Sizing up the pharmacist’s role in obesity management

GMCCP Spring Education Event
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Erin Newkirk, PharmD, BCPS, CDE
Tom Dilworth, PharmD
Nick Zupec, PharmD, BCPS
Medications in Weight Loss: When the goals aren't met despite the sweat

Erin Newkirk, Pharm.D. BCPS, CDE

Froedtert & the Medical College of Wisconsin
Objectives

- To describe the role of weight loss medications and appropriately select a weight loss agent based on co-morbid conditions
- To identify medications that are obesogenic and identify preferred alternatives that have less risk for weight gain
Pharmacist Role in Metabolic Clinic

Medically Supervised Weight Loss Clinic

- Provide education on weight loss pharmacological options
- Ensure safe and efficacious use of weight loss medications and minimize obesogenic medications
- Assist the care team with making progress towards therapeutic and lifestyle goals
- Discuss and refer patients for bariatric surgery
Obesity Treatment Pyramid

- Surgery
  - BMI 40+
  - BMI 35+ with comorbidities

- Pharmacotherapy
  - BMI 30+
  - BMI 27 with comorbidities

- Lifestyle Changes
  - BMI 30+
  - BMI 25+ with comorbidities

http://www.southcoast.org/pix/weightloss-obesity-pyramid.gif
Assessment Question 1

A 39 year old female presents to the metabolic clinic asking for assistance with weight loss. What is the patient’s weight loss option(s)?

Today’s Vitals: Weight: 249 lbs  BMI: 42.7

a. Lifestyle changes
b. Weight loss medications
c. Bariatric surgery
d. All of the above
1.2 In order to promote long-term weight maintenance, we suggest the use of approved weight loss medication (over no pharmacological therapy) to ameliorate comorbidities and amplify adherence to behavior changes, which may improve physical functioning and allow for greater physical activity in individuals with a BMI $\geq 30$ kg/m$^2$ or in individuals with a BMI of $\geq 27$ kg/m$^2$ and at least one associated comorbid medical condition such as hypertension, dyslipidemia, type 2 diabetes (T2DM), and obstructive sleep apnea.
FDA Requirements For Weight Loss Agent Approval

1. Statistically significant difference in weight loss between med and placebo
   – Mean absolute different of ≥ 5%

2. At least 35% of subjects receiving med experience ≥ 5% weight loss

3. Proportion of patients experiencing weight loss in the intervention group is ~double that in the placebo group

4. Multiple safety evaluations
Current FDA-approved Agents

• CNS activity
  – Phentermine
    • Short-term therapy only
  – Phentermine/topiramate ER (Qsymia®)
  – Naltrexone/bupropion (Contrave®)
  – Lorcaserin (Belviq®)
  – Liraglutide (Saxenda®)

• Peripheral activity
  – Orlistat (Xenical®, Alli®)
CNS activity

• Appetite Suppressant
  – Phentermine
  – Phentermine/topiramate ER

• Enhance satiety
  – Phentermine/topiramate ER
  – Lorcaserin
  – Liraglutide

• Reduce cravings
  – Naltrexone/bupropion

http://www.realize.com/education/understanding-metabolic-health
Phentermine

- Mechanism of action
  - Amphetamine derivative: increases NE release in hypothalamus

- Dose
  - 15-37.5mg daily given in 1-2 divided doses
  - Lowest effective dose

- Dosage adjustments
  - Caution in patients with renal impairment (may increase exposure)
  - Hepatic impairment: no dosage provided (has not been studied)

- Monitoring parameters
  - BP and HR at least monthly
Phentermine Evidence

- 36 week placebo-controlled study with 108 overweight or obese outpatients in 1968
  - Phentermine group: 20.6% weight loss
    - Mean 12.2 kg weight loss
  - Placebo group: 7.6% weight loss
    - Mean 4.8 kg weight loss

# Phentermine STEPS

| Safety | • CVD (CAD, stroke, arrhythmias, CHF, uncontrolled HTN)  
• Hyperthyroidism  
• Glaucoma  
• Drug abuse  
• Schedule IV—risk for dependence |
|---|---|
| Tolerability | • CV: Elevated blood pressure, palpitations, tachycardia, dizziness  
• GI: constipation, diarrhea  
• Neurological: insomnia, overstimulation, restlessness  
• Other: headache, xerostomia, unpleasant taste |
| Efficacy | Average 5-8 lbs weight loss |
| Preference | • Short-term (≤12 weeks) therapy  
• Appetite suppression |
| Simplicity | • Cost <$1.50 per day  
• Take in the AM before or 1-2 hours after breakfast  
• Many tablet/capsule strengths available: 15-37.5 mg |


Phentermine/Topiramate ER (Qsymia®)

- Topiramate is an antiepileptic: enhances GABA activity, amongst other mechanisms decreasing neurogenic activity
  - Exact weight loss MoA unclear

- Four different capsule strengths for titrating
  - Dose adjustment for moderate/severe renal impairment and/or moderate hepatic impairment
  - Fillable only at certified retail pharmacies

To begin, write 2 prescriptions:
- 14 days on starting dose (3.75 mg/23 mg)
- 30 days on recommended dose (7.5 mg/46 mg)
- Once daily, in the morning, with or without food

STARTING 3.75 mg/23 mg
RECOMMENDED 7.5 mg/46 mg
TITRATION 11.25 mg/69 mg
TOP 15 mg/92 mg
Phentermine/Topiramate ER (Qsymia®) Evidence

- 56-week randomized, double-blind, placebo-controlled with overweight or obese patients with 2+ co-morbidities

<table>
<thead>
<tr>
<th></th>
<th>Placebo</th>
<th>Qsymia 7.5/46 mg</th>
<th>Qsymia 15/92 mg</th>
</tr>
</thead>
<tbody>
<tr>
<td>n</td>
<td>979</td>
<td>488</td>
<td>981</td>
</tr>
<tr>
<td>Mean % wt loss</td>
<td>-1.2%</td>
<td>-7.8%</td>
<td>-9.8%</td>
</tr>
<tr>
<td>Difference from placebo (95% CI)</td>
<td>6.6 kg (5.8-7.4)</td>
<td>8.6 kg (8.0-9.3)</td>
<td></td>
</tr>
<tr>
<td>Proportion losing ≥5%</td>
<td>21%</td>
<td>62%</td>
<td>70%</td>
</tr>
<tr>
<td>Proportion losing ≥10%</td>
<td>7%</td>
<td>37%</td>
<td>48%</td>
</tr>
</tbody>
</table>

