Sizing up the pharmacist's role in obesity management

GMCCP Spring Education Event
May 10th, 2017

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Medications in Weight Loss: When the goals aren't met despite the sweat

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Objectives

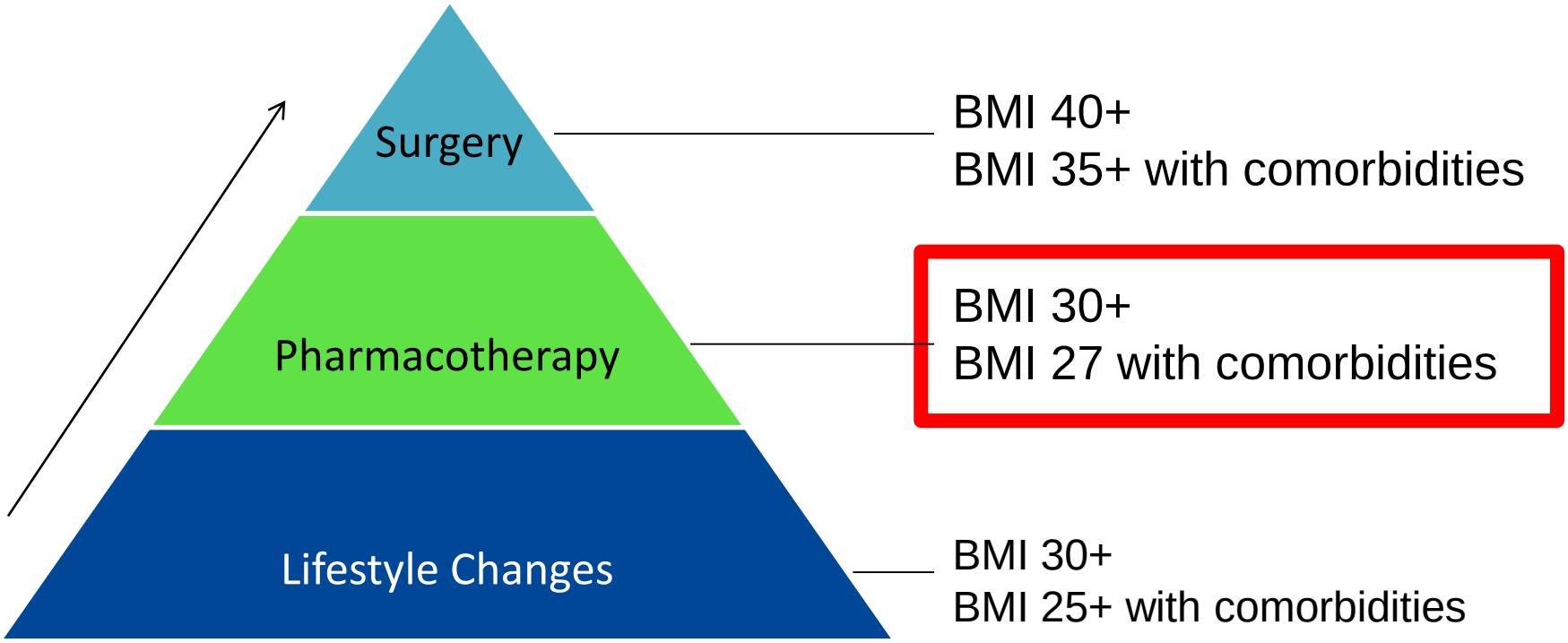
- To describe the role of weight loss medications and appropriately select a weight loss agent based on co-morbid conditions
- To identify medications that are obesogenic and identify preferred alternatives that have less risk for weight gain

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



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

2013 Endocrine Society Clinical Practice Guideline

1.2 In order to promote long-term weight maintenance, we suggest the use of approved[1] 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 ≥ 30 kg/m^2 or in individuals with a BMI of ≥ 27 kg/m^2 and at least one associated comorbid medical condition such as hypertension, dyslipidemia, type 2 diabetes (T2DM), and obstructive sleep apnea. (2|⊕⊕◯◯)

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Jensen MG, Ryan DH, Apovian CM, et al. 2013 AHA/ACC/TOS Guideline for the Management of Overweight and Obesity in Adults. *Circulation*. 2014;129[suppl 2]:S102-S138

