndrome  
   Answer: True

### References

8. The Lancet 2009;393:150.  
**Clostridium difficile** Infection: A Review of Pharmacologic and Non-Pharmacologic Treatment Options

Yesenia Camero, Pharm.D.
PGY-1 Pharmacy Practice Resident
Baptist Hospital of Miami

**Objectives**

- Compare and contrast available pharmacotherapeutic options for *Clostridium difficile* infection (CDI)
- Discuss the role of fidaxomicin in the treatment of CDI
- Formulate the most suitable treatment regimen based on patient specific parameters
- Describe various infection control strategies to prevent CDI

**Outline**

- Definition
- Epidemiology
- Etiology
- Risk Factors
- Pathophysiology
- Clinical Presentation
- Diagnosis
- Treatment
- Prevention
- Role of the Pharmacist

**Definition**

Presence of diarrhea (3 or more unformed stools in < 24 hours) and
Positive stool test result for *C. difficile* toxins or
Evidence of pseudomembranous colitis

**Epidemiology**

- Twenty to 30% of antibiotic-associated diarrhea
- Leading cause of infectious diarrhea in healthcare settings
- Recurrent CDI in ~20% of patients
- Increased incidence and virulence since 2001
  - Hypervirulent NAP1/BI/027 epidemic strain associated with increased fluoroquinolone use

**Etiology**

- *Clostridium difficile*
  - Anaerobic gram-positive rod
  - Spore-forming
    - Vegetative vs spore
  - Toxin-producing
    - Toxin A
    - Toxin B
    - Binary toxin?
**Risk Factors**

- Advanced age
- Exposure to antimicrobials
- Length of hospitalization
- Severe or multiple underlying diseases
- Cancer chemotherapy
- Gastrointestinal manipulation
- Acid-suppressing agents
- Low serum IgG anti-toxin A concentrations

**Pathophysiology**

- Disruption of normal bacterial flora of colon
- C. difficile exposure and colonization
- Release of toxins
- Mucosal damage and inflammation
- Diarrhea

**Clinical Presentation**

- Asymptomatic
- Mild to moderate diarrhea
- Fever, cramping, abdominal discomfort
- Leukocytosis and occult colonic bleeding
- Pseudomembranous colitis
- Fulminant colitis
- Toxic megacolon
- Hypotension, sepsis, death

**Classification of CDI**

<table>
<thead>
<tr>
<th>Severity Level</th>
<th>Supportive data</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mild to Moderate</td>
<td>WBC &lt; 15,000 cells/mL SCr &lt; 1.5x baseline level</td>
</tr>
<tr>
<td>Severe</td>
<td>WBC &gt; 15,000 cells/mL SCr &gt; 1.5x baseline level</td>
</tr>
<tr>
<td>Severe Complicated</td>
<td>Hypotension or shock ileus, megacolon</td>
</tr>
</tbody>
</table>

---


MMWR 2011; 60(34):1171.


Diagnosis

- Toxin testing
  - Cell cytotoxin assay
  - Enzyme immunoassay (EIA)
- Organism identification
  - Stool culture
  - EIA for detection of glutamate dehydrogenase
- Visualization of colon
  - Sigmoidoscopy
  - Colonoscopy

Treatment

General Principles

- Discontinue inciting antibiotic when possible
- Implement infection control strategies
- Avoid antimotility agents
- Initiate supportive care
- Consider surgical intervention in severe cases
- Administer antibiotics for 10 – 14 days

Guideline Recommendations

<table>
<thead>
<tr>
<th>Episode</th>
<th>Severity</th>
<th>Recommendation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Initial Episode</td>
<td>Mild to Moderate</td>
<td>Metronidazole 500 mg PO q8h</td>
</tr>
<tr>
<td></td>
<td>Severe</td>
<td>Vancomycin 125 mg PO q6h</td>
</tr>
<tr>
<td></td>
<td>Severe Complicated</td>
<td>Vancomycin 500 mg PO/NG q6h + Metronidazole 500 mg IV q8h ± Vancomycin rectal instillation</td>
</tr>
<tr>
<td>Second Episode (1st recurrence)</td>
<td>Same as for initial episode</td>
<td></td>
</tr>
<tr>
<td>Third Episode (2nd recurrence)</td>
<td>Vancomycin tapered/pulsed regimen 125 mg PO q6h for 10 – 14 days 125 mg PO q12h for 7 days 125 mg PO daily for 7 days 125 mg PO every 3 days for 2 – 8 weeks</td>
<td></td>
</tr>
</tbody>
</table>

Standard Treatment Comparison

<table>
<thead>
<tr>
<th></th>
<th>Vancomycin</th>
<th>Metronidazole</th>
</tr>
</thead>
<tbody>
<tr>
<td>Route</td>
<td>PO</td>
<td>PO and IV</td>
</tr>
<tr>
<td>Cost</td>
<td>$$$</td>
<td>$</td>
</tr>
<tr>
<td>Fecal concentration</td>
<td>+++</td>
<td>+</td>
</tr>
<tr>
<td>Side effects</td>
<td>Nausea/vomiting, Bitter taste, Fever, chills</td>
<td>Nausea, Metallic taste, Disulfiram reaction w/ alcohol, Discoloration of urine, Neurotoxicity (long-term use)</td>
</tr>
</tbody>
</table>

Alternative Therapies

- Antimicrobials
  - Fidaxomicin (Dificid®)
  - Rifaximin (Xifaxan®)
  - Nitazoxanide (Alinia®)
  - Tigecycline (Tygacil®)
- Probiotics
- Anion-binding resins
  - Cholestyramine
  - Colestipol
- Intravenous immunoglobulin

Fidaxomicin (Dificid®)

- Classification
  - Narrow spectrum macrolide
- FDA approved indication
  - Treatment of CDI in patients ≥ 18 years old
  - Dose: 200 mg PO BID for 10 Days
- Mechanism of action
  - Inhibits RNA polymerase resulting in inhibition of protein synthesis and cell death
  - Bactericidal against C. difficile
- Pharmacokinetics
  - Minimal systemic absorption
  - Intestinal hydrolysis to active metabolite OP-1118
Drug interactions
- P-glycoprotein inhibitors may increase fidaxomicin serum concentrations → no dosage adjustment required

Adverse effects
- Nausea (11%)
- Vomiting (7%)
- Abdominal pain (6%)
- Gastrointestinal hemorrhage (4%)
- Anemia (2%)
- Neutropenia (2%)

Clinical Trial Background

- **Objective**: To compare the efficacy and safety of fidaxomicin with vancomycin in the treatment of CDI
- **Design**: Prospective, multicenter, randomized, double-blind, non-inferiority, phase 3 trials
- **Intervention**: Fidaxomicin 200 mg PO twice daily for 10 days versus Vancomycin 125 mg PO four times daily for 10 days
- **Participants**: Adults ≥ 16 yo, 37% with severe CDI, 84% with first episode

Outcomes
- **Primary**: Clinical cure
- **Secondary**: Recurrence of infection, Global cure, Safety

Study conclusions
- Similar efficacy in clinical cure
- Lower recurrence rate
- Higher global cure rate
- Similar safety profile

Key points
- Majority of patients had mild-to-moderate CDI
- No comparison with metronidazole
- Recurrence rate was a secondary endpoint → unable to draw definite conclusions

Economic Considerations
- **Cost of therapy**
  - Fidaxomicin (10-day course): $2800
  - Vancomycin (10-day course): ~ $1300
  - Reconstituted injectable solution: < $60

- **Healthcare costs associated with CDI**
  - Primary episode: $2,871 - $4,846
  - Recurrent episode: $13,655 - $18,067

Does the high cost of recurrent CDI justify the use of fidaxomicin?

Place in therapy
- Potential cases for use
  - High-risk patients
  - Patients with recurrent episodes
Rifaximin (Xifaxan®)
- Analog of rifampin with minimal systemic absorption
- Off-label for CDI
- May be effective as a “chaser” following treatment with vancomycin for recurrent infection
- Concerns for resistance
- Dose: 400 – 800 mg/day
- Cost of therapy: ~$250 - $300

Nitazoxanide (Alinia®)
- Thiazolide compound with antibacterial, antiviral and antiparasitic activity
- Off-label for CDI
- Similar clinical efficacy compared to metronidazole and vancomycin
- Potential role as salvage therapy for refractory or recurrent CDI
- Dose: 500 mg PO BID x 10 days
- Cost of therapy: ~$450

Tigecycline (Tygacil®)
- Glycylcyline antibiotic
- Off-label for CDI
- Effective for severe, refractory CDI in a small case series of four patients with complicated infection
- Dose: 100 mg IV x 1, then 50 mg IV q12h
- Cost of therapy: ~$1500

Nitazoxanide (Alinia®)
- Off-label for CDI
- Similar clinical efficacy compared to metronidazole and vancomycin
- Potential role as salvage therapy for refractory or recurrent CDI
- Dose: 500 mg PO BID x 10 days
- Cost of therapy: ~$450

Probiotics
- Live, non-pathogenic bacteria
- Therapeutic mechanisms
  - Alteration of intestinal flora
  - Intestinal barrier protection
  - Immunomodulation
- Inconsistent evidence for efficacy in CDI
- *Saccharomyces boulardii*: effective for recurrent CDI
- Safety concerns
  - Bacteremia: *Lactobacillus rhamnosus*
  - Fungemia: *Saccharomyces boulardii*

Probiotics
- Treatment of Recurrent CDI

<table>
<thead>
<tr>
<th>Probiotic</th>
<th>Product</th>
<th>Regimen</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td><em>Saccharomyces boulardii</em></td>
<td>Florastar®</td>
<td>500 mg BID x 28 days</td>
<td>With vancomycin 500 mg PO QID x 10 days</td>
</tr>
<tr>
<td><em>Lactobacillus rhamnosus</em></td>
<td>Culturelle®</td>
<td>1-2 caps daily x 7-10 days</td>
<td></td>
</tr>
</tbody>
</table>

- Prevention of CDI

<table>
<thead>
<tr>
<th>Probiotic</th>
<th>Product</th>
<th>Regimen</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td><em>Lactobacillus acidophilus</em></td>
<td>Caps (from UK)</td>
<td>1 cap daily x 20 days</td>
<td>Initiate within 36h of antibiotic</td>
</tr>
<tr>
<td><em>Lactobacillus casei</em></td>
<td>Adimel® yogurt drink</td>
<td>105g BID 30 min before meals or 2-3h after meals</td>
<td>Initiate within 48h of antibiotic, continue for 1 wk after completion</td>
</tr>
</tbody>
</table>

Emerging Therapies
- Tolevamer
- Ramoplanin
- Fecal Bacteriotherapy
- Monoclonal antibodies
- *C. difficile* vaccine
Prevention

- Hand Hygiene

http://talktowarren.files.wordpress.com/2010/03/hand_washing.jpg; ossone.com

Prevention

- Contact precautions
- Isolation of infected patients
- Environmental cleaning and disinfection
- Antimicrobial stewardship

Role of the Pharmacist

- Educate patients and healthcare workers
- Recommend appropriate antibiotic treatment regimens for CDI
- Counsel patients about drug therapy
- Streamline antimicrobial therapy through antimicrobial stewardship programs

Patient Case

- MD is a 52 yo female who was receiving levofloxacin for treatment of an intra-abdominal infection. Following completion of therapy she began to complain of abdominal pain and diarrhea. Her home medications include lisinopril 10 mg PO daily, omeprazole 20 mg PO daily, and simvastatin 20 mg PO HS. Her current vitals and lab values are: T: 101°F, BP: 110/72 mmHg, WBC: 11,500 cells/mm³, SCr: 0.9 mg/dL, C. diff toxin +

- What risk factors does MD have for CDI?
  - Omeprazole use, recent antibiotic use
  - Metronidazole 500 mg PO q8hrs

- How long would you treat MD?
  - 10 – 14 days

Frequently Asked Questions

- When to seek medical attention?
  - Recent antimicrobial use accompanied by severe abdominal pain, multiple episodes of watery diarrhea per day, blood or pus in stool, signs of dehydration

- How can I prevent spreading C. difficile to family or household members?
  - Wash hands with soap and water after using the bathroom and before eating
  - Dry hands with paper towels instead of cloth towels
  - Disinfect bathroom surfaces using bleach (1:10 dilution)
  - Use detergent and bleach to wash clothes

- What else can I do to help my symptoms?
  - Drink lots of fluids
  - Eat starchy foods as tolerated
  - Avoid lactose-containing products

True or False?