31% of patients withdrew from study prior to week 56

Phentermine/Topiramate ER (Qsymia®) STEPS

Safety

- CV: Tachycardia
- Pregnancy (teratogenic)—REMS
- Glaucoma
- Hyperthyroidism
- Depression, mood/sleep disorders
- Avoid alcohol due to risk of CNS depression
- Hyperthermia
- Withdrawal: taper off high dose to reduce seizure risk
- Schedule IV—risk for dependence

Tolerability

Paraesthesia, dizziness, change in taste, insomnia, constipation, dry mouth

Efficacy

Average 20 lbs weight loss

Preference

- Long term/Chronic weight loss management, as adjunct to diet and exercise
- Appetite suppression

Simplicity

- Cost ~$7 per day
- Take in the AM without regards to meals
- Do not crush/chew

Naltrexone/bupropion ER
(Contrave®)

• Naltrexone 8 mg: pure opioid antagonist
• Bupropion 90 mg: weak inhibitor of dopamine and NE reuptake
• Titrate at weekly intervals from 1 tablets once daily to 2 tablets twice daily over 4 weeks
  – Dosage adjustments
    • CrCl <30 ml/min: maximum daily dose is 1 tablet BID; avoid in ESRD
    • Hepatic impairment: maximum daily dose is 1 tablet qAM

Naltrexone/bupropion ER (Contrave®)

• Drug-drug interactions
  – Opiates
  – Bupropion is metabolized by CYP2B6
    • 2B6 inducers: ritonavir
    • 2B6 inhibitors: ticlopidine, clopidogrel
  – Bupropion and its metabolites inhibit CYP2D6
    • 2D6 substrates: Beta-blockers, SSRIs, SNRIs, TCAs, Antipsychotics
Naltrexone/bupropion ER (Contrave®) Evidence

- 56-week randomized, double-blind, placebo-controlled with overweight or obese patients with ≥1 co-morbidities

<table>
<thead>
<tr>
<th></th>
<th>Placebo</th>
<th>Contrave</th>
</tr>
</thead>
<tbody>
<tr>
<td>n</td>
<td>536</td>
<td>538</td>
</tr>
<tr>
<td>Mean % wt loss</td>
<td>-1.3%</td>
<td>-5.4%</td>
</tr>
<tr>
<td>Difference from placebo (95% CI)</td>
<td>-4.1 kg (4.9, -3.3)</td>
<td>(-</td>
</tr>
<tr>
<td>Proportion losing ≥5%</td>
<td>17%</td>
<td>42%</td>
</tr>
<tr>
<td>Proportion losing ≥10%</td>
<td>7%</td>
<td>21%</td>
</tr>
</tbody>
</table>

50.1% of placebo and 49.2% of Contrave patients withdrew from study prior to week 56.
## Naltrexone/bupropion ER (Contrave®) STEPS

| Safety                  | • Uncontrolled HTN  
|                        | • Seizure disorder or history of seizures  
|                        | • Anorexia nervosa or bulimia  
|                        | • Chronic opioid use  
|                        | • Suicidal behavior and ideation (Black Box Warning)  
|                        | • Worsening of depression, anxiety, and sleep disorders  
|                        | • Drug interactions  
| Tolerability           | • GI: Nausea, Vomiting, Constipation, Diarrhea  
|                        | • Headache, Dizziness, Insomnia, Dry mouth  
| Efficacy               | Average weight loss ~9 lbs  
| Preference             | • Long term/chronic weight loss management, as adjunct to diet and exercise  
|                        | • Craving suppression  
| Simplicity             | • Costs ~$7 per day  
|                        | • Twice daily administration, requires titration  
|                        | • Do not administer with high-fat meal  
|                        | • Do not crush/chew  

Lorcaserin (Belviq®)

• 5-HT$_{2C}$ receptor agonist
  – Hypothalamus
  – Decreased food consumption and promotes satiety
• Exhibits 100 times greater affinity for 5-HT$_{2C}$ receptors than for 5-HT$_{2B}$ receptors
• Dose: 10 mg tablet BID
  – Adjustments
    • CrCl 30-50 ml/min: caution (increased exposure); CrCl <30 ml/min: avoid
    • Cirrhosis Child’s Pugh A/B: no adjustment; Child’s Pugh C: avoid
Lorcaserin (Belviq®) Evidence

- 52-week randomized, double-blind, placebo-controlled with overweight or obese patients with ≥1 co-morbidities

<table>
<thead>
<tr>
<th></th>
<th>Placebo</th>
<th>Belviq</th>
</tr>
</thead>
<tbody>
<tr>
<td>n</td>
<td>3038</td>
<td>3098</td>
</tr>
<tr>
<td>Mean % wt loss</td>
<td>-2.5%</td>
<td>-5.8%</td>
</tr>
<tr>
<td>Difference from placebo (95% CI)</td>
<td>-3.3 kg (-3.6, -3.0)</td>
<td></td>
</tr>
<tr>
<td>Proportion losing ≥5%</td>
<td>22.6%</td>
<td>47.1%</td>
</tr>
<tr>
<td>Proportion losing ≥10%</td>
<td>8.7%</td>
<td>22.4%</td>
</tr>
</tbody>
</table>

50% of patients withdrew from study prior to week 52
# Lorcanerin (Belviq®) STEPS

| Safety | • Pregnancy  
|        | • Serotonin syndrome (very low incidence)  
|        | • Depression or suicidal ideation  
|        | • Valvular heart disease (theoretical; $5\text{-HT}_2\text{C} >> 5\text{-HT}_2\text{B}$)  
|        | • Schedule IV  
|        | • Monitor CBC periodically (decreased WBC, Hgb)  |
| Tolerability | Headache, dizziness, fatigue, nausea, dry mouth, and constipation  |
| Efficacy | Averages ~7 lbs weight loss  |
| Preference | • Long term/Chronic weight loss management, as adjunct to diet and exercise  
|          | • Promotes satiety  |
| Simplicity | • Costs ~$7 per day  
|          | • Twice daily administration  
|          | • With or without food  |
Liraglutide (Saxenda®)