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

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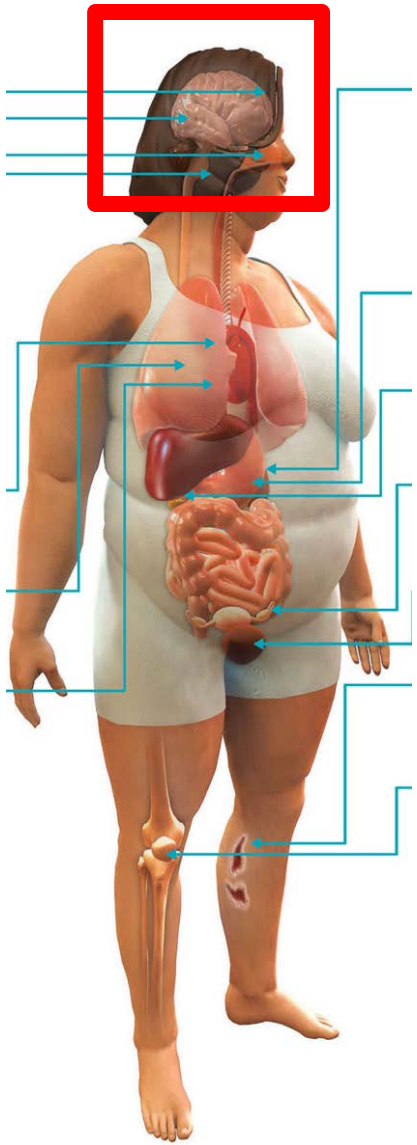
Khorassani FE, Misher A, Garris S. Past and present of antiobesity agents: Focus on monoamine modulators. Am J Health-Syst Pharm—Vol 72 May 1, 2015

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



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

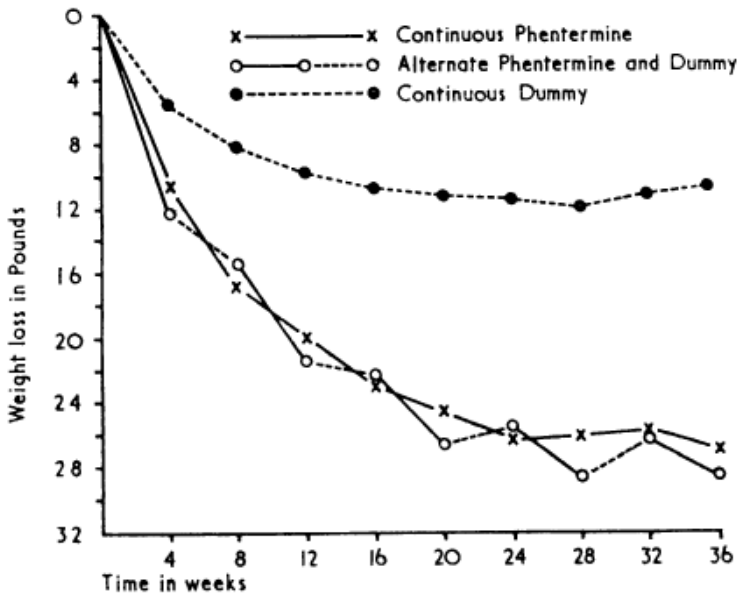
Phentermine

- 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

Khorassani FE, Misher A, Garris S. Past and present of antiobesity agents: Focus on monoamine modulators. Am J Health-Syst Pharm—Vol 72 May 1, 2015
Phentermine. [Package insert]. PUREPAC PHARMACEUTICAL CO. Elizabeth, NJ. Revised 01/2001.

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



Mean weight loss in each group during the study.

Munro JF, MacCuish AC, Wilson EM, Duncan LJ. Comparison of continuous and intermittent anorectic therapy in obesity. *Br Med J.* 1968; 1:352-4.

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

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Phentermine. [Package insert]. PUREPAC PHARMACEUTICAL CO. Elizabeth, NJ. Revised 01/2001.

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

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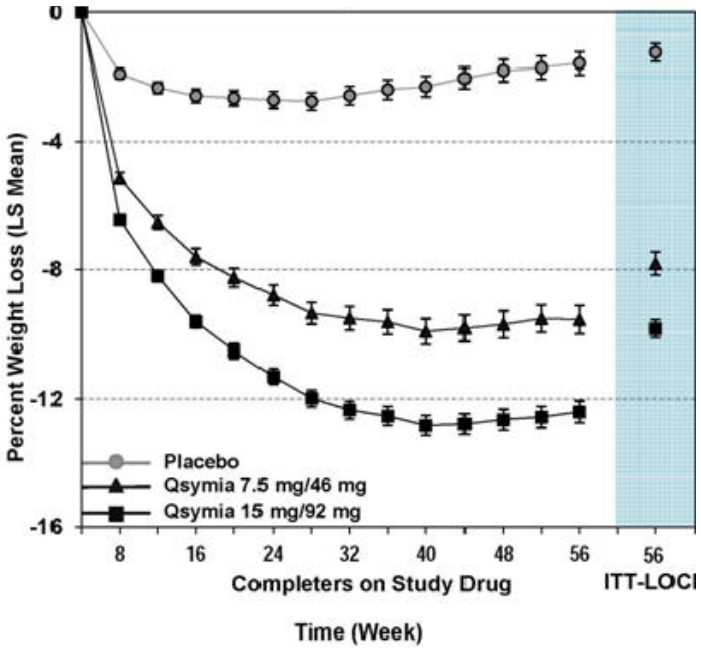
Phentermine & topiramate (Qsymia). [Package insert]. VIVUS, Inc. Mountain View, CA. Revised 10/2014.