- Using soap and water has proven to be more effective than alcohol-based hand rubs in reducing the risk of transmitting C. difficile infection. True

- The clinical trials for fidaxomicin showed superiority for fidaxomicin when compared to vancomycin for the primary endpoint of clinical cure rate. False

- The efficacy of probiotics has been proven in controlled clinical trials. False
Atrial Fibrillation and Prevention of Thrombotic Complications: Therapeutic Update

Andrea C. Flores Pharm.D
Pharmacy Resident at the Miami VA Healthcare System

Objectives

- Review the epidemiology, pathophysiology and complications of Atrial Fibrillation (AF)
- Identify anticoagulation therapy in AF
- Explain new anticoagulant agents
  - Outline current literature supporting the role of new anticoagulant agents in the prevention and treatment of thromboembolic disorders
  - Differentiate new anticoagulant agents with respect to their pharmacokinetics, pharmacodynamics, and recommended dosing strategies

Epidemiology of Atrial Fibrillation (AF)

- Most common arrhythmia in the U.S.
- Affects men more than women
- Incidence and prevalence increase with age
- Lifetime risk of AF in patients >40 yr ~25%

Stroke in AF

- Stroke is the most common and devastating complication of AF
- Incidence of all-cause stroke in patients with AF is 5%
- AF is an independent risk factor for stroke
- Approximately 15% of all strokes in the U.S. are caused by AF
- Stroke risk persists even in asymptomatic AF

Pathophysiology of Stroke in AF: Role of Virchow’s Triad

- Abnormal blood stasis
  - Blood pools in the left atria
  - Due to loss of organized atrial contraction and atrial dilation
- Hypercoagulable state
  - Increase concentration of prothrombotic factors
- Endothelial/Endocardial injury
  - Structural changes occur in the atria

Stroke Risk Stratification in AF

CHADS2 score

- Congestive heart failure = 1 point
- Hypertension = 1 point
- Age ≥75 years = 1 point
- Diabetes = 1 point
- Stroke/TIA = 2 points
CHADS² Score and Risk

Adjusted Stroke Rate per 100 patient years

<table>
<thead>
<tr>
<th>Score</th>
<th>Number of patients</th>
<th>Risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>120</td>
<td>1.9(1.2 – 3)</td>
</tr>
<tr>
<td>1</td>
<td>463</td>
<td>2.8(2 – 3.8)</td>
</tr>
<tr>
<td>2</td>
<td>523</td>
<td>4.0(3.1 – 5.1)</td>
</tr>
<tr>
<td>3</td>
<td>337</td>
<td>5.9(4.6 – 7.3)</td>
</tr>
<tr>
<td>4</td>
<td>220</td>
<td>8.5(6.3 – 11.1)</td>
</tr>
<tr>
<td>5</td>
<td>65</td>
<td>12.5(8.2 – 17.5)</td>
</tr>
<tr>
<td>6</td>
<td>5</td>
<td>18.2(10.5 – 27.4)</td>
</tr>
</tbody>
</table>

Oral Anticoagulation

Warfarin

- Main agent for prevention and treatment of thromboembolic disease > 50 years
- Challenges still exist in determining optimal and safest dose
- Associated with adverse events
  - Bleeding

Ideal Anticoagulant

- Fast onset of action, allows post-procedure use
- Fast resolution of actions, allows pre-procedure use
- No routine blood monitoring
- No drug interactions
- No interactions with diet
- Fixed doses
- Predictable dose response
- Safe in pregnancy
- Immediate reversibility

New and Emergent Oral Anticoagulants

<table>
<thead>
<tr>
<th>Brand Name</th>
<th>Pradaxa®</th>
<th>Xarelto®</th>
<th>Eliquis®</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mechanism of action</td>
<td>Direct IIa inhibitor</td>
<td>Direct Xa inhibitor</td>
<td>Direct Xa inhibitor</td>
</tr>
<tr>
<td>Approval Status</td>
<td>• 2008: approved in Eur/Can for VTE px in ortho surgery</td>
<td>• 2008: approved in Eur/Can for VTE px in ortho surgery</td>
<td>• 2008: approved in Eur/Can for VTE px in ortho surgery</td>
</tr>
<tr>
<td></td>
<td>• 10/2010: approved by FDA for stroke prevention in AF</td>
<td>• 7/2011: approved by FDA for VTE px in ortho surgery</td>
<td>• 11/2010: Submitted to FDA for stroke prevention in AF (pending approval)</td>
</tr>
</tbody>
</table>

RE-LY Trial

- Dabigatran Etexilate vs. Warfarin (INR 2-3) in AF
- Randomized open label
  - N = 18,113 patients (mean CHADS: 2.1)
  - Non-inferiority design
  - 64% time in range to warfarin
- Drug and dose: Dabigatran 150mg and 110 mg BID
RE-LY Trial

- Primary Outcome: Stroke or systemic embolism
  - Warfarin vs. Dabigatran 150mg
    - 1.69 vs. 1.11 p < 0.001
  - Warfarin vs. Dabigatran 110mg
    - 1.69 vs. 1.53 p < 0.001
- Dabigatran 150 mg is NON-INFERIOR and possibly SUPERIOR to warfarin
- Dabigatran 110 mg is NON-INFERIOR to warfarin

ROCKET- AF Trial

- Rivaroxaban vs. Warfarin (INR 2-3) in AF
- Randomized double blind
  - N = 14,171 patients (mean CHADS: 3.5)
  - Non-inferiority design
  - 58% time in range for warfarin
- Drug and dose: Rivaroxaban 20 mg daily
  - If CrCl 30-49 ml/min: 15mg daily

ARISTOTLE Trial

- Apixaban vs. warfarin (INR 2-3)
- Randomized double blind, placebo controlled
  - N = 18,201 (mean CHADS: 2.1)
  - Non-inferiority design
  - 66% time in range to warfarin
- Drug and dose: Apixaban 5 mg BID
  - If 2 of: age >80, wt <60 kg or SrCr>1.5: 2.5 mg BID

ROCKET- AF Trial

- Primary endpoint: Stroke of systemic embolism
  - Warfarin vs. rivaroxaban:
    - 2.42 vs. 2.12 p = 0.12
- Major bleeding:
  - Warfarin vs. rivaroxaban:
    - 3.45 vs. 3.6 p = 0.58
- Rivaroxaban is non-inferior to warfarin

ARISTOTLE Trial

- Primary efficacy endpoint: Stroke or systemic embolism
  - Warfarin vs. apixaban
    - 1.60 vs. 1.27 p < 0.001 for noninferiority and P = 0.01 for superiority
- Major bleeding:
  - Warfarin vs. Apixaban
    - 3.09 vs. 2.13 p < 0.001
- Apixaban was possibly superior to warfarin in preventing stroke or systemic embolism

RE-LY Trial

- Major bleeding (%/year):
  - Warfarin vs. Dabigatran 150mg
    - 3.36 vs. 3.11 p = 0.31
- Intracranial bleeding (%/year)
  - Warfarin vs. Dabigatran 150mg
    - 0.74 vs. 0.30 p < 0.001
AVERROES Trial

- Apixaban vs. aspirin (81-324 mg)
- Randomized, double blind, placebo controlled
  - N = 5,599 (CHADS ≥1)
    - Failed or unsuitable for warfarin therapy
  - Superiority design
- Drug and dose: Apixaban 5 mg BID
  - If 2 of: age >80, wt <60 kg or SrCr>1.5:
    - 2.5 mg BID

Primary efficacy endpoint: stroke of systemic embolism
Aspirin vs. Apixaban (%/year): 3.7 vs. 1.6 p < 0.001

Major bleeding
Aspirin vs. Apixaban (%/year): 1.2 vs. 1.4 p = 0.57

Apixaban reduced the risk of stroke or systemic embolism

Warfarin Comparison Trials in AF

<table>
<thead>
<tr>
<th>Trial</th>
<th>RE-LY</th>
<th>ROCKET-AF</th>
<th>ARISTOTLE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Drug</td>
<td>Dabigatran 150 mg BID</td>
<td>Rivaroxaban 20 mg daily</td>
<td>Apixaban 5 mg BID</td>
</tr>
<tr>
<td>Efficacy vs Warfarin</td>
<td>1.69 vs. 1.11 p &lt; 0.001</td>
<td>2.42 vs. 2.12 p = 0.12</td>
<td>1.60 vs. 1.27 p &lt; 0.001</td>
</tr>
<tr>
<td>Major Bleeding %</td>
<td>3.36 vs. 3.11 p = 0.31</td>
<td>3.45 vs. 3.6 p = 0.58</td>
<td>3.09 vs. 2.13 p &lt; 0.001</td>
</tr>
<tr>
<td>ICH %</td>
<td>0.74 vs. 0.30 p &lt; 0.001</td>
<td>0.74 vs. 0.49 p = 0.019</td>
<td>0.47 vs. 0.24 p &lt; 0.001</td>
</tr>
<tr>
<td>Summary</td>
<td>Possibly superior efficacy</td>
<td>Non-inferior in efficacy and safety measures</td>
<td>Possibly superior efficacy</td>
</tr>
<tr>
<td></td>
<td>Similar bleeding</td>
<td>Less ICH</td>
<td>Less major and ICH</td>
</tr>
<tr>
<td></td>
<td>Lower mortality</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

2011 ACCF/AHA/HRS Guidelines

Dabigatran given a Class I (LOE B) recommendation

Dabigatran is useful as an alternative to warfarin for prevention of stroke and systemic thromboembolism in patients with paroxysmal to permanent AF and risk factors for stroke or systemic embolization who do not have the following:

- Prosthetic heart valve or hemodynamically significant valve disease
- CrCl <15 mL/min
- Advanced liver disease

2011 ACCF/AHA/HRS Guidelines

Patients already taking warfarin with excellent INR control may have little to gain by switching to dabigatran because of dabigatran’s:
- Twice-daily dosing
- Greater risk of nonhemorrhagic side effects

Selection of patients with AF and ≥1 additional risk factor for stroke who could benefit from treatment with dabigatran as opposed to warfarin should consider individual factors, including:
- Ability to comply with twice-daily dosing
- Availability of an anticoagulation management program to sustain routine monitoring of INR
- Patient preferences
- Cost
- Other factors
**Pharmacology of Novel Oral Anticoagulants**

<table>
<thead>
<tr>
<th></th>
<th>Dabigatran (Pradaxa®)</th>
<th>Rivaroxaban (Xarelto®)</th>
<th>Apixaban (Eliquis®)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Target</strong></td>
<td>Factor IIa (reversibly binds to site)</td>
<td>Factor Xa (reversibly binds to site)</td>
<td>Factor Xa (reversibly binds to site)</td>
</tr>
<tr>
<td><strong>Dosage Form (mg)</strong></td>
<td>Capsule (75, 150)</td>
<td>Tablet (10, 15, 20)</td>
<td>Tablet</td>
</tr>
<tr>
<td><strong>Bioavailability</strong></td>
<td>6%</td>
<td>60-80%</td>
<td>50-85%</td>
</tr>
<tr>
<td><strong>Time to peak</strong></td>
<td>1-2 hours</td>
<td>2-4 hours</td>
<td>1-3 hours</td>
</tr>
<tr>
<td><strong>Metabolism</strong></td>
<td>Conjugation; NO CYP involvement</td>
<td>Oxidation (via CYP3A4 &amp; CYP2J2) + hydrolysis</td>
<td>Oxidation (via CYP3A4) + conjugation</td>
</tr>
<tr>
<td><strong>Renal Excretion</strong></td>
<td>80%</td>
<td>66%</td>
<td>25%</td>
</tr>
<tr>
<td><strong>Half-Life</strong></td>
<td>14-17 hours</td>
<td>9-13 hours</td>
<td>9-14 hours</td>
</tr>
<tr>
<td><strong>Dosing frequency, major Trials</strong></td>
<td>BID</td>
<td>Daily</td>
<td>BID</td>
</tr>
</tbody>
</table>

**New Anticoagulants Renal Dosing**

- Dabigatran
  - CrCl > 30 ml/min: 150 mg po BID
  - CrCl 15-29 ml/min: 75mg po BID
  - CrCl < 15 ml/min: not recommended

- Rivaroxaban
  - CrCl ≥ 30 ml/min: 20 mg po daily
  - CrCl 15-29 ml/min: 15 mg po daily
  - CrCl < 30 ml/min: Excluded from ROCKET AF

- Apixaban
  - 5 mg po BID
  - 2.5 mg po BID for patients ≥ 80 years old, wt ≤ 60kg or SrCr ≥ 1.5 mg/dl in ARISTOTLE (CrCl <25 ml/min: excluded)

**Potential Drug Interactions New Anticoagulants**

<table>
<thead>
<tr>
<th>Interaction</th>
<th>Dabigatran</th>
<th>Rivaroxaban</th>
<th>Apixaban</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anticoagulant and antiplatelet agents</td>
<td>Increased bleeding</td>
<td>Increased bleeding</td>
<td>Increased bleeding</td>
</tr>
<tr>
<td>H2 antagonist and PPIs</td>
<td>Minimal interaction</td>
<td>No interaction</td>
<td>Likely no interaction</td>
</tr>
<tr>
<td>CYP 450 enzyme metabolism</td>
<td>No</td>
<td>Yes (3A4)</td>
<td>Yes (3A4)</td>
</tr>
<tr>
<td>P-Glycoprotein substrate</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
</tbody>
</table>

**CYP 3A4 Drug Interactions**

- **Inducers:**
  - Carbamazepine, phenytoin, rifampin, St John’s Wort
- **Inhibitors:**
  - Itraconazole, ketoconazole, ritonavir

**P-glycoprotein Drug Interactions:**

- **Inducers:**
  - St John’s Wort, phenytoin, rifampin
- **Inhibitors:**
  - Itraconazole, ketoconazole, dronedarone

**Potential Advantages of New Oral Anticoagulants**

- Oral administration
- Rapid onset of action
- Predictable effect with fixed or weight-based dosing
- Less food/drug interactions
- Short half-life
- More cost effective
- Possibly superior efficacy
- Possibly superior safety

**Potential Disadvantages of New Oral Anticoagulants**

- Renal dose adjustment
- P-glycoprotein drug interactions
- Lack of reversibility
- Less provider face to face encounters
- Twice daily dosing vs. daily dosing with warfarin therapy
**Other factor Xa Inhibitors in Clinical Trials**

- Betrixaban
  - Oral, once daily dosing
- Edoxaban
  - Oral, once daily dosing
- Idraparinux
  - Subcutaneous injection, weekly
- Darexaban
  - Oral, once or twice daily

**Questions (True/False)**

**AF is an independent risk factor for stroke**

**Patient Case**

AC is a 66 yo WM with AF and a CHADS score of 3. His baseline SrCr is 1.3, CrCl 54 ml/min. The patient has been on warfarin therapy with a history of subtherapeutic INR despite compliance to medication therapy (patient can not stop eating greens). AC is interested in starting the new medication for his heart condition that does not require monitoring.