• Glucagon-like peptide-1 (GLP-1) analog
  – Increases glucose-dependent insulin secretion
  – Decreases inappropriate glucagon secretion
  – Slows gastric emptying

• Titrate at weekly intervals from 0.6 mg to 3 mg SQ daily over 5 weeks
  – Dosage adjustments
    • <50 ml/min: caution (limited experience, no adjusted provided by manufacturer)
    • Hepatic impairment: caution (limited experience, no adjusted provided by manufacturer)
Liraglutide (Saxenda®) Evidence

- 56-week randomized, double-blind, placebo-controlled with overweight or obese patients with ≥1 co-morbidities

<table>
<thead>
<tr>
<th></th>
<th>Placebo</th>
<th>Saxenda</th>
</tr>
</thead>
<tbody>
<tr>
<td>n</td>
<td>1244</td>
<td>2487</td>
</tr>
<tr>
<td>Mean % wt loss</td>
<td>-3.0</td>
<td>-7.4</td>
</tr>
<tr>
<td>Difference from placebo (95% CI)</td>
<td>-4.5 kg (-5.2; -3.8)</td>
<td></td>
</tr>
<tr>
<td>Proportion losing ≥5%</td>
<td>34.4%</td>
<td>62.3%</td>
</tr>
<tr>
<td>Proportion losing ≥10%</td>
<td>15.4%</td>
<td>33.9%</td>
</tr>
</tbody>
</table>

27% of Saxenda & 35% of placebo patients withdrew from study prior to week 56.
# Liraglutide (Saxenda®) STEPS

| Safety                  | • Unknown risk of medullary thyroid carcinoma (MTC) in humans *(Black Box Warning)*  
|                        | • Personal or family history of medullary thyroid carcinoma or Multiple Endocrine Neoplasia syndrome type 2 *(Black Box Warning)*  
|                        | • Acute pancreatitis (0.3%)  
|                        | • Jaundice and acute hepatitis (post-marketing)  
|                        | • Renal impairment (post-marketing) |
| Tolerability           | • GI: nausea, diarrhea, constipation, vomiting, decreased appetite, dyspepsia, abdominal pain  
|                        | • Other: fatigue, dizziness, headache, hypoglycemia |
| Efficacy               | • Average 10 lbs weight loss |
| Preference             | • Long term/Chronic weight loss management, as adjunct to diet and exercise  
|                        | • Appetite suppressant & promotes satiety  
|                        | • Pre-diabetes |
| Simplicity             | • Subcutaneous injection once daily  
|                        | • Requires weekly titration  
|                        | • Costs ~$40 per day |

Peripheral activity: Orlistat

- MoA:
  - Reversible inhibitor of gastric and pancreatic lipases, inhibiting absorption of dietary fats by 30%
  - Not systemically absorbed, mechanism located in gut

- Dosing: 1 tablet TID with meals that contain fat
  - Xenical: one tab contains 120 mg orlistat
  - Alli: one tab contains 60 mg orlistat

http://www.realize.com/education/understanding-metabolic-health
## Orlistat STEPS

<table>
<thead>
<tr>
<th>Safety</th>
<th>Chronic malabsorption syndrome (prior RYGB surgery)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Cholestasis</td>
</tr>
<tr>
<td></td>
<td>Acute hepatic failure (rare)</td>
</tr>
<tr>
<td></td>
<td>Kidney stones (rare)</td>
</tr>
<tr>
<td></td>
<td>Drug interactions</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Tolerability</th>
<th>Oily spotting, flatus with discharge, fecal urgency, fatty/oily stool, oily evacuation, increased defecation, fecal incontinence</th>
</tr>
</thead>
</table>

<table>
<thead>
<tr>
<th>Efficacy</th>
<th>Average 7.5 lbs weight loss</th>
</tr>
</thead>
</table>

<table>
<thead>
<tr>
<th>Preference</th>
<th>Long term/chronic weight loss management, as adjunct to diet and exercise</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No effect on appetite</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Simplicity</th>
<th>Xenical (Rx): ~$16 per day</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Alli (OTC): $1.50 per day</td>
</tr>
<tr>
<td></td>
<td>Take up to 1 hour after each meal containing fat</td>
</tr>
</tbody>
</table>

Comparisons of available agents
## Pharmacological Management of Obesity

<table>
<thead>
<tr>
<th>Medication Class</th>
<th>Associated with Weight Gain</th>
<th>Preferred Alternatives</th>
</tr>
</thead>
<tbody>
<tr>
<td>Antidiabetic medications</td>
<td>Insulin, Sulfonylureas, Metglitinides (Repaglinide &gt; Nateglinide), Thiazolidinedione</td>
<td>Metformin, GLP-1 analogs, DPP-4 inhibitors, α-glucosidase inhibitors, SGLT-2 inhibitors</td>
</tr>
<tr>
<td>Antihypertensive agents</td>
<td>Propranolol, Metoprolol</td>
<td>ACE-I/ARB, CCB, Carvedilol, Nebivolol</td>
</tr>
<tr>
<td>Antidepressants</td>
<td>Paroxetine, Sertraline, Citalopram, Esitalopram, Amitriptyline, Nortriptyline, Doxepin, Desipramine, Mirtazapine, Venlafaxine, Duloxetine, phenelzine</td>
<td>Bupropion</td>
</tr>
<tr>
<td>Antipsychotics</td>
<td>Clozapine, Olanzapine, Quetiapine, Risperidone, Perphenazine</td>
<td>Ziprasidone, Aripiprazole, Lurasidone, Amisulpiride</td>
</tr>
<tr>
<td>Antiepileptics</td>
<td>Gabapentin, Pregabalin, Valproic acid, Vigabatrin, Carbamazepine, Lithium</td>
<td>Felbamate, Topiramate, Zonisamide, Lamotrigine, Levetiracetam, Phenytoin</td>
</tr>
<tr>
<td>Contraception</td>
<td>Depo-Provera injectable (high effectiveness in obese)</td>
<td>Copper IUD, Levonorgestrel IUD (Mirena), Etonogesterol implant (Nexplanon), combined hormone pill, progestin-only pill</td>
</tr>
<tr>
<td>Inflammatory Disease (e.g., rheumatoid arthritis)</td>
<td>Corticosteroids</td>
<td>NSAIDs, Disease-modifying Antirheumatic drugs</td>
</tr>
<tr>
<td>Antihistamines</td>
<td>1st generation</td>
<td>2nd generation</td>
</tr>
</tbody>
</table>