Phentermine/Topiramate ER (Qsymia®) Evidence

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

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



31% of patients withdrew from study prior to week 56

Khorassani FE, Misher A, Garris S. Past and present of antiobesity agents: Focus on monoamine modulators. Am J Health-Syst Pharm—Vol 72 May 1, 2015
Phentermine & topiramate (Qsymia). [Package insert]. VIVUS, Inc. Mountain View, CA. Revised 10/2014.

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: tapper 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

Khorassani FE, Misher A, Garris S. Past and present of antiobesity agents: Focus on monoamine modulators. Am J Health-Syst Pharm—Vol 72 May 1, 2015
Phentermine & topiramate (Qsymia). [Package insert]. VIVUS, Inc. Mountain View, CA. Revised 10/2014.

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

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Khorassani FE, Misher A, Garris S. Past and present of antiobesity agents: Focus on monoamine modulators. Am J Health-Syst Pharm—Vol 72 May 1, 2015
Naltrexone & bupropion (Contrave). [Package insert]. Takeda Pharmaceuticals America, Inc. Deerfield, IL. Revised 09/2014.

Naltrexone/bupropion ER (Contrave®)

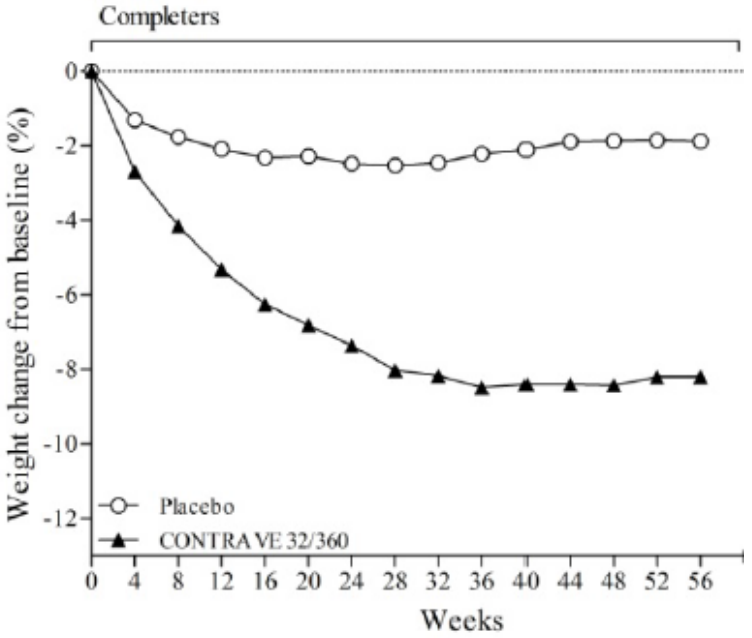
- Drug-drug interactions
  - Opiates
  - Bupropion is metabolized by **CYP2B6**
    - 2B6 inducers: ritonavir
    - 2B6 inhibitors: ticlopidine, clopidogrel
  - Bupropion and its metabolites inhibit **CYP2D6**
    - 2D6 substrates: Beta-blockers, SSRIs, SNRIs, TCAs, Antipsychotics

Khorassani FE, Misher A, Garris S. Past and present of antiobesity agents: Focus on monoamine modulators. Am J Health-Syst Pharm—Vol 72 May 1, 2015
Naltrexone & bupropion (Contrave). [Package insert]. Takeda Pharmaceuticals America, Inc. Deerfield, IL. Revised 09/2014.

Naltrexone/bupropion ER (Contrave®) Evidence

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

	Placebo	Contrave
n	536	538
Mean % wt loss	-1.3%	-5.4%
Difference from placebo (95% CI)		-4.1 kg (-4.9, -3.3)
Proportion losing ≥5%	**17%**	**42%**
Proportion losing ≥10%	7%	21%



50.1% of placebo and 49.2% of Contrave patients withdrew from study prior to week 56

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Naltrexone & bupropion (Contrave). [Package insert]. Takeda Pharmaceuticals America, Inc. Deerfield, IL. Revised 09/2014.