What parameters do you need to keep in mind when recommending dabigatran to a patient?

A) Ability to comply with twice daily dosing
B) Patient preferences
C) Renal Function
D) Cost
E) All of the above

**Conclusions**

Dabigatran is a currently available alternative to warfarin for stroke prevention in AF and has been shown to be cost effective for the highest risk stroke patients (CHADS ≥3) unless there is excellent INR control

**Questions (True/False)**

Dabigatran FDA – labeled indication includes postoperative deep vein thrombosis prophylaxis
Conclusions

Rivaroxaban has been shown to be non-inferior to warfarin for stroke prevention in AF with comparable rates of major bleeding (recently approved by FDA)

Conclusions

Apixaban has shown superiority to aspirin and warfarin for preventing stroke in AF, with a lower rate of bleeding and reduction in mortality compared to warfarin

References

- Wann LS et al. Heart Rhythm. 2011; 8:e1-e8
- Gage BF et al. JAMA. 2001;285:2864-70
Effect of β-Blockers in Treatment of Chronic Obstructive Pulmonary Disease

Wei Li Pharm.D.
PGY-1 Pharmacy Resident
Palmetto General Hospital
January 2012

Objectives
- Review β-adrenergic blockers
- Discuss the risks and benefits of β-blocker usage in COPD patients
- Discuss new studies that suggest addition of β-blockers can be beneficial in patients with COPD
- Discuss pharmacist’s role

Conundrum
Should patients with a diagnosis of chronic obstructive pulmonary disease (COPD), which is a relative contraindication to β-blocker therapy, receive a β-blocker when a strong indication exists?
- Risks vs. Benefits
- Review literature available

COPD
- Fourth leading cause of death worldwide
- Characterized by airflow limitation that is not fully reversible and usually progressive
- Diagnosis: Post-bronchodilator FEV1/FVC < 0.70 confirms the presence of airflow limitation in:
- Consider COPD and perform spirometry if an individual is older than 40 years and:
  - Dyspnea
  - Chronic cough
  - Chronic sputum production
  - History of exposure to risk factors

Management of COPD

<table>
<thead>
<tr>
<th>Stage</th>
<th>Characteristics</th>
<th>Recommended Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stage I: Mild</td>
<td>FEV1 ≥ 80% predicted</td>
<td>Regimen A: Reduction of risk factors; influenza vaccination + SABA as needed</td>
</tr>
<tr>
<td>Stage II: Moderate</td>
<td>50% &lt; FEV1 &lt; 80% predicted</td>
<td>Regimen B = Regimen A + Regular treatment with one or more long-acting bronchodilators</td>
</tr>
<tr>
<td>Stage III: Severe</td>
<td>30% &lt; FEV1 &lt; 50% predicted</td>
<td>Regimen C = Regimen B + ICS if repeated exacerbations and rehabilitation</td>
</tr>
<tr>
<td>Stage IV: Very severe</td>
<td>FEV1 &lt; 30% predicted</td>
<td>Regimen D = Regimen C + Long-term oxygen therapy and consider surgical procedures</td>
</tr>
</tbody>
</table>

β-blockers
- Block the action of endogenous catecholamines on:
  - β1-adrenergic receptors: Heart and in the kidneys.
  - β2-adrenergic receptors: Mainly in the lungs, gastrointestinal tract liver, uterus, vascular smooth muscle, and skeletal muscle.
  - β3-adrenergic receptors: are located in fat cells
- Cardiac Effects
  - Decrease contractility = (negative inotropy)
  - Decrease relaxation rate = (negative lusitropy)
  - Decrease heart rate = (negative chronotropy)
  - Decrease conduction velocity = (negative dromotropy)
**β-blockers**

- **Vascular Effects**
  - Smooth muscle contraction = (mild vasoconstriction)
- **Kidneys**
  - Inhibit renin by the kidneys
  - Tone down the Renin Angiotensin Aldosterone System (RAAS)
- **Nervous system**
  - Blockade of adrenaline and noradrenaline
  - Decrease anxiety, tremor and migraines

**Therapeutic use of β-blockers**

- Hypertension
- Angina
- Myocardial infarction
- Heart failure
- Significant reduces mortality and hospitalizations in
  - Post MI
  - HF with LVEF dysfunction

**Types of β-blockers**

- Non-Cardioselective
  - propranolol
  - nadolol
  - timolol
  - pindolol
- Mixed beta and alpha-1 activity
  - carvedilol
  - labetalol
- Cardioselective
  - acebutolol
  - atenolol
  - bisoprolol
  - esmolol
  - metoprolol
  - nebivolol

**Risks of β-blockers in COPD**

- Historically β-blockers have been avoided in asthma and COPD
- β blockers → potential bronchoconstriction
  - Reduction in forced expiratory volume in one second (FEV)
  - Increased airway hyperresponsiveness
  - Inhibition of bronchodilator response to β agonists
  - Exacerbation of COPD and complications

**GLOBAL INITIATIVE FOR CHRONIC OBSTRUCTIVE LUNG DISEASE (GOLD)**

- “Cardiovascular disease (including ischemic heart disease, heart failure, atrial fibrillation, and hypertension) is a major comorbidity in COPD and probably both the most frequent and most important disease coexisting with COPD”
- “Cardioselective β-blockers are NOT contraindicated in COPD”


**What does ACC/AHA say?**

- 2009 ACC/AHA Guidelines for the Management of Patients With ST-Elevation Myocardial Infarction Suggest that β-blocker therapy after acute MI IS APPROPRIATE for many patients with COPD or other relative contraindications

- 2009 ACC/AHA Focused Update Guidelines for the Diagnosis and Management of Heart Failure in Adults
  - “MOST patients with chronic obstructive pulmonary disease do not have a bronchospastic component to their illness and remain REASONABLE candidates for β-blockade”

J Am Coll Cardiol. 2009; 54:2205-2241
Warnings and Precautions:
- Chronic obstructive pulmonary disease ...
  - "metoprolol should be used with caution, in ...COPD with a bronchoespastic component..."
  - "Use only if the potential benefit outweighs the potential risk"

Package Inserts

Study Design:
- **Objective**: To examine the effect of β blockers in all-cause death and COPD exacerbation associated with the use of β-blockers in COPD patients
- **Design**: Retrospective cohort study using Cox proportional (CP) hazards regression analyses
- **Setting**: 23 general practices in Netherlands
- **Population**:
  - Total 2230 patients, β-blocker use N =665, non β-blocker use N=1565
  - Subjects > 45 yr with an incident or prevalent diagnosis of COPD between 1996 – 2006
  - Study length: ~7.2y

Results:
- All cause mortality adjusted HR in patients on β-blocker was 0.68 (95% CI, 0.56-0.83)
- Adjusted HR for COPD exacerbation in patients on β-blocker was 0.68 (95% CI, 0.46-1.02)

CRITIQUE:
- Retrospective and observational study
- Misclassification and misdiagnosis of patients
- Cannot completely correct for confounders
  - Severity of COPD illness
  - Benefits of concomitant drug use (ACE –I, ARB’s and statins)
Study Design

- **Objective:** To examine the effect of β-blockers in the management of COPD assessing effect on mortality, hospital admissions, and exacerbations of COPD
- **Design:** Retrospective cohort study
- **Setting:** Tayside, Scotland (2001–2010)
- **Population:** 5977 patients aged >50 years with a diagnosis of COPD

Results

- B-blocker use was associated with an overall 22% reduction in mortality HR = 0.78 (95% CI of 0.67 to 0.92)
- 2005 patients died equating to an annual mortality of 34%.

Critique

- Author’s conclusions: β-blockers may reduce mortality and COPD exacerbations when added to established inhaled stepwise therapy for COPD
- However, it’s retrospective study. Results should be interpreted cautiously
- Many confounding variables (severity of CV disease COPD among groups)
- Prospective randomized double blinded controlled trial needed to confirm these findings

Role of Pharmacist

- It is necessary:
  - To proper understand management of COPD
  - Evaluate literature in this controversial topic
  - No definite clinical trial exists to safely recommend β-blockers for all COPD patients.
  - Monitor initiation and up-titration of dose of β-blockers closely
  - Reduce dose/hold β-blocker if bronchospam or complication occurs

Keep in Mind

- Smoking cessation
- Influenza vaccine annually
- Pneumococcal vaccine
- Not recommended
  - Antibiotics, other than for treating infectious exacerbations of COPD
  - Mucolytic agents
  - Antioxidant agents such as N-acetylcysteine
  - Regular use of antitussives
**Patient Case**

- B.P. is a 55 yo male who comes to the ER with CC of SOB due to COPD exacerbation and constant productive cough. This is the 3rd time in this year B.P is admitted to the hospital due to SOB.
- PMH: CAD with a MI 8 years ago with stent x 1, HTN, COPD (1 pack of cigarettes x 50 years, CHF.
- Vitals: BP 145/85, HR: 88 bpm, RR: 24, Temp: 98.4F.
- Allergic to PCN.
- Home Rx: crestor 20mg daily, lisinopril 40mg daily, plavix 75mg daily, aspirin 81mg, carvedilol 6.25 mg q12h, advair diskus 250/50 mg 1 puff BID, furosemide 1 puff daily and albuterol MDI q4h PRN for SOB.
- Last spirometry test shows: FEV1 = 45% and FEV1/FVC = 55%. In the hospital he was started on oxygen therapy, prednisolone 40mg IV q8h, furosemide 20mg IV q12h, Diureeb q6h ATC as well as continuing his home medications in the hospital.
- CXR rules out pneumonia. Echocardiogram shows mild mitral regurgitation with LVEF of ~50%.

Besides anticoagulation therapy the physician asks for your recommendation on the β-blocker

**Summary**

- β-Blocker therapy for cardiovascular indications is underutilized in patients with COPD.
- Mortality benefits are seen in patients with mild to moderate COPD who receive cardioselective β-blockers.
- In conclusion patients with MILD TO MODERATE COPD should receive cardioselective β-blocker therapy when a strong indication exists.
- A reliable prospective randomized controlled trial needed to answer this conundrum.

**True or False Questions**

- β-blockers are indeed contraindicated in asthmatic and COPD patients.
- β-blockers may actually be beneficial for those with mild and moderate COPD and CV disease.
- β-blockers (predominantly cardioselective) reduced mortality and COPD exacerbations when added to stepwise inhaled therapy for COPD in one of the studies.

**References**

Overview of Enteral & Parenteral Nutrition

Diana Carolina Andrade, Pharm.D.
Pharmacy Practice Residency
Cleveland Clinic Florida

Objectives

- Discuss nutrition screening and assessment
- Examine the gastrointestinal anatomy and its role in nutrition
- Review the ASPEN guidelines as it pertains to the adult critically ill patients
- Discuss nutrition requirements in special populations
- Review short and long term complications of nutrition support

Importance of Nutritional Screening

- Malnutrition
  - 10-40% hospitalized patients
  - 1 in 7 patients over 65 yo
  - ↑ LOS
  - ↑ hospital costs
- Obesity
  - Class I, II, III
  - 1 in 5 adults
  - ↑ health problems

Nutritional Screening

- Nutritional screening is the 1st step
  - Weight & height status, weight Δ, food intake, disease severity
- Nutritionally-at-Risk:
  - Involuntary weight loss/gain of > 10% of UBW within 6 months or:
    - > 5% in 1 month
    - 20% over or under IBW
  - Presence of chronic disease
  - Inadequate nutrition intake

Nutrition Assessment

- Medical & nutrition history
- Physical examination
- Anthropometric parameters
- Nitrogen balance
  - Starvation, catabolism, PEM

Assessment for Protein-Calorie Malnutrition

- Hormonal and cell-mediated response to stress
  - Acute illness or trauma causes inflammatory stress
  - Cytokines re-orient hepatic synthesis of plasma proteins
  - Interpretation could be problematic
- Respondents
  - Negative acute-phase
  - Positive acute-phase
Laboratory Testing

- Hepatic transport proteins
  - Valuable tool in non-ICU setting
  - Negative acute phase protein: albumin, transferrin, pre-albumin
  - Positive acute phase protein: Complement system, coagulation & fibrinolytic system, transport proteins, CRP
- Vitamins and minerals
  - B12, folate, vitamin D & K, calcium, magnesium
- Lipids
- CMP

Acute-Phase Proteins

PAB does not accurately measure nutritional repletion

Change in Plasma Concentration (%)

<table>
<thead>
<tr>
<th>Time after Inflammatory Stimulus (days)</th>
<th>CRP</th>
<th>albumin</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>7</td>
<td>300</td>
<td>300</td>
</tr>
<tr>
<td>14</td>
<td>500</td>
<td>500</td>
</tr>
<tr>
<td>21</td>
<td>700</td>
<td>700</td>
</tr>
</tbody>
</table>

Acute-Phase Proteins and Other Systemic Responses to Inflammation. NEJM. 1999;340:448-54.