Patient Case

• Encounter #1:
• 39 y/o female with HTN, depression, osteoarthritis of both knees, tobacco use, and morbid obesity
• Presents to you in the your clinic asking for assistance with weight loss
Patient Case

• Today’s Vitals:
  – Weight: 249 lbs
  – BMI: 42.7
  – BP: 138/79
  – Pulse: 92 bpm

• Today’s Labs:
  – Creatinine: 0.8 mg/dL
  – A1c: 5.9%
  – TSH: 1.66

• Medications
  – amlodipine 10 mg once daily
  – **fluoxetine 80 mg once daily**
  – hydrocodone/APAP 5/325 mg 1-2 tablets q6 hr prn
  – Lisinopril/hydrochlorothiazide 20/25 mg once daily
  – Zyban® 150 mg BID

• Which of the following weight loss medications would be *most* appropriate for this patient?
  a) Qsymia (phentermine/topiramate)
  b) Belviq (locaserin)
  c) Contrave (bupropion/naltrexone)
  d) Saxenda (liraglutide)
Patient Case

• Encounter #2:
  • Patient returns 1 month later with 8 pound weight loss, but not tolerating the Saxenda, complaining of intolerable occasional nausea and vomiting, currently taking 2.4 mg daily.

• Of note you also started carvedilol 12.5 mg BID since last visit.
Patient Case

• Vitals:
  – Weight: 241 lbs
  – BMI: 41.4
  – BP: 130/82
  – Pulse: 60 bpm

• You decide to discontinue Saxenda and start Qsymia

• What should be addressed during the visit?
  a) Contraception
  b) Increased risk of seizure
  c) Dispensing pharmacy restriction
  d) a & c
  e) All of the above
Summary

• Escalate obesity treatment based on BMI
• The building blocks to weight loss
  – Calorie-deficient diet
  – Health-enhancing physical activity
• Weight loss medications are preferred over no therapy in obese patients when indicated
• Individualize treatment based on comorbid conditions and concurrent medications
Antimicrobial Dosing in Obesity

Tom Dilworth, PharmD
May 10th, 2017

thomas.dilworth@aurora.org
Disclosure

- I have no conflicts of interest to disclose.
Objectives

• Understand how obesity can alter antimicrobial pharmacokinetics
• Describe strategies to improve antimicrobial dosing precision in obese patients
Obesity

- **Overweight** refers to an excess amount of body weight that may come from muscles, bone, fat, and water.
- **Obesity** refers to an excess amount of body fat.

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

<table>
<thead>
<tr>
<th>Classification</th>
<th>BMI Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal weight</td>
<td>18.5 to 24.9</td>
</tr>
<tr>
<td>Overweight</td>
<td>25 to 29.9</td>
</tr>
<tr>
<td>Obesity</td>
<td>30 +</td>
</tr>
<tr>
<td>Extreme obesity</td>
<td>40 +</td>
</tr>
</tbody>
</table>
BMI and Other Obesity “Metrics”

- We have no accurate, reliable measure of adiposity and adiposity distribution
- BMI, IBW, Adjusted BW, etc. all rely on patient height

I’m 5’7” and 155 lbs. My BMI is 24.3 (“normal”)

If I gained 5 lbs of muscle at the gym my BMI would be 25.1 (overweight)
Obesity across the U.S.

Leanest State: Colorado 21.0%

Fattest State: Mississippi 35.1%

Percentage of Obese Adult Population (3-year average from 2012-14 CDC Behavioral Risk Factor Surveillance System data)

CalorieLab's United States of Obesity 2015

Antimicrobial Dosing in Obesity Data

• Generally **POOR**

• Obesity is not a special population requiring Phase I PK studies to define dosing
  – Guidelines for comparing obese to non-obese patients in post-marketing Phase III studies do not exist

• Often hard to apply available literature to specific patients for whom you are caring
  – Anecdotes, case series, healthy PK studies, etc.

• **Use broad concepts and ideas to inform decisions**
Obesity in Antimicrobial Clinical Trials

Percentage of Patients in Clinical Trials with BMI ≥ 30

Dalbavancin: 71.8% had BMI ≥ 25

- Ceftaroline: 26.5%
- Ceftolozane/Tazobactam: 23.6%
- Isavuconazole: 10.8%
- Oritivancin: 28.4%
- Tedezolid: 29.8%

U.S. Food and Drug Administration. Drugs@FDA. Available at: https://www.accessdata.fda.gov/scripts/cder/daf/index.cfm
Obesity in Antimicrobial Clinical Trials

- **Varbobactam, Phase I**
  - Median BMI (range):
    - Single dose: 24.55 (19.0 – 29.6)
    - Multiple doses: 25.5 (19.1 – 29.8)

- **Ceftazidime/Avibactam, cIAI**
  - Mean BMI ±SD: 24.4 ± 5.2

- **Plazomicin, Phase I**
  - Mean BMI (range): 24.16 (19.3 – 29.1)

- **Telavancin, HAP/VAP**
  - Mean BMI ±SD: 24.8 ± 5.69

4. Drugs@FDA. Available at: https://www.accessdata.fda.gov/scripts/cder/daf/index.cfm
Current Drug Dosing Paradigm

• Drugs are generally dosed according one or more strategies:
  – Fixed dosing: Levofloxacin 750mg
  – Weight-stratified, fixed dosing: Ribavirin
  – Weight-based dosing: Aminoglycosides
  – Body surface area-based dosing: Anti-neoplastics
  – “Mixed” dosing: Vancomycin

• Dosing on body weight or BSA assumes that drug PK parameters increase proportionally with body size...fixed dosing does not.