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

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Khorassani FE, Misher A, Garris S. Past and present of antiobesity agents: Focus on monoamine modulators. Am J Health-Syst Pharm—Vol 72 May 1, 2015
Naltrexone & bupropion (Contrave). [Package insert]. Takeda Pharmaceuticals America, Inc. Deerfield, IL. Revised 09/2014.

Lorcaserin (Belviq®)

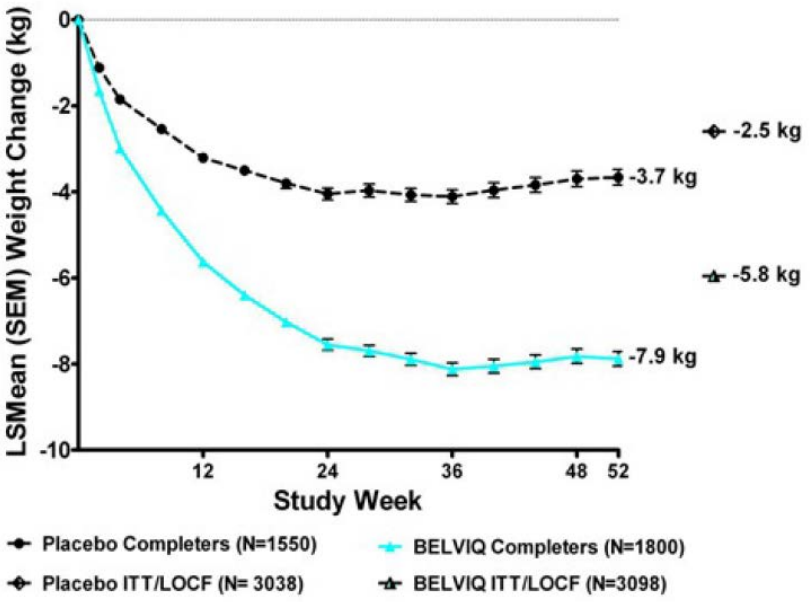
- 5-HT_{2C} receptor agonist
  - Hypothalamus
  - Decreased food consumption and promotes satiety
- Exhibits 100 times greater affinity for 5-HT_{2C} receptors than for 5-HT_{2B} receptors
- Dose: 10 mg tablet BID
  - Adjustments
    - CrCl 30-50 ml/min: caution (increased exposure); CrCl <30 ml/min: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

Khorassani FE, Misher A, Garris S. Past and present of antiobesity agents: Focus on monoamine modulators. Am J Health-Syst Pharm—Vol 72 May 1, 2015
Lorcaserin (Belviq). [Package insert]. Arena Pharmaceuticals GmbH, Zofingen, Switzerland. Revised 12/2014.

Lorcaserin (Belviq®) Evidence

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

	Placebo	Belviq
n	3038	3098
Mean % wt loss	-2.5%	-5.8%
Difference from placebo (95% CI)		-3.3 kg (-3.6, -3.0)
Proportion losing ≥5%	**22.6%**	**47.1%**
Proportion losing ≥10%	8.7%	22.4%



50% of patients withdrew from study prior to week 52

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Lorcaserin (Belviq). [Package insert]. Arena Pharmaceuticals GmbH, Zofingen, Switzerland. Revised 12/2014.

Lorcaserin (Belviq®) STEPS

Safety	• Pregnancy • Serotonin syndrome (very low incidence) • Depression or suicidal ideation • Valvular heart disease (theoretical; 5-HT_{2C} >> 5-HT_{2B}) • 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

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Khorassani FE, Misher A, Garris S. Past and present of antiobesity agents: Focus on monoamine modulators. Am J Health-Syst Pharm—Vol 72 May 1, 2015
Naltrexone & bupropion (Contrave). [Package insert]. Takeda Pharmaceuticals America, Inc. Deerfield, IL. Revised 09/2014.

Liraglutide (Saxenda®)