Overview of Upper GI Tract

- Stomach
  - Volume: 45mL-4 L
  - Converts food boluses to chyme
  - 40min- 2 hours by peristaltic contractions
  - Ulcerative colitis
  - Crohn's Disease
  - Fistulas
  - Depression & dysphoria
- Liver & gallbladder
  - Bile
- Pancreas
  - Bicarbonate, trypsin, lipase, amylase

Overview Small & Large Intestine

- Duodenum:
  - Nutrient extraction & chemical digestion begins
  - 10-12" long
- Jejunum:
  - 8ft in length
  - Majority of nutrients absorbed
- Ileum:
  - 33ft in length
  - Vitamin B12 & bile salts absorbed
- Colon:
  - 5 ft length: ascending, transverse, descending, sigmoid
  - Water balance, vitamin absorption

Small Bowel Obstruction (SBO)

- Definition:
  - Partial or complete, simple or strangulated obstruction
  - Obstruction →dilation→ necrosis + strangulation → perforation + sepsis
- S&S:
  - Dehydration, N/V, abdominal pain, constipation
- Treatment:
  - IVF, NG tube, surgery
  - Early post-op obstruction: Bowel rest, hydration, parenteral nutrition (PN)

Conditions Affecting Nutrition

- Gastro-paresis
- GI bleeding
- Malignancy
- Gastric Outlet Obstruction (GOO)
- Malabsorption
  - Multiple surgeries
  - Medication
- Endocrine disorders
- End organ disease
- GI disorders
  - Ulcerative colitis
  - Crohn’s Disease
  - Fistulas
  - Depression & dysphoria
- Gastro-jejunal reflux
  - Bile backflow, esophageal irritation

Overview of Upper GI Tract

- Right upper quadrant pain
  - Ulcerative colitis
  - Crohn’s Disease
  - Fistulas
- Left upper quadrant pain
  - Pancreatic disease
  - Spleen disease

Overview Small & Large Intestine

- Entero-adhesive vs. non-adhesive: sticky vs. non-sticky
- Intestinal obstruction
  - Mechanical: complete obstruction
  - Paralytic: partial obstruction

Small Bowel Obstruction (SBO)

- Definition:
  - Partial or complete, simple or strangulated obstruction
  - Obstruction →dilation→ necrosis + strangulation → perforation + sepsis
- S&S:
  - Dehydration, N/V, abdominal pain, constipation
- Treatment:
  - IVF, NG tube, surgery
  - Early post-op obstruction: Bowel rest, hydration, parenteral nutrition (PN)
Crohn’s Disease

- **Definition:**
  - Inflammatory bowel disease leading to ulcerations and nutrient deficiency (65-75%)
  - PO intake, malabsorption, malnutrition, drug-nutrient interaction, nutrient deficiency
- **S&S:**
  - Abdominal pain, diarrhea, weight loss
- **Treatment:**
  - Induce & maintain remission
  - Corticosteroid therapy, immunomodulatory agents, biologic therapy, 5-ASA products, antibiotic treatment
  - Surgery requiring peri-operative PN
  - Restricted to 1) Seriously malnourished 2) Non-responding to pharmacological therapy

Fistula

- **Definition:**
  - An abnormal communication between 2 epithelialized surfaces
  - Recto-vaginal, ano-vaginal, uro-genital tract, anal-rectal, pancreatic fistula
  - Enterocutaneous fistula
    - Low output fistula drains less than 200 mL/day
    - Moderate output fistula drains between 200 and 500 mL/day
    - High output fistula drains more than 500 mL/day
- **S&S:**
  - Fever, leukocytosis, abdominal tenderness, wound infection, anorexia, failure to recover, malnutrition

Enterocutaneous Fistula

- **Intestinal or stomach contents** can leak through this connection
- **Treatment:**
  1. Fluid & electrolyte replacement
  2. Abscess drainage
  3. Infection treatment
  4. Nutrition
     - CHO & lipid: 30 kcal/kg/day
     - Protein: 1.5-2.5 g/kg/day
  5. Surgery

Post Operative Ileus

- **Definition:**
  - Inflammatory process inhibits smooth-muscle contraction and decreases the normal propulsive activity
  - Time for hospital D/C, $750 million - $1 billion/year
- **S&S:**
  - N/V, abdominal distention, inability to tolerate liquids/solids
  - Gradual resolution (small intestine [24 hrs] > stomach [48 hrs] > colon [3-5 days])
- **Treatment:**
  - Prevention is the key
  - Early feedings to mucosal immunity + mucosal atrophy

Short Bowel Syndrome (SBS)

- **Definition:**
  - < 200 cm residual small bowel without a colon
  - Significant energy and fluid loss requiring PN
- **S&S:**
  - Diarrhea, weight loss, malabsorption
- **Important factors:**
  - Intact colon
  - Presence of ileocecal valve
  - Condition of remaining bowel (micronutrient supplements)
  - Segment of bowel removed (dietary management)
- **Treatment:**
  - TPN (intestinal adaptation with time)
  - Diet: high carbohydrate-low fat (HCLF) if colon is present
  - Vitamin B12, folic acid, iron supplements
Ulcerative Colitis

- **Definition:**
  - Continuous inflammation of colon (50% left colon)
  - Malnutrition (18-62%), anemia (80%), electrolyte depletion
- **S&S:**
  - Bloody diarrhea, distension, incontinence
- **Treatment:**
  - Pharmacological (corticosteroids, 5-ASA products)
  - PN & EN have no therapeutic role in uncomplicated UC
  - 0.4 mg-1 mg/d folate
  - Omega-3-fatty acids

Diverticular Disease

- **Definition:**
  - Chronic contraction resulting in muscular hypertrophy and presence of diverticula
  - Diverticulosis (diverticula) vs. diverticulitis (diverticula perforation + inflammation)
- **S&S:**
  - Diverticulitis (90% colon), diverticular bleeding → macro-perforation → peritonitis, abscess, fistula, strictures
- **Treatment:**
  - Dietary restrictions (avoid pieces of fiber)
  - Antibiotic therapy (GNB rods, anaerobes) 7-14 days
  - Surgery (complicated cases)

A.S.P.E.N: Nutrition Assessment

Enteral Nutrition → Parenteral Nutrition

- **Time**
  - Short-term (<3 weeks)
  - Long-term (>4-8 weeks)
- **Access requirement**
  - Prior or post pyloric
  - Severe reflux, delayed gastric emptying, tube feeding related-aspiration (TFRA)
- **Personnel & resources available**
- **Complications**
  - Clogging, esophageal perforation, pulmonary intubation, nasal mucosal ulceration, wound infection, dislodgment

Selection of Enteral Feeding Route

- **Time**
  - Short-term (<3 weeks)
  - Long-term (>4-8 weeks)
- **Access requirement**
  - Prior or post pyloric
  - Severe reflux, delayed gastric emptying, tube feeding related-aspiration (TFRA)
- **Personnel & resources available**
- **Complications**
  - Clogging, esophageal perforation, pulmonary intubation, nasal mucosal ulceration, wound infection, dislodgment
**Enteral Nutrition Access**

- Short-Term non-surgical pre-pyloric tube
  - Nasogastric (NGT) or orogastric
  - Nasoenteric or oroenteric
- Short-Term surgical Pre and Post pyloric tube
  - Gastrostomy (PEG)
  - Jejunostomy
- Long-Term pre-pyloric tube
  - Gastrostomy (PEG)
- Long-Term post-pyloric tube
  - Jejunostomy (PEJ or JET-PEG)

**Choosing Appropriate Formulas**

- Carbohydrate
  - 40-90% of total caloric content
- Fiber
  - Soluble (trophic effect, ↓diarrhea) vs. insoluble (↑stool consistency)
  - Requirement 20-35 g/d
- Lipid
  - Corn and soybean oil (<10% to >50% Ω-6 fatty acids)
  - MCT do not stimulate pancreatic lipase secretion
- Protein
  - Whole vs. hydrolyzed vs. free amino acid
  - Arginine, glutamine, BCAA

**Appropriate Indications for EN**

**Indications**

- Malnourished, expected unable to eat >5-7 days
- Nourished, expected unable to eat >7-9 days
- Adaptive phase of SBS
- NPO but functional bowel
- Surgery

**Contraindications**

- Malnourished, expect to eat within 5-7 days
- Severe acute pancreatitis
- High output proximal fistula
- Inability to gain access
- Intractable vomiting, diarrhea
- Nourished, expect to eat within 7-9 days

**Common Enteral Feeding Formulas**

<table>
<thead>
<tr>
<th>Product Name</th>
<th>Indication</th>
<th>Features</th>
</tr>
</thead>
<tbody>
<tr>
<td>Jevity® 1.2</td>
<td>Standard</td>
<td>High protein w/ fiber</td>
</tr>
<tr>
<td>Glucerna® 1.2</td>
<td>Glycemic control</td>
<td>Contains chromium, Ω-3 fatty acids</td>
</tr>
<tr>
<td>Nepro®</td>
<td>Hemodialysis</td>
<td>Low in Na, K, Phosphate</td>
</tr>
<tr>
<td>Multiple formulations</td>
<td>Immune-enhancing</td>
<td>Arginine, glutamine, Ω-3 fatty acids, nucleotides</td>
</tr>
<tr>
<td>Perative®</td>
<td>Metabolic stress, wound healing</td>
<td>Contains added Arginine &amp; hydrolyzed peptide-based protein</td>
</tr>
</tbody>
</table>

**Monitoring Enteral Feedings**

- GI:
  - Pain, abdominal distension, diarrhea, N/V
- Mechanical:
  - Tube placement, feeding tube, clogging, aspiration
  - Gastric residual volume
    - Holding < 500 mL w/o symptoms not recommended
    - 200 mL may be reasonable to hold, recheck in 2 hrs
- Metabolic:
  - CMP, glucose, calcium, magnesium
  - Fluid and electrolytes imbalances

**Labs + clinical judgment**
**Appropriate Indications for PN**

- Post-op ileus
- Failed tube feeding
- High-output fistula
- Prolonged NPO
  - Malnourished
  - Greater than 5-7 days
- Tube feeding contraindicated
- Ischemic bowel
- Malabsorption
- SBO

**Parental Nutrition Access**

- **Central Venous Access (CVC)**
  - Long term: non-tunneled (weeks), PICC (months), tunneled or port (month-yrs)
  - Complications: pneumothorax, pericardial tamponade
- **Peripheral Access**
  - Short term: 10-14 days
  - Formulation osmolarity <600-900 mOsm/L
  - Complication: peripheral vein thrombophlebitis

**Adult Energy Requirement** *

- **Maintenance** (Mild stress)
  - 25-30 kcal/kg/day
- **Moderate Stress**
  - 30-35 kcal/kg/day
- **Severe Stress**
  - 35-40 kcal/kg/day

(*Based on Actual BW in non-obese patients)

**Adult Protein Requirements** *

- **Maintenance**
  - 0.8 – 1 g/kg/day
- **Mild Stress**
  - 1 – 1.2 g/kg/day
- **Moderate Stress**
  - 1.2 – 1.5 g/kg/day
- **Severe Stress**
  - 1.5 – 2 g/kg/day

(*Based on Actual BW in non-obese patients)

**Adult Electrolyte Requirements** *

<table>
<thead>
<tr>
<th>Electrolyte</th>
<th>Requirement</th>
<th>Explanation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sodium</td>
<td>70-100 mEq/day</td>
<td>1-2 mEq/kg</td>
</tr>
<tr>
<td>Potassium</td>
<td>40-100 mEq/day</td>
<td>1-2 mEq/kg</td>
</tr>
<tr>
<td>Calcium</td>
<td>10-15 mEq/day</td>
<td>As needed for acid/base</td>
</tr>
<tr>
<td>Chloride</td>
<td>As needed for acid/base</td>
<td></td>
</tr>
<tr>
<td>Magnesium</td>
<td>8-20 mEq/day</td>
<td></td>
</tr>
<tr>
<td>Phosphate</td>
<td>20-40 mmol/day</td>
<td></td>
</tr>
<tr>
<td>Acetate</td>
<td>As needed for acid/base</td>
<td></td>
</tr>
</tbody>
</table>