Obesity PK Changes

- CL: can increase but not more than 50%
  - Not proportional to body size
  - Increased kidney size and GFR
- Vd: will increase; relevance depends on the drug
  - Tigecycline (Vd 7-9L/kg) will leave the serum regardless of body size
- Hepatic metabolism: changes due to obesity not well characterized
PK/PD Refresher

Cmax

Cmax/MIC (aminoglycosides and fluoroquinolones)

AUC/MIC (vancomycin, azithromycin, fluoroquinolones, aminoglycosides, tigecycline and linezolid)

T>MIC (β-lactams, vancomycin, macrolides, clindamycin)

AUC

Antibiotic serum concentration

Time after antibiotic administration

MIC
PK/PD Considerations in Obesity

• $C_{\text{max}} = \frac{\text{dose}}{\text{Vd}}$
  – Relationship of Vd to body size is most relevant

• $\text{AUC} = \frac{\text{dose}}{\text{CL}}$
  – Relationship of CL to body size most relevant

• Vd increase in obesity w/o change in CL will lower $C_{\text{max}}$ but will not sig. change AUC

• Time-dependent: CL and Vd both impact time above MIC
  – Increased CL = decreased time $> \text{MIC}$
  – Increased Vd = decreased time $> \text{MIC}$
  – Often you “catch up” with maintenance doses
Time Dependent Antibiotic Exposure

Hypothetical Time Dependent Antibiotic Exposure

- Concentration (mg/L)
- Time (hours)

Graph showing the concentration over time for different groups:
- Blue line: Non-obese
- Red line: Obese
**Time Dependent Antibiotic Exposure**

Hypothetical Time Dependent Antibiotic Exposure

Larger first dose (e.g. load or weight-based using ABW)
Initial Dose in Obesity

• “Allometry”...
• Obese dose = avg. dose \( \frac{\text{pt wt}}{\text{avg wt}} \) \( \beta \)
  – \( \beta \): 0.5-0.75

60-90kg
*Reference

120-180kg
Reference x2

180-270kg
Reference x3

“Normal” dose

150% “Normal”

200% “Normal”

Vancomycin – How Do You Dose It?

- Lack of pharmacy consensus\(^1\)
- Current guidelines recommend weight-based dosing\(^2\) but package insert says fixed\(^3\)
- AUC drives efficacy (Dose \(\div\) CL) so why do we dose upon weight?

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**TABLE 1. New AUC Vancomycin Dosing Chart Based on CrCl Estimated by the\(^7\) Formula of Matzke et al.**

<table>
<thead>
<tr>
<th>Complicated Infection(^4), Target: AUC(<em>{24})/MIC (\geq 100)(^5), (C</em>{Trough}) (= 15-20) mg/L</th>
<th>Vancomycin AUC Dosing Chart to Initiate Therapy*</th>
</tr>
</thead>
<tbody>
<tr>
<td>CrCl(\text{in} / \text{min})^(\dagger)</td>
<td>High-Dose Regimen</td>
</tr>
<tr>
<td>(\approx 175)</td>
<td>1250 mg q6h</td>
</tr>
<tr>
<td>155–174</td>
<td>1000 mg q6h</td>
</tr>
<tr>
<td>100–134</td>
<td>750 mg q6h</td>
</tr>
<tr>
<td>85–99</td>
<td>750 mg q8h</td>
</tr>
<tr>
<td>65–84</td>
<td>500 mg q6h</td>
</tr>
<tr>
<td>45–64</td>
<td>500 mg q8h</td>
</tr>
<tr>
<td>30–44</td>
<td>500 mg q12h</td>
</tr>
</tbody>
</table>

*This chart is intended to determine starting empiric dosing regimen based on vancomycin population pharmacokinetics.

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Estimating Vancomycin Exposure in Obese Patients (n=12)

- Median BMI 45 kg/m² (40 - 52)
- Five PK concentrations were measured and 4 pop PK models were used to estimate AUC (AUC\textsubscript{FULL})
- Data-depleted PK subsets were used to estimate the 24-hour AUC
  - Peak and trough data [AUC\textsubscript{PT}]
  - Midpoint and trough data [AUC\textsubscript{MT}]
  - Trough only data [AUC\textsubscript{T}]
- AUC\textsubscript{PT} provided the best approximation of the AUC\textsubscript{FULL}
- AUC\textsubscript{MT} and AUC\textsubscript{T} overestimated AUC\textsubscript{FULL}
Estimating CL in Obesity

• CL does not increase proportional to body size
  – Think allometry again
• CrCl is an imperfect estimate of CL
• What other ways can we determine true clearance?
• What data support increasing the dose for augmented renal clearance?
Other Agents

- Linezolid: Obesity impacts exposure but 600mg BID is likely sufficient up to 150kg\textsuperscript{1}
- Voriconazole: should dose on adjusted BW\textsuperscript{2}
  - Crucial for CYP2C19 poor metabolizers or omeprazole
  - Often less of an issue given populations in which we use
- Acyclovir: adjusted BW may be more precise than IBW for obesity\textsuperscript{3}
  - Exposure IBW\textsubscript{Obese} < Exposure ABW\textsubscript{Non-obese}
- Ganciclovir and Foscarnet: adjusted BW\textsuperscript{4}
  - Hydrophilic, risk of nephrotoxicity & bone marrow toxicity

Case

AA is a 46yo male patient presenting to the ED in extremis likely secondary to a non-healing lower extremity wound. His past medical history is significant for COPD, type II diabetes, hypothyroidism, obesity and recent hospitalization for the same wound from which MRSA was recovered (vancomycin MIC 2mg/L).

He is 5’9” and weights 129kg (current BMI 42kg/m²; ideal. He is given 30cc/kg of crystalloid, started on vasopressive support with norepinephrine, intubated for airway protection, and admitted to the intensive care unit. Today his CrCl is estimated to be 83mL/min.