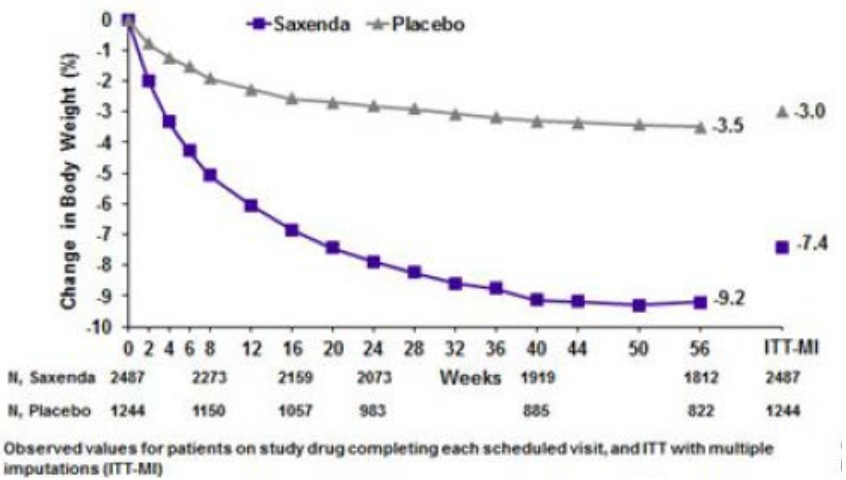
- Glucagon-like peptide-1 (GLP-1) analog
  - Increases glucose-dependent insulin secretion
  - Decreases inappropriate glucagon secretion
  - Slows gastric emptying
- Titrate at weekly intervals from 0.6 mg to 3 mg SQ daily over 5 weeks
  - Dosage adjustments
    - <50 ml/min: caution (limited experience, no adjusted provided by manufacturer)
    - Hepatic impairment: caution (limited experience, no adjusted provided by manufacturer)

Khorassani FE, Misher A, Garris S. Past and present of antiobesity agents: Focus on monoamine modulators. Am J Health-Syst Pharm—Vol 72 May 1, 2015
Saxenda (Saxenda). [Package insert]. Novo Nordisk. Bagsvaerd, Denmark. Revised 01/2015.

Liraglutide (Saxenda®)Evidence

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

	Placebo	Saxenda
n	1244	2487
Mean % wt loss	-3.0	-7.4
Difference from placebo (95% CI)		-4.5 kg (-5.2; -3.8)
Proportion losing ≥5%	**34.4%**	**62.3%**
Proportion losing ≥10%	15.4%	33.9%



27% of Saxenda & 35% of placebo patients withdrew from study prior to week 56

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Lorcaserin (Belviq). [Package insert]. Arena Pharmaceuticals GmbH, Zofingen, Switzerland. Revised 12/2014.

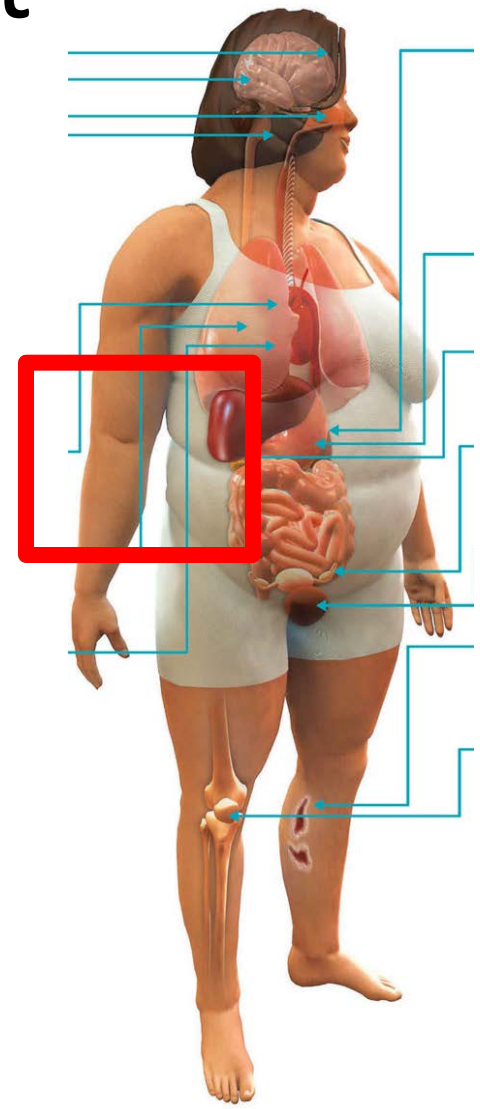
Liraglutide (Saxenda®) STEPS

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

Khorassani FE, Misher A, Garris S. Past and present of antiobesity agents: Focus on monoamine modulators. Am J Health-Syst Pharm—Vol 72 May 1, 2015
Naltrexone & bupropion (Contrave). [Package insert]. Takeda Pharmaceuticals America, Inc. Deerfield, IL. Revised 09/2014.