(*Assuming normal age-related organ function)

**Importance of Electrolyte Repletion**

- **Sodium (Na⁺)**:
  - Hypokalemia (<135 mmol/L), hyperkalemia (>145 mmol/L)
  - Osmolality, volume of body fluids, neuromuscular activity
- **Potassium (K⁺)**:
  - Hypokalemia (< 3.5 mmol/L), hyperkalemia (> 5 mmol/L)
  - Membrane potential activity, neuromuscular function
- **Calcium (Ca²⁺)**:
  - Hypocalcemia (< 9.2 mg/dL), hypercalcemia (> 11 mg/dL)
  - Cofactor (i.e. clotting cascade), muscle contraction
- **Magnesium (Mag²⁺)**:
  - Hypomagnesemia (< 0.8 mEq/L), hypermagnesemia (>2.4 mEq/L)
  - Metabolic reactions, electrolyte homeostasis
- **Phosphorus (P)**:
  - Hypophosphatemia, hyperphosphatemia (>4.7 mg/dL)
  - Structural support, synthesis of RBCs, tissue oxygenation
Obesity

- **Protein requirements**
  - BMI 30-40: ≥2g/kg IBW/day
  - BMI >40: 2.5g/kg IBW/day

- **Kcal requirements**
  - 15-20kcal/kg Actual BW/day (non-ICU)

Renal Disease

- **Protein requirements**
  - ARF: No adjustment
  - Stage III/IV CKD: 0.6-1.2g/kg/day
  - Maintenance HD: 1.2g/kg/day
  - CRRT: 1.8-2.5g/kg/day
    - Removes 20 g protein/day

Short-term Metabolic Complications

- **Electrolyte and fluid abnormalities**
- **Macronutrient related complications**
  - Hyperglycemia or hypoglycemia
  - Azotemia, ↑ BUN, hyperammonemia
  - Essential Fatty Acid Deficiency (EFAD) or hyperlipidemia
- **Re-feeding syndrome**
  - CHO metabolism → ↑ insulin secretion → ↑ cellular uptake of anabolic electrolytes
  - Potassium and magnesium
  - Start slow go slow + replenish electrolytes

Long-term PN Complications (2-6 weeks)

- **Cholestasis, gallbladder stasis**
  - Lack of hepatic bile stimulation
  - ↑ Bilirubin and alkaline phosphatase
- **Gastrointestinal atrophy**
  - Villus hypoplasia, colonic atrophy, ↓ motility, ↓ GI immunity, ↑ bacterial growth
- **Gastric hyper-secretion and hyperacidity**
  - Diarrhea, dehydration, electrolyte disturbances
- **Metabolic bone disease**
  - Bone pain, bone fracture, hypercalcuria

Conclusion

- Nutritional screening is an important part of patient assessment
- Enteral route is preferred for functional GI tract
- Continuous reassessment of patient and adjusting nutritional plan is the key

Review Questions (T or F)

- Gastroparesis, gastro-intestinal bleeding and malignancies are conditions that can affect absorption of nutrient
- Parenteral nutrition should not be terminated until >90% of target requirements are being delivered by enteral nutrition
- Re-feeding syndrome occurs usually within 24 hours of PN initiation
HCG DIET – Is it a fad?

Connie Man
PGY-1 Pharmacy Practice Resident
Miami Veterans Affairs Medical Center

Objectives
- To define the role and nature of HCG (Human chorionic gonadotropin) hormone in the human body
- To describe the general structure and proposed rationale of the HCG diet protocol
- To evaluate the efficacy of HCG diet based on a meta-analysis

Outline
- Obesity Overview
- Human Chorionic Gonadotropin (HcG)
  - Mechanism of action
  - FDA-approved indications
  - Adverse effects
  - Contraindications & Precautions
- HcG diet
  - History
  - Proposed theory & claims
  - Meta-analysis
  - Conclusion

Obesity Trend in U.S.

Obesity
- Prevalence of obesity and overweight has been increasing remarkably in the United States since the 1980s
- Multifactorial – contributory to genetics, environmental, and physiologic factors
Obesity - Classification

\[
\text{BMI} = \frac{\text{Weight (kg)}}{\text{Height (m)}^2}
\]

<table>
<thead>
<tr>
<th>BMI (kg/m²)</th>
<th>Weight status</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;18.5</td>
<td>Underweight</td>
</tr>
<tr>
<td>18.5 – 24.9</td>
<td>Normal</td>
</tr>
<tr>
<td>25.0 – 29.9</td>
<td>Overweight</td>
</tr>
<tr>
<td>30.0 – 34.9</td>
<td>Class I Obesity</td>
</tr>
<tr>
<td>35.0 – 39.9</td>
<td>Class II Obesity</td>
</tr>
<tr>
<td>&gt;40.0</td>
<td>Class III Obesity</td>
</tr>
</tbody>
</table>

Obesity - Risk factors

- Hypothyroidism
- Medication-induced weight gain
- Smoking cessation
- Stress, anxiety, depression
- Menopause

Obesity - Complications

Associated with number of serious health risks, disease states, and increased mortality:

- **Cardiovascular**
  - HTN, LV hypertrophy, CHF, CAD, Stroke
- **Metabolic**
  - Hypercholesterolemia, ↑ TG, ↓ HDL, diabetes
- **Pulmonary**
  - Sleep apnea, obstructive airway disease, Pulm HTN
- **Gastrointestinal**
  - GERD, hiatal hernia, cholelithiasis
- **Psychological**
  - Depression, affective disorders, eating disorders
- **Neoplasm**
  - Breast cancer, colon cancer

HCG Hormone

- FDA-approved Indications
  - Ovulation & pregnancy induction in anovulatory, infertile females
  - Treatment of hypogonadotrophic hypogonadism
  - Treatment of pre-pubertal cryptorchidism
  - Spermatogenesis induction with follitropin alfa

Human Chorionic Gonadotropin

- Brands: Novarel®, Pregnyl®
- Pharmacologic class: Ovulation Stimulator
- Mechanism of action:
  - Stimulation of androgen production in testes, thereby enhancing gonadal steroid hormones production
  - Acts as a substitute for luteinizing hormone (LH)
**HCG – Dosing**

- Ovulation induction
  - 5000-10,000 units IM 1 day after last menotropin dose

- Spermatogenesis induction
  - 1000-2000 units IM 2-3 times weekly
  - May require 2 – 3 months in duration

**HCG – Adverse Effects**

- Edema
- Depression, fatigue, headache, restlessness
- Gynecomastia, precocious puberty
- Local injection site reaction, pain
- Hypersensitivity reaction
- Arterial thrombus, ovarian hyperstimulation syndrome, ovarian cyst rupture (<1% frequency but significant or life-threatening)

**Human Chorionic Gonadotropin**

- Contraindications
  - Hypersensitivity to medication
  - Prostatic carcinoma
  - Precocious puberty
  - Pregnancy

- Precautions
  - Asthma
  - Cardiovascular disease
  - Migraine
  - Renal impairment
  - Seizure disorder

**The HCG DIET**

**HCG Diet – As Advertised**

- Fastest way to lose weight and keep it off
- Lose at least 15 – 30 pounds in a month
- HCG Diet is “FREE”!

**HCG Diet – As Advertised**

- No feelings of hunger through process
- HCG helps reset hypothalamus
  - Distribute fats
  - Make permanent changes to eating habits
**HCG Diet – History**

Dr. Simeons 1954
- Obesity: a disorder due to abnormal functioning of body
- Three types of stored fat
  - Structural fat
  - Normal fat
  - Abnormal fat
- Exercise & starvation results in exhaustion of “normal fat” and “structural fat”

**HCG Diet – Proposed theory**
- HCG hormone is released in large quantities during pregnancy
- Dr. Simeons calls it a “diencephalic change” – and claims it a phase brought about by HCG production
- In the human body, fixed “abnormal fat” deposits can be transferred back into the “normal fat” current only during pregnancy

**HCG Diet – The Claim**
- People who adhere to HCG diet will:
  - Lose weight quickly
  - Do not feel weak
  - Do not feel hungry
  - Preferentially burn stored fat

**HCG Diet – The DIET**
- Also known as Simeons therapy
- Two components:
  1. HCG hormone use
     - 125 IU - IM injection or oral drops
  2. Very low calorie diet:
     - 500-800 calories/day
- Duration of therapy - varies

**HCG Diet – The DIET**

HCG Diet Meal Plan:
- **Days 1 – 2**: Loading phase
  - No restriction in food intake
- **Beginning on day 3**: Maintenance phase
  - Restricted to 500-calorie-per-day diet
  - Calorie restriction applied through 72 hours after last HCG injection
- **For 3 weeks after last injection**:
  - No sugar & starch

**Meta-analysis**
- *The effect of human chorionic gonadotropin (HCG) in the treatment of obesity by means of the Simeons therapy*
- Found 8 uncontrolled & 16 controlled trials
- Studies scored for quality of methods
  - Study population
  - Interventions
  - Measurement of effect
  - Data presentation and analysis
- Methodological scores: 16 – 73 (maximum 100 points)
Meta-analysis

<table>
<thead>
<tr>
<th>Study</th>
<th>Metformin</th>
<th>Placebo</th>
<th>HCG</th>
<th>Placebo</th>
<th>Follow-up</th>
<th>Weight Loss (kg)</th>
<th>Authors' conclusion</th>
</tr>
</thead>
<tbody>
<tr>
<td>Johns [18]</td>
<td>20 weeks</td>
<td>20 weeks</td>
<td>20 weeks</td>
<td>20 weeks</td>
<td>20 weeks</td>
<td>15 weeks</td>
<td>Insignificant difference</td>
</tr>
<tr>
<td>Miller [19]</td>
<td>9 weeks</td>
<td>9 weeks</td>
<td>9 weeks</td>
<td>9 weeks</td>
<td>9 weeks</td>
<td>9 weeks</td>
<td>Insignificant difference</td>
</tr>
<tr>
<td>Fausto [20]</td>
<td>6 weeks</td>
<td>6 weeks</td>
<td>6 weeks</td>
<td>6 weeks</td>
<td>6 weeks</td>
<td>6 weeks</td>
<td>Insignificant difference</td>
</tr>
</tbody>
</table>

Meta-analysis - Conclusion

- A number of studies using HCG in treatment of obesity have been conducted and published
- No scientific evidence of HCG hormone efficacy
- Weight loss resulting from Simeons therapy is attributed to its very-low-calorie diet
- Weight loss is regarded as an inappropriate indication for HCG use

True/False

- The HCG diet protocol requires a period of 500-calorie daily intake  **True**
- HCG has FDA-labeled indications for infertility in women and hypergonadism in men  **False (HYPOgonadism)**
- Prescription HCG advertised for weight loss purpose is available in both sublingual and nasal spray formulations  **True**

HCG Diet – The Products

http://2.bp.blogspot.com/-Rzk-BE1wuPY/Tt-jqbzJwWI/AAAAAAAAATw/NapNgGKRG-U/s1600/120611_HCGProductsFDA.jpg

FDA Consumer Update 12/2011

- HCG not approved for OTC sale
- HCG is not listed under Homeopathic Pharmacopoeia of the United States – thus cannot be sold legally as homeopathic medication
- 500-calorie-a-day diet increases health risks and may be fatal
**FDA Consumer Update 12/2011**

- FDA and FTC taking action on illegal HCG products
- Warning letters issued to seven companies
- Fifteen days allotted for companies to notify FDA regarding their plans
- FDA encouraging consumers to report any side effects associated with the use of these products to MedWatch

**Conclusion**

- Prevalence of obesity in U.S. has increased dramatically over the past decades
- Two components to the HCG diet: HCG injection (or alternative forms) in adjunct to a 500-calorie-a-day diet
- A meta-analysis has shown no effect of HCG hormone in the weight loss

**Case Practice**

A 29 yo female comes into your pharmacy to pick up her prenatal vitamins and would like to talk to you, the pharmacist, regarding the HCG diet that she had recently learned from a TV advertisement. She expresses a very strong interest in this diet but has a fear for needles, and would like to know if there are other routes in which she can ‘consume’ this HCG hormone. What would you tell her?

**Answer:**

HCG hormone products marketed for weight loss also comes in an oral sublingual formulation.

---

**FDA Consumer Update 12/2011**

“These products are marketed with incredible claims and people think that if they’re losing weight, HCG must be working. But the data simply does not support this; any loss is from severe calorie restriction. Not from the HCG.”