Broad-spectrum antibiotic therapy was initiated in the ED: daptomycin 8mg/kg (adjusted body weight) Q24h, piperacillin-tazobactam 4.5g IV Q8hours over 4 hours and tobramycin (pharmacy to dose).
Case continued

You elect to give 7mg/kg tobramycin x 1 based upon an adjusted body weight (650mg) and you order to levels. Your peak is 18.1mg/L (1-hour post infusion) and your random 12 hours later is 7.5mg/L. You then calculate the following tobramycin PK for AA:

\[
Ke=0.073\text{hr}^{-1}, \text{ half-life } 9.5\text{hours}, C_{\text{max}} 19.5\text{mg/L}, \\
V_d 33.3L (0.25L/kg), \textbf{clearance 2.4L/hour (40mL/min)}
\]

On day 2 gram-positive cocci in clusters are recovered from a BAL and the \textit{meca} PCR test is positive. His \underline{creatinine clearance on hospital day 2} is estimated to be 71mL/min. The ICU team wishes to start linezolid.
Which of the following statements is most appropriate related to administering linezolid to AA for MRSA pneumonia?

a) Linezolid exposure is reduced in obese patients compared to non-obese patients and AA should receive a linezolid dose of 600mg IV Q8 hours.

b) Linezolid is duplicative anti-MRSA therapy and should not be administered to AA. Daptomycin will suffice for AA.

c) Linezolid exposure in obese patients is similar to linezolid exposure in non-obese patients up to approximately 150kg and AA should receive a linezolid dose of 600mg IV Q12hours.

d) There are insufficient data to guide a linezolid dosing recommendation for AA. He should be given either high-dose, intravenous trimethoprim-sulfamethoxazole or intravenous telavancin.
Key clinical takeaways

• We don’t have a good measure of “obesity” and adipose distribution
• We don’t have good data for antimicrobial dosing in obesity
• Understand PD parameters of each agent and apply obesity PK alterations to inform dosing
• For serious infections one must weigh the risk of under-dosing against the risk of toxicity
thomas.dilworth@aurora.org
Considerations for weight when we anticoagulate

Nick Zupec, PharmD, BCPS

GMCCP Spring Education Event
May 10th, 2017
Objectives

At the end of this presentation, participants should be able to:

• Select appropriate doses of injectable and oral anticoagulants for obese patient populations.

• Recommend appropriate monitoring for injectable and oral anticoagulants for obese patient populations.
Disclosures

• The speaker has no actual or potential conflicts of interests to disclose
Disclaimer

• Limited data in this area
  – Often excluded from clinical trials
  – Available data is low quality
  – Many studies retrospective, low “n”s
  – Variable or contradictory results
Obesity can affect the PK/PD of different medications

Are obese patients at an increased risk of developing clots?
Risk of developing a blood clot

Air travel passengers sitting in a window seat compared to sitting in an aisle seat\(^1\)

- Normal body weight (BMI < 25 kg/m\(^2\)) – OR 2.2
- Overweight patients (BMI 25-29.9 kg/m\(^2\)) – OR 2.6
- Obese patients (BMI > 30 kg/m\(^2\)) – OR 6.1

Chest guidelines list severe obesity as a risk factor for VTE\(^2\)

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Obesity as a risk factor

Obesity versus normal body weight³

- DVT: RR 2.50; 95% CI 2.49-2.51
- PE: RR 2.18; 95% CI 2.16-2.19

The relationship is fairly linear with increasing body weight⁴

The effect is larger at lower ages

Box 1. Proposed thrombotic mechanisms in obesity

Enhanced platelet activity
- Adipokines (leptin, adiponectin)
- Insulin resistance
- Low-grade inflammation
- Stasis resulting in UL-vWF

Procoagulant state
- Increased tissue factor
- Increased fibrinogen, factor VII and factor VIII
- Increased thrombin generation

Impaired fibrinolysis
- Overproduction of PAI-1 and TAFI

Activation of endothelial cells
- Tissue hypoxia

PAI-1: Plasminogen activator inhibitor-1; TAFI: Thrombin-activatable fibrinolysis inhibitor; UL-vWF: Ultra-large von Willebrand factor.
Prevention vs. treatment

Prevention: oz
Cure: lb
Unfractionated Heparin (UFH)

• Fixed dosing
• Typical dosing: 5000 units subcut Q8-12H
• Studies show that obese patients receiving this dose are at a higher risk of developing a clot than normal body weight patients

• Guideline recommendations
  – CHEST Guidelines
  – American Society for Metabolic and Bariatric Surgery Guidelines
  – Anyone

Enoxaparin

- Fixed dosing
- Typical dosing: 40 mg subcut daily or 30 mg subcut Q12H
- PK/PD studies show that anti-Xa levels are inversely proportional to BMI\textsuperscript{6}
- Similar findings in studies with higher incidence of thrombosis in obese patients\textsuperscript{7,8}

8.10 Obese Patients\textsuperscript{9}

Obese patients are at higher risk for thromboembolism. The safety and efficacy of prophylactic doses of Lovenox in obese patients (BMI >30 kg/m\textsuperscript{2}) has not been fully determined and there is no consensus for dose adjustment. These patients should be observed carefully for signs and symptoms of thromboembolism.