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



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

Orlistat STEPS

Safety	• Chronic malabsorption syndrome (prior RYGB surgery) • Cholestasis • Acute hepatic failure (rare) • Kidney stones (rare) • Drug interactions
Tolerability	• Oily spotting, flatus with discharge, fecal urgency, fatty/oily stool, oily evacuation, increased defecation, fecal incontinence
Efficacy	• Average 7.5 lbs weight loss
Preference	• Long term/chronic weight loss management, as adjunct to diet and exercise • No effect on appetite
Simplicity	• Xenical (Rx): ~$16 per day • Alli (OTC): $1.50 per day • Take up to 1 hour after each meal containing fat

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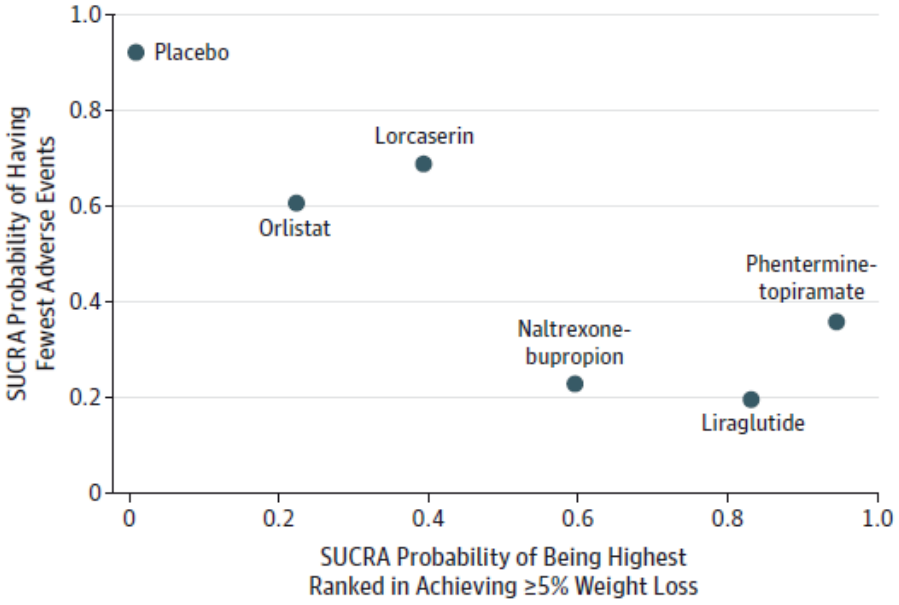
Naltrexone & bupropion (Contrave). [Package insert]. Takeda Pharmaceuticals America, Inc. Deerfield, IL. Revised 09/2014.

Comparisons of available agents



	Placebo	Orlistat	Lorcaserin	Naltrexone-bupropion	Liraglutide	Phentermine-topiramate
Weight loss rank (95% CrI)	6 (6-6)	5 (4-5)	4 (3-5)	3 (2-4)	2 (2-3)	1 (1-1)
Adverse event rank (95% CrI)	1 (1-1)	3 (2-4)	2 (2-3)	5 (5-6)	6 (4-6)	4 (3-6)

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Khera R, Murad MH, Chandar AK, et al. Association of Pharmacological Treatments for Obesity With Weight Loss and Adverse Events A Systemic Review and Meta-analysis. *JAMA*. 2016;315(22):2424-2434. doi:10.1001/jama.2016.7602

Pharmacological Management of Obesity

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

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Apovian CM, Aronne LJ, Bessesen DH, et al. Pharmacological Management of Obesity: An Endocrine Society Clinical Practice Guideline. *J Clin Endocrinol Metab*. 2015;100(2):342-62. DOI:10.1210/jc.2014-3415.

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)

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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

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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**

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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

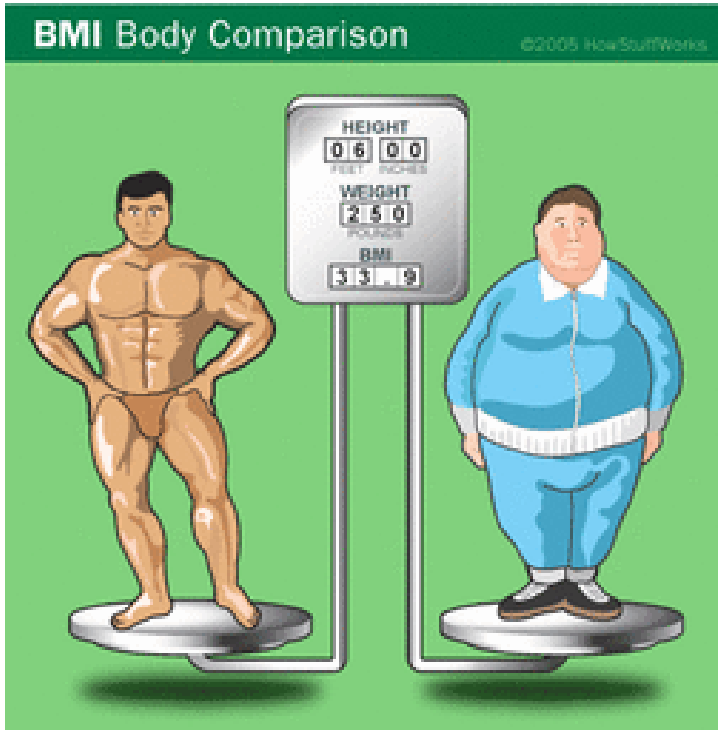
$$BMI = \frac{\text{Weight (kg)}}{\text{Height (m)}^2}$$