- Elizabeth Miller
  Director of FDA’s Division of Non-Prescription Drugs and Health Fraud

**Conclusion**

- The increasing popularity of this diet has encouraged the emergence of OTC products that claim to contain HCG hormone
- HCG hormone is only FDA-approved for infertility and other health conditions
- FDA and FTC taking action on illegal HCG products
- FDA warns public: a very-low-calorie diet poses health risks and may be dangerous

**Case Practice**

The following information are found in her profile:

- Height: 5’5
- Weight: 91 kg
- Allergies: NKDA
- PMH
  - HTN
  - GERD
  - DM II
  - Dyslipidemia
  - Anxiety
  - Low back pain
  - Allergic rhinitis
- Active medications
  - Acetaminophen 500mg Q6H prn pain
  - Diphenhydramine 50mg po Q6H prn allergy
  - Folic acid 1mg po daily
  - Insulin Glargine 17 units QHS
  - Insulin Aspart 8 units TID AC
  - Metformin 1g po BID
  - Methyldopa 250mg po BID
  - Ranitidine 150mg po BID
  - Prenatal vitamin tablet 1 tab po daily
Case Practice

Would you recommend the HCG diet for this patient? Why or why not?

**Answer:**
No. HCG products are absolutely contraindicated in pregnancy. Animal studies have revealed evidence of forelimbs and CNS defects in fetuses.

---

References


---

Questions?

- FDA Consumer Health Information. “HCG diet products are illegal.” Food and Drug Administration. 12 Dec 2011.
Medications to Avoid After Bariatric Surgery

Jayme L. Dinsmore, Pharm.D.,
PGY-1 Pharmacy Practice Resident
Miami VA Medical Center

Goals

- Goal 1: To provide an introduction of the physical changes that occur to the gastrointestinal tract after bariatric surgery.
- Goal 2: To describe the ways drug absorption is affected after bariatric surgery
- Goal 3: To provide recommendations for medication management based on theoretical and evidence-based medicine in patients after bariatric surgery

Introduction

- Bariatric surgery has become the preferred therapy for severely obese patients who are refractory to traditional medical therapy.
- Traditional medical therapy is largely behavioral modification therapy +/- medications.
- Almost all weight loss medications reaching the market have been withdrawn due to increased cardiovascular risks

Obesity is epidemic

- Obesity affects over 300 million individuals worldwide.
- Over the past 20 years, the subgroup of obese considered ‘severe’ has nearly quadrupled throughout Northern America and Europe.
- In 2008, medical costs associated with obesity were estimated at $147 billion; the medical costs paid by third-party payors for people who are obese were $1,429 higher than those of normal weight.

Obesity Trends

Adapted from www.cdc.gov/obesity/data/trends

Consequences of Obesity

Obesity is associated with extensive morbidity and premature mortality.

- Type 2 Diabetes
- Dyslipidemia
- Hypertension
- Obstructive sleep apnea
- Heart Disease
- Stroke
- Asthma
- Weight-bearing degenerative problems
- Depression
- Cancer

**Relative Risk of Morbidities from Obesity**

<table>
<thead>
<tr>
<th>Morbidity</th>
<th>Greatly increased (relative risk &gt;&gt;3)</th>
<th>Moderately increased (relative risk 2-3)</th>
<th>Slightly increased (relative risk 1-2)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diabetes</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gall bladder disease</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hypertension</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dyslipidemia</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Insulin resistance</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Breathlessness</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sleep apnea</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Coronary heart disease</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Osteoarthritis (knees)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hyperuricemia and gout</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cancer, postmenopausal women, endometrial cancer</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Reproductive hormone abnormalities</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Polycystic ovary syndrome</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Impaired fertility</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Low back pain</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Increased anesthetic risk</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fetal defects arising from maternal obesity</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Bariatric Surgery**

National Institute of Health recommendations for patients over age of 18:

Body Mass Index (BMI) greater than 40

**Demand**

- In 2008, over 350,000 procedures performed globally
- Most popular worldwide
  1. Adjustable gastric banding (AGB; 42%)
  2. Roux-en-Y gastric bypass (RYGB; 39%)
  3. Sleeve gastrectomy (SG; 5%) (14).
- Most popular in United States: Roux-en-Y


**Types of Bariatric Surgery**

**Purely Restrictive**
- Vertical-banded gastroplasty
- Adjustable gastric banding

**Restrictive > Malabsorptive**
- Roux-en-Y gastric bypass (RYGB)

**Malabsorptive > Restrictive**
- Biliopancreatic diversion

**Purely Malabsorptive**
- Jejunooileal bypass
- Jejunocolonic bypass

**Adjustable Gastric Banding**

[Image: http://www.ebariatricsurgery.com/adjustablegastricbanding.html]

**Vertical Banded Gastroplasty**

[Image: http://bodiesurgery.info.webs.com/surgical_procedures.html]
**Sleeve Gastrectomy**

- Esophagus
- Gastric Sleeve
- Removed portion of Stomach

**Roux-en-Y Gastric Bypass**

- Restrictive
- Malabsorptive

---

**Efficacy for Weight Loss**

Mean percentage excess weight loss:

- 61.2% - All Patients
- 47.5% - Gastric Banding
- 61.6% - Gastric Bypass
- 68.2% - Gastroplasty

---

**Oral drug absorption is a prerequisite for pharmacological effects.**

---

**Drug Absorption**

1. Disintegration
2. Dissolution
3. Gastric emptying
4. Intestinal transit time
5. Blood flow to gastrointestinal tract
6. Metabolism of drug within gastrointestinal tract

---

**Disintegration & Dissolution**

**Stomach**

- Main role is to mix, reduce, & dissolve ingested food/drugs for delivery to the small intestine
- Not a major site of drug absorption except weak acidic drugs (aspirin)
Post-Bariatric Surgery

Stomach
- Surface area reduced
  - Impaired drug disintegration/dissolution
- Loss of gastric acid production
  - Increased pH of stomach
Medications dependent on acidic pH for bioavailability:
1. Itraconazole
2. Ketoconazole
3. Atorvastatin

Small Intestine
- Most important site of drug absorption in the body
- Villi & micro-villi (caves) = Huge surface area
- Presence of numerous drug influx and efflux pumps along lining of the small intestine
- Most recognizable, P-glycoprotein

Drug Transporters

<table>
<thead>
<tr>
<th>Transport Protein</th>
<th>Drug substrates</th>
</tr>
</thead>
<tbody>
<tr>
<td>PepT1</td>
<td>Beta lactam antibiotics, ACE inhibitors, antivirals</td>
</tr>
<tr>
<td>OATP2B1</td>
<td>DHEA, salicylate, valproate, pravastatin, atorvastatin, fexofenadine</td>
</tr>
<tr>
<td>PCFT</td>
<td>Folate, methotrexate, pemetrexed,</td>
</tr>
</tbody>
</table>

Post-Bariatric Surgery

- Roux-en-Y gastric bypass reduces small intestine length which dramatically reduces overall surface area
- Length reduction highly variable
- Drug transporter distribution heterogeneous and so drug absorption not predictable
- Complex pharmacodynamics

Clinical Translation

- Paucity of clinical studies comparing the pharmacokinetics/dynamics of medications pre- and post-bariatric surgery.
- Most clinical data was obtained from outdated bypass procedures
- Reduction of small intestine length and/or stomach size not consistently reported
- Lack of comparators in trials & case reports makes data interpretation difficult

pH-Partition Theory of Drug Absorption

- The rate & extent of drug absorption (bioavailability) is dependent only on:
  1. Drug pKa
  2. pH at site of absorption
  3. Partition co-efficient
- Weak acidic drugs are unionized/more lipophilic in stomach → site of absorption
- Weak basic drugs are unionized/more lipophilic in small intestine → site of absorption
### Evidence-Based Medicine

**Trial Design**
- Comparison of acetaminophen pharmacokinetics/dynamics in subjects before, at 3 months, and 1 year after surgery
- Oral, liquid acetaminophen
- Post-surgery
  - $C_{\text{Pmax}}$ doubled ($p<0.01$)
  - $T_{\text{max}}$, 10 minutes vs. 45 minutes
- Results consistent with a previous, analogous trial


### Clinical Translation

- **Nutrient deficiencies**
  - Most studied
  - Endocrine Society published guidelines in 2010 on the Nutritional Management of the Post-Bariatric Surgery Patient
- **Medication pharmacokinetic data**
  - Case studies
  - *In vitro* testing
  - Theoretical

### Vitamin Supplementation

- Daily multivitamin and calcium supplementation with added vitamin D for all weight-loss surgery patients.
- Calcium citrate preferred
  - Salt is better absorbed in the absence of gastric acid production.


### Osteoporosis

- Well documented, especially in women
- Several studies have documented the high incidence of secondary hypoparathyroidism (30-60%) at one year
- Medications contributing to hypocalcemia:
  1. Loop diuretics
  2. Carbamazepine
  3. Oxcarbazepine


### Bisphosphonates

- Increased risk of esophagitis with adjustable gastric band
- Potentiates risk of developing malabsorptive hypocalcemia
- However, extensive weight loss leads to bone demineralization
- Risk vs. benefit
- Recommend once yearly IV zoledronic acid to minimize risk of esophagitis

### NSAIDs

- Chronic use of NSAIDs increases risk of gastric ulcers
- 11-fold increased risk of ulcers with chronic NSAID use after bariatric surgery
- Recommendation: avoid use
  - topical alternatives (diclofenac gel, capsaicin, menthol, camphor)
  - Switch to another class of medications (tramadol)

Gout

- Both surgery and weight loss after bariatric surgery increase risk of acute gout attacks.
- Prophylactic gout therapies should be initiated prior to surgery to minimize risk.
- Avoid medications known to precipitate gout.
- Consider use of colchicine over NSAIDs for acute gout attacks.


Warfarin

- Very close INR monitoring suggested in patients after bariatric surgery.
- Unknown if warfarin bioavailability affected.
- Vitamin K intake unpredictable:
  - Diet restrictions post-operatively
  - Stable diet
  - Change in eating habits
- Consider low-molecular weight heparins, which have established safety and efficacy in this population.

Case

- A 50-year-old, 250 lb woman suffered idiopathic proximal right popliteal and calf deep vein thrombosis (DVT) 3 years previously. Her warfarin has been managed successfully by a centralized pharmacist-run anticoagulation service, and she has easily achieved and maintained her target international normalized ratio range between 2.0 and 3.0. She has had no bleeding or thrombotic complications. The surgeon calls to notify you the patient will undergo RYGB surgery in two weeks. As a pharmacist, what will you recommend?

Warfarin

- One case report of warfarin resistance following RYGB.
- Chronic atrial fibrillation patient previously therapeutic (INR 2-3) on 5 mg warfarin daily required doses up to 20 mg/day after surgery in order to maintain INR goal.

Tamoxifen

- Three case reports documenting subtherapeutic tamoxifen levels in patients after RYGB.
- Therapeutic range 95-520 ng/ml.
- Recommend steady-state tamoxifen levels or use of intravenous chemotherapy agents, when appropriate.


Contraception

- Women of child-bearing age are advised to avoid pregnancy for up to 2 years post-surgery.
- Evidence limited.
- Efficacy of contraception medication has not been established.
- Recommendation: IV, transdermal, intrauterine, or barrier contraceptive methods that do not rely on gut absorption.

Summary
In lack of evidence-based medicine to support safety & efficacy of a given medication, the pharmacist should:
1. Suggest an alternative dosage form that does not depend on gut absorption
2. Recommend liquid dosage forms whenever possible to avoid problems associated with drug disintegration and dissolution
3. Remember pharmacokinetics/dynamics of drug absorption
4. Use therapeutic drug monitoring to evaluate efficacy

Summary
5. Use medications that do not depend on food for bioavailability
6. Ask physician and/or patient for surgical details in order to make educated conclusions as to the degree of restriction and/or malabsorption
7. Remember that older studies are mostly based on outdated surgical procedures causing extensive malabsorption and should be interpreted with caution

True or False?
- True/False. A patient who has received a Roux-en-Y bypass procedure will have decreased surface area of the small intestine?
  - Answer: True

- True/False. Calcium carbonate is the best choice for calcium supplementation in a patient after bariatric surgery.
  - Answer: False, calcium citrate

True or False?
- True or False. Ketoconazole is a medication that relies on an acidic medium for absorption and so will have increased drug absorption necessitating dose reduction following bariatric surgery.
  - Answer: False, decreased drug absorption possibly necessitating dose increase
**Strategies in Pain Management:**
Scheduled, Breakthrough, and Dose Adjustments

Tamara M. Green, Pharm.D
PGY-1 Resident
Florida A & M University

**Objectives**
- Classify and distinguish between different types of pain
- Discuss processes of risk-stratification
- Identify indications required for use of opioid therapy
- Organize an opioid treatment plan
- Determine when and how to initiate scheduled and breakthrough pain management
- Identify indications for dose adjustments
- Evaluate the need for discontinuation of pain management
- Discuss current therapies in pain management

**Pain**
- In 2001, JCAHO endorsed pain as a 5th vital sign
- Chronic pain is defined as pain that persists beyond normal tissue healing time, which is assumed to be three months
- Pain is subjective
- Neuropathic pain is defined as pain that results from damage to or pathology within the nervous system.
  - I.e. diabetes mellitus and stroke
- Nociceptive pain is defined as pain that is caused by stimuli that threatens or provokes actual tissue damage.
  - I.e. inflammation and musculoskeletal conditions