\textsuperscript{6} Frederiksen SG, Hedenbro JL, Norgren L. Enoxaparin effect depends on body-weight and current doses may be inadequate in obese patients. Br J Surg. 2003;90:547-8
High dose thromboprophylaxis

• Large retrospective cohort study with 9241 patients\textsuperscript{10}
• Obese = weight >100 kg and BMI $\geq$ 40 kg/m$^2$
• High intensity prophylaxis
  – Heparin 7500 mg subcut Q8H
  – Enoxaparin 40 mg subcut Q12H

<table>
<thead>
<tr>
<th></th>
<th>Standard prophylaxis</th>
<th>High dose prophylaxis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rate of VTE</td>
<td>1.48%</td>
<td>0.77% (p=0.047)</td>
</tr>
<tr>
<td>Bleeding</td>
<td>8.44%</td>
<td>7.18% (p=0.15)</td>
</tr>
</tbody>
</table>

• BMI was an independent predictor of VTE (as was male patients, surgery, and cancer)

Enoxaparin

- Different approaches\(^4,7,8,10,11\)

<table>
<thead>
<tr>
<th></th>
<th>Pros</th>
<th>Cons</th>
</tr>
</thead>
<tbody>
<tr>
<td>40 mg subcut Q12H</td>
<td>• More validated in clinical trials</td>
<td>• Fixed dose</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0.5 mg/kg Q12H</td>
<td>• Supported by anti-Xa levels</td>
<td>• Based PK/PD data</td>
</tr>
<tr>
<td></td>
<td>• Takes into account the spectrum of obesity</td>
<td>• Requires calculations</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Fixed syringe sizes</td>
</tr>
</tbody>
</table>

Enoxaparin

• Scholten, et al. ¹¹
• 481 bariatric surgery patients

<table>
<thead>
<tr>
<th></th>
<th>30 mg Q12H (n=92)</th>
<th>40 mg Q12H (n=389)</th>
<th>P values</th>
</tr>
</thead>
<tbody>
<tr>
<td>BMI</td>
<td>51.7</td>
<td>50.3</td>
<td>NS</td>
</tr>
<tr>
<td>VTE incidence</td>
<td>1.4% (n=5)</td>
<td>0.6% (n=2)</td>
<td>p &lt; 0.01</td>
</tr>
<tr>
<td>Clinically relevant bleeding</td>
<td>1.09% (n=1)</td>
<td>0.26% (n=1)</td>
<td>NS</td>
</tr>
</tbody>
</table>

Thromboprophylaxis controversies

• What about BMI 30-40 kg/m²?

• What about BMI ≥ 50 kg/m²?

• What about fondaparinux?
Assessment question #1

JP is a 62 y/o female hospitalized for a diabetic foot infection. She is not currently ambulating due to extreme pain in her left foot. Which dose of enoxaparin is most appropriate for VTE prevention while in the hospital? Weight: 174 kg, CrCl 48, BMI 62

A. 40 mg daily
B. 30 mg Q12H
C. 40 mg Q12H
D. 170 mg Q12H
Prevention vs. treatment
Primary treatment options

- Heparin
- LMWH
- Warfarin
- DOACs
  - Dabigatran
  - Rivaroxaban
  - Apixaban
  - Edoxaban
Unfractionated heparin

• Dosing is already weight based (since mid 1990s)\textsuperscript{12}
  – Controversy: what weight?
• Regular monitoring with PTT or anti-Xa levels
• However, failure to achieve therapeutic PTT within 24 hours increases the chance of recurrence\textsuperscript{13,14}
• Obese patients often take longer to get to therapeutic range\textsuperscript{15}
• Controversy: Should we use dose capping?

Unfractionated heparin

• Studies have shown that non-capped heparin protocols based on actual body weight help patients achieve therapeutic PTT faster\textsuperscript{16}

• Study at the Mayo clinic
  – Initial PTT was higher as BMI increased
  – No significant difference in proportion of patients therapeutic at first PTT check among different BMI groups
  – No difference in bleeding

Enoxaparin

• Typical treatment dosing
  – 1 mg/kg subcut Q12H
  – 1.5 mg/kg subcut Q24H

• No recommendations for treatment dosing in obesity in the Prescribing Information

• Controversy: Should dose capping be considered to decrease bleeding risk?
Enoxaparin

• For obese patients, dosing should be based off of actual body weight and should not be capped.\textsuperscript{17}

• Twice daily dosing should be encouraged in obese patients.
  – More stable drug levels
  – Easier to monitor if needed
  – Maximum syringe size 150 mg

• Patients greater than \textasciitilde190 kg have not been represented in clinical trials

• In patients \textasciitilde 190 kg, factor Xa monitoring is recommended\textsuperscript{18}


Assessment question #2

JP develops a new onset PE. Which dose of enoxaparin is most appropriate for her now?

Weight: 174 kg, CrCl 48, BMI 62

A. 40 mg daily
B. 40 mg Q12H
C. 150 mg Q12H
D. 170 mg Q12H
Anti-Xa monitoring

- Peak level should be monitored\(^{19,20}\)
  - 3-4 hours after dose for BID dosing
  - 4-6 hours after dose for once daily dosing
- Should check after 3\(^{rd}\), 4\(^{th}\), or 5\(^{th}\) dose for BID dosing, after 2\(^{nd}\) or 3\(^{rd}\) dose for daily dosing\(^{20,21}\)
- Twice daily dosing is preferred

<table>
<thead>
<tr>
<th>Regimen</th>
<th>Reference Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>Twice daily treatment dosing</td>
<td>0.6-1 IU/mL</td>
</tr>
<tr>
<td>Once daily treatment dosing</td>
<td>1-2 IU/mL</td>
</tr>
<tr>
<td>Prophylactic dosing(^*)</td>
<td>0.2-0.5 IU/mL</td>
</tr>
</tbody>
</table>

\(^*\) Anti-Xa monitoring not generally recommended for prophylactic dosing, even in obesity

Anti-Xa monitoring

- Anti-Xa levels can be used to adjust dosing but no specific recommendations are available
- Can use trial-and-error approach and recheck levels
- Nomogram may assist in dosing adjustments for therapeutic dosing:22

<table>
<thead>
<tr>
<th>Anti-Factor Xa Level U/mL</th>
<th>Hold Next Dose?</th>
<th>Dose Change?</th>
<th>Repeat Anti-Factor Xa</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; 0.35</td>
<td>No</td>
<td>Increase by 25%</td>
<td>4 h after next dose</td>
</tr>
<tr>
<td>0.35–0.49</td>
<td>No</td>
<td>Increase by 10%</td>
<td>4 h after next dose</td>
</tr>
<tr>
<td>0.5–1.0</td>
<td>No</td>
<td>No</td>
<td>Next day, then 1 wk later and monthly thereafter while receiving reviparin-Na treatment (at 4 h after AM dose)</td>
</tr>
<tr>
<td>1.1–1.5</td>
<td>No</td>
<td>Decrease by 20%</td>
<td>Before next dose</td>
</tr>
<tr>
<td>1.6–2.0</td>
<td>3 h</td>
<td>Decrease by 30%</td>
<td>Before next dose then 4 h after next dose</td>
</tr>
<tr>
<td>&gt; 2.0</td>
<td>Until anti-factor Xa 0.5 U/mL</td>
<td>Decrease by 40%</td>
<td>Before next dose, if not &lt; 0.5 u/mL, repeat q12h</td>
</tr>
</tbody>
</table>

The physician would like to monitor the effectiveness of the enoxaparin due to JP’s morbid obesity. He would like to check anti-Xa activity. When should the level be drawn?