25 to 29.9	Overweight
30 +	Obesity
40 +	Extreme obesity

https://www.niddk.nih.gov/health-information/health-statistics/overweight-obesity

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)

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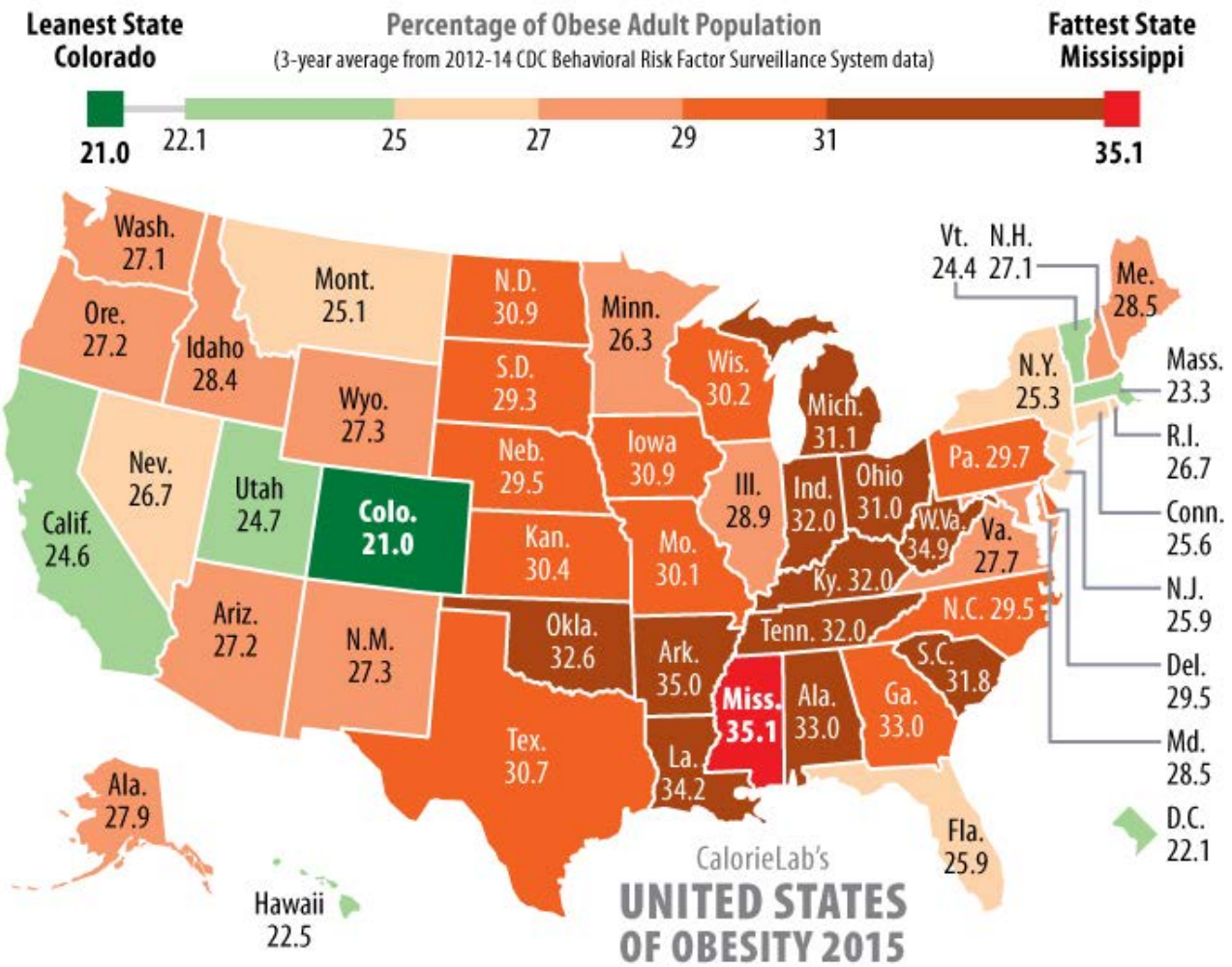
Obesity across the U.S.