**Controversy**
- Chronic opioid use has been acceptable in cancer patients
- Controversy exists in regards to chronic use in non-cancer patients due to:
  - Diversion
  - Tolerance
  - Abuse
  - Physical and Psychological Dependence
  - Lack of evidence of efficacy

**Risk Stratification**
- All clinicians prescribing opioids should be knowledgeable about risk factors for opioid abuse and methods for assessing risk
- Documentation of benefit-harm evaluation
  - ALL patients should complete a thorough history and physical examination
    - Medical, family, psychosocial, drug/alcohol abuse, suicidal risk
  - When assessing a patient, it is important to determine if the patient should be treated non-opioid vs. opioid
    - Diagnostic tests and assessments
- Attempt to determine a specific diagnosis
  - Nociceptive vs. Neuropathic

Stratify Low vs. High risk patients

- Factors that have been associated with opioid misuse, abuse, and diversion:
  - Personal or family history of alcohol/drug abuse
  - Young age w/ psychiatric condition

Factors that have been associated with opioid misuse, abuse, and diversion:
- Personal or family history of alcohol/drug abuse
- Young age w/ psychiatric condition
- History of substance use
- History or coexisting psychiatric disorder
- History of suicide attempt
- Any positive HIV
- Any history of legal problems
- Young age (less than 21)


Indications for Chronic Opioid Therapy (COT)

- May be initiated in patients in which the benefits of the use of COT outweigh the risk AND there is no alternative therapy that will be of benefit to the patient
- Patients that are risk stratified and are carefully selected for COT
- Patients that will be closely monitored
- Patients that have failed to respond to non-opioid treatments


Opioid Management Plan

- Discuss goals of therapy
- Describe how opioids will be prescribed and should be taken
- Explain expectations for clinic follow-up and monitoring
- Explain expectations in the total management of COT

Discuss potential indications for tapering or discontinuing COT
- Discuss possible adverse effects
- Determine and discuss consequences of aberrant drug related behaviors


Not a "one size fits all plan"
- Informed consent should be obtained
- Avoid unrealistic expectations
- Determine whether patient warrants multidisciplinary treatment options
  - Psychology, Psychiatry, Counseling, Family support, and alternative medicine
- Importance: Emphasizes expectations regarding appropriate and safe use of opioids


Non-Opioid Management of Pain

- Acetaminophen (Tylenol, Ofirmev)
  - MOA: unknown; but may inhibit central prostaglandin synthesis and ↑ pain threshold
  - Analgesic and Antipyretic properties
  - Max dose: 3000 mg daily
  - 325 mg per dosage unit limit
  - Does not cover OTC products
  - Caution: Renal Impairment
  - BBW: Potential for severe liver injury


Non-Opioid Management of Pain

- Acetaminophen (Tylenol, Ofirmev)
  - MOA: unknown; but may inhibit central prostaglandin synthesis and ↑ pain threshold
  - Analgesic and Antipyretic properties
  - Max dose: 3000 mg daily
  - 325 mg per dosage unit limit
  - Does not cover OTC products
  - Caution: Renal Impairment
  - BBW: Potential for severe liver injury

### NSAIDS
- **MOA:** Reversibly binds to COX 1&2 enzymes which inhibits prostaglandin synthesis
- Analgesic, Antipyretic, and Anti-inflammatory
- **BBW:**
  - May ↑ risk of serious cardiovascular events
  - May ↑ risk of serious GI bleeding/ perforation
- **Adverse Effects:** Dyspepsia, ↑ BP, GI irritation, Dizziness, Confusion, and Fatigue
- Pregnancy: C/C/D

### Gamma Aminobutyric Acids
- **MOA:** Binds to the voltage-gated calcium channels at the alpha 2-delta subunit and inhibit neurotransmitter release.
- **Gabapentin (Neurontin)**
  - Max 3600 mg divided in 3 doses
  - Side Effects: Peripheral edema, dizziness, somnolence
- **Pregabalin (Lyrica)**
  - 50-450 mg daily
  - Side Effects: Peripheral edema, angioedema, and renal dysfunction

### Tricyclic Antidepressants
- **Amitriptyline:**
  - 5-100 mg at bedtime
- **Nortriptyline:**
  - 25 mg TID/QID Max:150mg/day
- **Side Effects:** Dry mouth, sweating, orthostatic hypotension, dizziness, and constipation
- **GI:** Cardiac conduction disturbances

### SNRI
- **Duloxetine (Cymbalta)**
  - 30-60 mg daily
- **Venlafaxine (Effexor)**
  - 37.5 – 300 mg daily
- **Side Effects:** BP, sexual dysfunction, sweating

### Initiating COT
- Initiation of COT is referred to as a short term, therapeutic trial
  - Used to determine whether COT will be appropriate
  - Duration: weeks to months
- Opioid selection, initial dosing, and titration should be individualized according to:
  - Health status, previous exposure to opioids, attainment of therapeutic goals, and predicted or observed harms

---

![Pain Ladder](https://example.com/pain-ladder.png)


http://painladder.com/pharmacologic-therapies-for-pain
"Start low and go slow"

There is insufficient evidence to recommend specific optimal starting doses and methods of dose titration.

There is insufficient evidence to recommend short acting versus long-acting opioids, or as-needed versus around-the-clock dosing of opioids.

For continuous, persistent daily pain

- **Option One**: Initiate a short acting opioid
  - **Advantage**: shorter half life
  - **Disadvantage**: Rapid rise and fall in serum level
- **Option Two**: Initiate a long acting opioid
  - **Advantages**: Gradual increase to therapeutic level, half-life, more-consistent control, may ↑ adherence, and lower risk of abuse
  - **Disadvantages**: Exaggerated side effects

For episodic pain

- **Option Three**: Initiate a short acting opioid as needed

### Titrating Doses

- Always evaluate a need for dose titration
- Careful titration is warranted in COT to:
  - Allow time to build tolerance to side effects
  - Reduce risk of toxicity
  - Attain optimal dose to reduce pain symptoms
- Daily dose can be ↑ by 25-100% at a given time
- Do not dose more than every five half lives
- If patient is on more than one opioid, titrate one medication at a time
- Titrate up to a 200 mg/day morphine equivalent
- May be increased further until side effects limit dosing

### Opioid conversion tips

1. Calculate the total daily dose of the opioid being titrated onto.
2. Adjust the total daily dosage of the new opioid to match the old opioid.

### Changing to another oral opioid

**Question:** A patient is taking sustained-release oxycodone, 100 mg every 12 hours, but has developed intolerable side effects. She would like to try an immediate-release opioid, hydrocodone. What is the equivalent dose of hydrocodone?

**Answer:** The "Dosage and Conversion Chart for Opioid Analgesics" will help you calculate the equivalent dose of the new opioid, but you must allow for the complete nature of cross tolerance to opioid side effects.

- After patients take the same opioid for a week or two, they become tolerant of the opioid's sedative and respiratory depressive effects.
- When another opioid is substituted for the original opioid, patients will not be completely tolerant to the new opioid's side effects, which can lead to over sedation or confusion.

- Use the "Dosage and Conversion Chart for Opioid Analgesics" to calculate the equivalent dose of hydrocodone:
  - Use the conversion rate of 20 mg of oxycodone to equivalent the 40 mg of hydrocodone:
  - 40 mg of oxycodone is equivalent to 80 mg of hydrocodone.

### Dose Chart

<table>
<thead>
<tr>
<th>Opioid</th>
<th>Oral Dose (mg)</th>
<th>Parenteral Dose (mg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Morphine</td>
<td>80</td>
<td>15</td>
</tr>
<tr>
<td>Codeine</td>
<td>120</td>
<td>45</td>
</tr>
<tr>
<td>Hydrocodone</td>
<td>50</td>
<td>15</td>
</tr>
<tr>
<td>Methadone</td>
<td>10</td>
<td>10</td>
</tr>
<tr>
<td>Levorphanol</td>
<td>4</td>
<td>4</td>
</tr>
<tr>
<td>Hydromorphone</td>
<td>40</td>
<td>10</td>
</tr>
<tr>
<td>OxyContin</td>
<td>20</td>
<td>2</td>
</tr>
<tr>
<td>Hydrocodeine</td>
<td>20</td>
<td>10</td>
</tr>
<tr>
<td>Hydromorphone</td>
<td>20</td>
<td>10</td>
</tr>
</tbody>
</table>

**Note:** When converting to an acute care setting, start with the lowest dose and adjust as needed.

**Additional Resources:**
- [Opioid Titration Practice: A Consensus Building Group. VA/DoD CLINICAL PRACTICE GUIDELINE FOR MANAGEMENT OF OPIOID USE IN CHRONIC PAIN](https://www.pubmed.gov/79532905)
Opioid Rotation

- Studies have shown that patients with non-cancer pain may switch opioids approximately 3-4 times before achieving optimal analgesia.
- Shown effective in noncancer pain.
  - Manages adverse effects and inadequate analgesia in patients on long-term COT.
  - May improve efficacy.
  - Patients may respond differently to different types of opioids.


- Adequate Pain Relief but Adverse Effects
  - Starting dose of new drug should be ↓ by 50-75% equianalgesic dose of old drug.

- Poor Pain Control and Adverse Effects
  - Starting dose of new drug should be ↑ by 75-100% of equianalgesic dose of old drug.

Multimodal Analgesia

- The administration of two or more analgesics acting by different mechanisms with the goal of providing analgesic efficacy superior to a single analgesic.
- Targets different pain pathways.


Opioids

- MOA: Work by binding to mu, kappa, and delta opioid receptors to decrease pain perception and reaction to pain.
- Adverse Effects are dose dependent.
  - Constipation
  - Nausea/Vomiting
  - Sedation
  - Pruritis
  - Rare: CV effects, hyperalgesia, respiratory depression.

- Fentanyl
  - ∆ Patch q 72 hrs.
  - Should not be used PRN or as INITIAL therapy.
  - Use caution with heat.
  - Do not use more than 1 patch at a time.

- Hydromorphone
  - CI in opioid naïve patients.
  - 2 week washout with Exalgo and MAOIs.

- Meperidine
  - Seizures: Normeperidine (active metabolite).

- Methadone
  - T ½: 15-55 h.
  - Arrhythmias: QT prolongation.

Opioids

<table>
<thead>
<tr>
<th>Drug</th>
<th>Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Morphone (MS Contin, Avinza, Kadian, Oramorph SR, Roxanal, Embeda)</td>
<td>ER: 10-30 mg q 4 ER: 15-30-60-100-200 mg q 8-12 h</td>
</tr>
<tr>
<td>Fentanyl (Duragesic)</td>
<td>Patch: 12,25,50,75, 100 mcg/h</td>
</tr>
<tr>
<td>Hydromorphone (Dilaudid)</td>
<td>2-4 mg</td>
</tr>
<tr>
<td>Oxycodone (Oxycotin, Endocet, Percocet, Brisket)</td>
<td>IR: 5,10,15,20,30 mg CR: 15, 15, 20, 30, 60, 80, 160 mg</td>
</tr>
<tr>
<td>Oxymorphone (Opana, Opana ER, Opana Inj)</td>
<td>Opana ER: 5-30 mg BID Opana IR: 5-10 mg PRN</td>
</tr>
<tr>
<td>Methadone (Dolophine, Methadose)</td>
<td>2.5 – 10 mg q 8-12 h</td>
</tr>
<tr>
<td>Meperidine (Demerol)</td>
<td>0.1-150 mg q 2-4 hrs PRN</td>
</tr>
<tr>
<td>Hydrocodone + APAP (Lorcet, Lortab, Vicodin, Norco)</td>
<td>2, 5, 5, 3-5 mg hydrocodone w/ 500, 650, 660, 750 APAP</td>
</tr>
<tr>
<td>Codeine + APAP (Tylenol #2,3,4)</td>
<td>15-120 mg q 4-6 hrs PRN</td>
</tr>
<tr>
<td>Tramadol (Ultram, Ultram ER, Ryzolt-ER)</td>
<td>50 mg; 37.5 mg w/ 325 mg APAP 1-2 tabs q 4 h PRN</td>
</tr>
<tr>
<td>Tapentadol (Nucynta)</td>
<td>50-100 mg q 4-6 hrs PRN</td>
</tr>
</tbody>
</table>

Clinical Pearls

- Fentanyl
  - Δ Patch q 72 hrs.
  - Should not be used PRN or as INITIAL therapy.
  - Use caution with heat.
  - Do not use more than 1 patch at a time.

- Hydromorphone
  - CI in opioid naïve patients.
  - 2 week washout with Exalgo and MAOIs.

- Meperidine
  - Seizures: Normeperidine (active metabolite).