A. 4 hours after the first dose
B. 4 hours after the 3rd dose
C. 12 hours after the first dose
D. 12 hours after the 3rd dose
Assessment question #4

What is a reasonable target range for JP’s anti-Xa activity?

A. 0.6-1 units/mL
B. 0.2-0.5 units/mL
C. <0.2 units/mL
D. Anti-Xa activity is not an appropriate marker for JP
Warfarin

- Dosing is extremely variable due to multiple factors besides obesity
- Obesity also plays a role, although still lack of studies
- Wallace et al (n=211) – hospitalized new start warfarin patients

<table>
<thead>
<tr>
<th></th>
<th>Therapeutic INR at discharge</th>
<th>Time to therapeutic INR</th>
<th>Average daily dose at discharge (therapeutic patients)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal body weight</td>
<td>71.1%</td>
<td>6 days</td>
<td>5 mg</td>
</tr>
<tr>
<td>Obese</td>
<td>42.3%</td>
<td>8 days</td>
<td>6.6 mg</td>
</tr>
<tr>
<td>Morbidly obese</td>
<td>38%</td>
<td>10 days</td>
<td>7.6 mg</td>
</tr>
</tbody>
</table>

- Can monitor INR and adjust as needed, can use bridging

Direct oral anticoagulants (DOACs)

• Direct thrombin inhibitors
  – Dabigatran

• Factor Xa Inhibitors
  – Rivaroxaban
  – Apixaban
  – Edoxaban
Dabigatran

- No recommendations for dose adjustments in obesity (not even listed under special populations in the PI)\(^2\)\(^4\)
- RELY trial did not exclude patients based on weight\(^2\)\(^5\)
  - Mean weight \(\sim 82\) kg

Dabigatran

- Subgroup analysis of RELY trial

<table>
<thead>
<tr>
<th>Weight group</th>
<th>Mean dose normalized dabigatran trough level (ng/mL per mg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; 50 kg</td>
<td>0.998</td>
</tr>
<tr>
<td>50-100 kg</td>
<td>0.824</td>
</tr>
<tr>
<td>&gt; 100 kg</td>
<td>0.652</td>
</tr>
</tbody>
</table>

- Case report describes 48 y/o male, weight 153 kg, BMI 44.7, that had been on dabigatran for 4 weeks before developing an ischemic stroke while reportedly compliant
  - 9 hours post reported dose, serum level 0 ng/mL
  - Once restarted, peak level 2 hours post dose- 0.5 ng/mL (less than 25th percentile of therapeutic trough levels)

Rivaroxaban

- No recommendations for dose adjustments in obesity (not even listed under special populations in the PI)\textsuperscript{27}

\textsuperscript{27} Xarelto [package insert]. Titusville, NJ: Janssen Pharmaceuticals, Inc; 2011.
Rivaroxaban

- EINSTEIN DVT/PE trial did not exclude patients based on weight\textsuperscript{28}
  - 14.3 % of patients > 100 kg
- Subgroup analysis showed no difference in clinical outcomes related to body weight
- PK studies also show normal PK profile\textsuperscript{29}
- Clinical trials have not shown differences in incidence of VTE based on body weight in bariatric surgery patients
- Low volume of distribution
- No dose adjustment recommended


Apixaban

• No recommendations for dose adjustments in obesity (not even listed under special populations in the PI)\textsuperscript{30}

- Significant differences in C\textsubscript{max} and AUC based on body weight

Apixaban

- Apixaban has ~30% lower max concentration and ~20% lower AUC in patients with weight $>120$ kg and BMI $\geq 30$ kg/m$^2$ 31
- Clinical relevance unknown
- No dose adjustment recommended but caution using in patients with morbid obesity

Edoxaban

- No recommendations for dose adjustments in obesity (not even listed under special populations in the PI)\(^{32}\)
- Hokusai VTE Trial- mean weight \(~84\) kg, \(14.8\%\) of patients weight > 100 kg\(^{33}\)
- Minimal subgroup analyses
- No significant differences in safety or efficacy noted
- No dose adjustment recommendations


DOAC Summary

• No dosage adjustment recommendations based on body weight

• May want to avoid use in morbidly obese patients due to lack of data and lack of quantitative monitoring

• Warfarin may be better option for some of these patients

• Rivaroxaban may be a better choice than other DOACs due to drug properties and available evidence
Assessment question #5

When comparing dosing of the direct oral anticoagulants between obese patients and patients of normal body weight, most literature suggests that obese patients will require ______________.

A. A higher dose
B. A lower dose
C. The same dose
D. Weight stratified dosing
DOAC Monitoring

- Therapeutic drug monitoring – none required

- **Signs and symptoms of bleeding (and clotting)**
- Compliance
- Periodic renal function assessment
- Other medications for DDIs

- Reasonable labs:
  - CBC (H/H, PLT)
  - SCr
  - LFTs (rivaroxaban and apixaban)
Assessment question #6

For a morbidly obese patient taking a DOAC for treatment of a recent PE, it is reasonable to increase monitoring of:

A. Signs and symptoms of bleeding and clotting
B. Clotting factor levels
C. Compliance
D. Serum creatinine
Sizing up the pharmacist’s role in obesity management

Questions?

GMCCP Spring Education Event
May 10th, 2017

Erin Newkirk, PharmD, BCPS, CDE
Tom Dilworth, PharmD
Nick Zupec, PharmD, BCPS