- Methadone
  - T ½: 15-55 h.
  - Arrhythmias: QT prolongation.
Oxymorphone
- Take on an empty stomach
- Do not consume alcohol
- CI in moderate to severe liver impairment

Oxycodone
- BBW: Providers must report abuse/diversion

Tramadol
- ↓ Seizure threshold

Tapentadol
- ↓ Seizure threshold, renal/hepatic impairment
- Do not crush, chew, or break extended release
- CI within 2 weeks of MAOIs

Follow-up Visits
- Every week to 6 months
- Evaluate progress towards therapeutic goals
  - Physical and psychosocial assessment
  - Evaluate pain severity
  - Determine patients functional ability
  - Evaluate actual or potential adverse effects
- Drug screenings
  - Re-emphasizes expectations regarding appropriate and safe use of opioids
- Restructure opioid treatment plan as needed

Discontinuing COT
- Discontinue in pts who:
  - Continue aberrant drug-related behaviors
  - Lack progress toward therapeutic goals
  - Experience intolerable adverse effects
- Slow Taper
  - ↓ dose by 10% weekly
- Rapid Taper
  - ↓ dose by 25-50% every few days

True OR False?
- Total pain relief with chronic opioid therapy is common.
  - False
- Opioids do not have a ceiling effect.
  - True
- Patients become tolerant to constipation with continuous exposure to opioids.
  - False

A.K is a 57 year old male who presents to the pain clinic today with a chief complaint of chronic, dull, lower back pain. A.K describes the pain as a 6/10, however during work his pain may escalate to 8/10. A.K has been a truck driver for a local soda company for the past 20 years. He states that lately it is very difficult to bend and lift crates, and is very concerned about the pain and its interference with his performance at work.

A.K has a past medical history of hypertension, diabetes, and hyperlipidemia. His labs are within normal limits.

His current medications include Amlodipine 10 mg daily, Crestor 20 mg at bedtime, Actos 30 mg daily, Metformin 1000 mg twice daily, and Diovan-HCTZ 160 mg/25 mg.

References
Florida’s Claim to Fame: Pain Clinics and Narcotic Fraud

Dr. Cheryl A. Lindo, PharmD
Miami VA Medical Center
Miami, FL
January 20, 2012

Objectives

- Highlight Florida’s pharmaceutical trends
- Review diversion methods
- Discuss HB 7095 and E-FORCSE
- Review concerns about the Pill Mill Laws
- Discuss effects of Florida’s new laws

Where We Live

- South Florida’s Metropolitan Statistical Area includes Miami-Dade, Broward, and Palm Beach Counties
- International transportation hub and gateway to commerce and trade between the Americas
  - Port of entry for illicit drugs
- South Florida, specifically Broward County leading the nation in “Pill Mill” clinics

Florida Trends 2010

- 5,647 deaths with at least one prescription medication
- 7.4 deaths each day
- Broward County greatest number of deaths
- Miami-Dade County lowest per capita rates of prescription drug abuse
- Palm Beach County reported decline in mortalities
Florida Trends 2010

- Oxycodone
  - Nonmedical use in Florida
  - Higher ED reports than national rate
  - 93% deaths in combination with other drugs
- Oxymorphone
  - Fastest rising among opioid deaths
- Methadone
  - Most lethal prescription opioid


Florida Trends 2010

- Leading benzodiazepine occurrences
  - Alprazolam
  - Diazepam
- Greatest increase in total drug-related death occurrences
  - Nordiazepam (Nordaz®)
  - Oxazepam (Serax®)
  - Temazepam (Restoril®)


Drug Overdose Deaths

- Study in Palm Beach County
  - White male, late 30’s, high school diploma or GED
  - Death at home while asleep
  - One-third with substance abuse history and drug-related arrests
  - Most had prior non-fatal drug overdose
  - Most death were preventable with early intervention and public education


Oxycodone Sources 2009

- Dispensed by Practitioner, 83,000,000
- Dispensed by Pharmacist or Hospital, 440,000,000

Sources: DAMRSA - Treatment Episode Data Set. Submitted by the Florida Dept. of Children and Families as of January 6, 2011.
Dispensing in Florida

- Average dose unit of oxycodone
  - 18mg compared to 13mg nationally
- 16.9% of the total grams of oxycodone distributed in the US
- Ranked #1 in total grams of oxycodone distributed nationally

Pain Clinics

- "Pill mills"-nickname for walk-in rogue pain-management clinics
- Source of prescription painkillers
- Florida’s reputation as "Oxy Express"
- Broward County
  - ~130 pain clinics operating
  - >1 million oxycodone tablets prescribed every month

Pain Clinic Doctors

- Complicit doctors agreed to prescribe oxycodone and other controlled substances without regard to medical necessity
- Only cursory physical examination
- Prescribed "cocktail" of controlled substances
- No individualized treatment plans or showing medical need
- Physicians paid on per capita basis depending on number of patients examined each day

Diversion Methods

- Pain Management Clinics and inappropriate prescribing
- Doctor shopping
- Prescription fraud (forged, stolen, altered prescriptions)
- Pharmacy thefts; employee thefts
- Internet websites

Pain Clinics

- Knowingly prescribe large quantities of pain medications and other lucrative drugs
- No legitimate medical purpose
- Not within the usual course of professional medical practice
- Inferior, over-aggressive interpretations of radiological exams to justify prescriptions
- Drug tests falsified for a fee
- Required immediate cash payments or "visit fee"

Doctor Shopping

- Individual visits several different doctors to obtain prescriptions for the same medication
- Prescriptions filled at different pharmacies
- Allows individual to obtain more of a prescribed substance than any one physician or pharmacist would allow
- Primary means for addicts to obtain prescription medication for illicit use
- Felony, punishable by up to 5 years in prison


Pain Clinics

- "Pill mills"-nickname for walk-in rogue pain-management clinics
- Source of prescription painkillers
- Florida’s reputation as "Oxy Express"
- Broward County
  - ~130 pain clinics operating
  - >1 million oxycodone tablets prescribed every month

Pain Clinic Doctors

- Complicit doctors agreed to prescribe oxycodone and other controlled substances without regard to medical necessity
- Only cursory physical examination
- Prescribed "cocktail" of controlled substances
- No individualized treatment plans or showing medical need
- Physicians paid on per capita basis depending on number of patients examined each day

Diversion Methods

- Pain Management Clinics and inappropriate prescribing
- Doctor shopping
- Prescription fraud (forged, stolen, altered prescriptions)
- Pharmacy thefts; employee thefts
- Internet websites
Prescription Fraud
- Prescriptions issued by physicians
  - Not for legitimate medical purpose
  - Not usual course of professional practice
  - Use of blank prescription forms by unauthorized persons
    - Filled in the controlled substance, dosage to be prescribed, or DEA number of a physician without his or her knowledge or participation
    - Forged signature of physician

Prescription Fraud
- Providing false documentation in patient files to support issuance of fraudulent prescriptions for controlled substances
- Allowing the dispensing of controlled substances at the pharmacy
  - by persons not authorized to fill prescriptions
  - without the presence of supervision by a pharmacist
- Unlawful distribution of controlled substances without any prescription

Trafficking & Health Care Fraud
- Facilitators recruited beneficiaries of Medicare
- Provided transportation to pain clinics and pharmacies prior to taking and distributing drugs
- Beneficiaries brought prescriptions to complicit pharmacies that billed Medicare, knowing drugs medically unnecessary and are being re-sold
- Proceeds from drug trafficking $40,000,000

Pharmacy Theft
- Pharmacy employees
  - Manipulate computer inventory systems
  - Drug addiction
  - Trafficking
- Drug addicts and dealers
  - Robbing stores
  - Posing as repairman
  - Activate “false” alarm
  - Hide in stores until closed

Internet Websites
- Delivery to front door
- Offer to sell narcotics without a prescription
- "Membership fee" for no prior-prescription access
- Cursory written or oral “exam” with a physician
- Websites selling access to other sites that directly sells drugs without face-to-face physician consultation
- May sell real, similar, or counterfeit drugs

Consequence to Florida
- Prescription drug abuse fastest growing drug problem
- Pill mills facilitating the growth of this epidemic
- Increased numbers in
  - Drug addiction
  - Overdose
  - Pain and suffering
  - Death
- Rogue doctors running facilities and violating professional oath
**House Bill 7095**

- New Pill Mill Law, July 1, 2011
- Provides $3 million to support law enforcement and state prosecutors
- Requires doctors to report to Health Department within 10 days when starting or stopping work at a pain clinic.
- Levies fines of $10,000 and 6-month suspensions, on physicians who “over-prescribe” painkillers


**Florida’s New Pill Mill Law**

- Prescriptions and pain treatment plans technically more difficult for average doctor to write
- Requiring of electronic or counterfeit-proof prescription pads purchased from Health Department-approved vendors
- Pharmaceutical wholesaler/suppliers required to report all sales of controlled substances to the state
- Eliminates requirement for search warrant by law enforcement officers to view and copy a pain clinic’s records


**HB 7095 Impacts Pharmacy**

- Allows only SEVEN days for pharmacies to report prescription information to the drug database
- First-degree misdemeanor on pharmacists who knowingly fail to report to authorities, any attempts to purchase drugs fraudulently
- Community pharmacies must be re-licensed by July 1, 2012


**Counterfeit-Proof Prescription Blanks/Pads**

- Resist erasures and reproductions
- Blue or green background ink that resists reproduction
- “VOID” or “ILLEGAL” when copied
- Preprinted name, address, & category of professional licensure of prescribing practitioner and space for DEA number
- List of security features and description
- Unique tracking identification number
- No advertisement on blank

Florida’s New Database

- Creation of prescription drug monitoring database program
- Live November 1, 2011
- E-FORCSE
  - Electronic-Florida Online Reporting of Controlled Substances Evaluation
- To discourage doctor shopping and overprescribing
- Reduction of timeframe for dispensers to report from 15 days to 7 days

Reporting Requirements

- Doctor’s name and DEA number
- Date prescription filled
- Method of payment
- Full name, address, and DOB of person obtaining the prescription
- Name, quantity, and dosage of controlled substance
- Name & address of pharmacy or office dispensing medication
- Number of refills authorized and whether first-time request from medical practitioner

Who Can Access Information

- Health care practitioners (pharmacists and physicians) registered with the DOH
- Requests to database’s program manager (PM) by
  - Appropriate medical regulatory board
  - Attorney General’s Medicaid Fraud Unit
  - Law enforcement
  - Patients
  - Department of Health
  - Implementation & Oversight Task Force

Benefits of E-FORCSE

- Physicians or pharmacist can access database for patients
  - To avoid drug interactions
  - To determine if doctor shopping
- Identification of potential illegal diversion pattern for drugs
  - Patient Activity Report (PAR) disseminated
- Allows law enforcement, medical regulatory board/Medicaid fraud unit to request information for an active investigation

Opposition to HB 7095

- Restricts small, independently owned retail pharmacies from filling narcotic prescriptions
- The cost of record keeping will drive local community pharmacists out of business
- Loss of quality of standard of care provided by independent pharmacies
- Inconvenience to patients in need of chronic pain management therapy

Patient Concerns

- Requirement of using state Health Department-approved prescription pads
- Approximately 50,000 licensed physicians prescribing controlled substances in Florida
- Fear of inability to obtain legitimate prescriptions
- Requirement suspended until August 29 by State Surgeon General Frank Farmer
Drug Treatment Center Concerns
- Centers prepare for influx of new patients seeking help to overcome addiction
- State treatment facilities already at capacity prior to bill’s passing
- Funding by Florida Department of Children and Families (DCF) of locally-based drug programs ~$215 million possibly no longer enough
- Assistance with drug addiction issues can call the South Florida hotline 211 (Ft. Lauderdale) or 305-358-HELP (Miami)

Internet Concerns
- Online drugstores remain for drug seekers
- “Foreign” drugstores having ties to the U.S.
- Social internet medias, web browsers used
- Rising purchases in the last year
- 1,000+ Rogue internet pharmacies vanish and reappear
- Many pill mills have Internet businesses established

Other Concerns
- Addicts turning to other drugs
- Increase in heroin use
  - Increase prescription drug prices -$15 from $8 per pill
  - Increase difficulty of obtaining prescription medications
- Increase crime rate
- Lag time of reporting to database
- Not required to check database before writing prescription or dispensing drug
- Smaller pharmacies difficulty reporting

Florida War on Pill Mills
- Organized Crime Drug Enforcement Task Force (OCDETF)
- Crackdown on Pill Mills
  - Operation Oxy Alley
  - Operation Pill Nation
  - Operation Snake Oil
  - Operation Juice Doctor 2
- DEA Pill Mill Tip Line

Case Presentation
- A patient comes into the pharmacy and presents a prescription for oxycodone. What should you do?
  - Check E-FORSCE
  - Evaluate prescription for fraud
  - Enter prescription into E-FORSCE
  - Bonus question: It is discovered that the prescription is fraudulent. What does the new law require a pharmacist to do?
  - Report to the sheriff within 24 hours after learning of fraud or attempt at fraud

True of False?
- The length of time pharmacies are given to report prescription information into the state drug database is 15 days
  - False, it was shortened from 15 days to 7 days.
- People who are looking for assistance with drug addiction issues can call the South Florida hotline
  - True, 211 (Ft. Lauderdale) or 305-358-HELP (Miami)
- The name of the new Florida drug database is called The Electronic Florida Online Reporting of Controlled Substances Evaluation
  - True, also known as E-FORSCE