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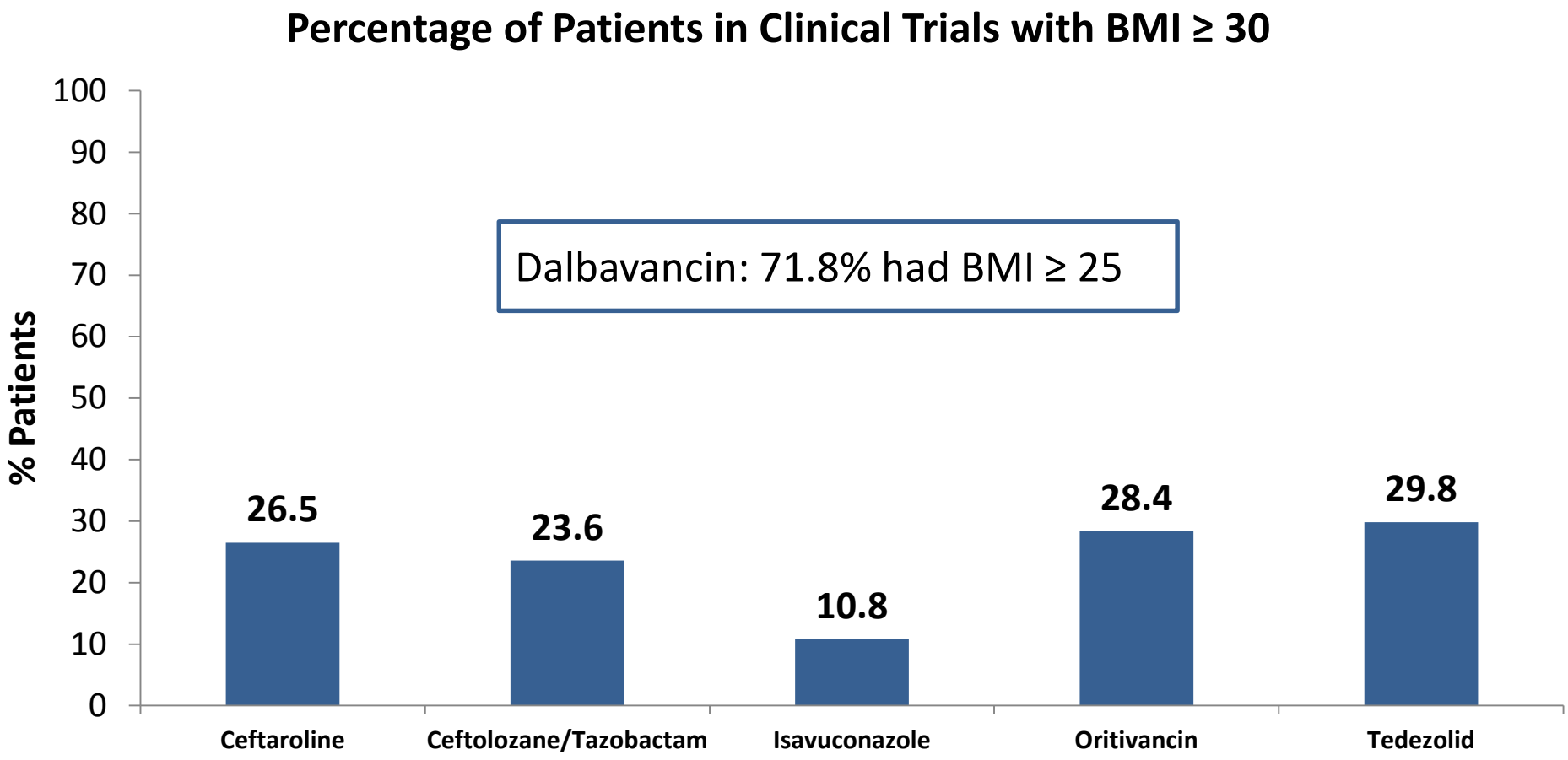
http://calorielab.com/news/2015/10/31/fattest-states-2015/

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



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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[1]
  - Median BMI (range):
    - Single dose: 24.55 (19.0 – 29.6)
    - Multiple doses: 25.5 (19.1 – 29.8)
- Ceftazidime/Avibactam, cIAI[2]
  - Mean BMI±SD: 24.4±5.2
- Plazomicin, Phase I[3]
  - Mean BMI (range): 24.16 (19.3 – 29.1)
- Telavancin, HAP/VAP[4]
  - Mean BMI±SD: 24.8±5.69

1. Griffith DC, et al. *Antimicrob Agents Chemother*. 2016;60(10):6326-32
2. Lucasti C, et al. *J Antimicrob Chemother.* 2013;68(5):1183-92.
3. Cass RT, et al. *Antimicrob Agents Chemother*. 2011;55(12):5874-80.
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.

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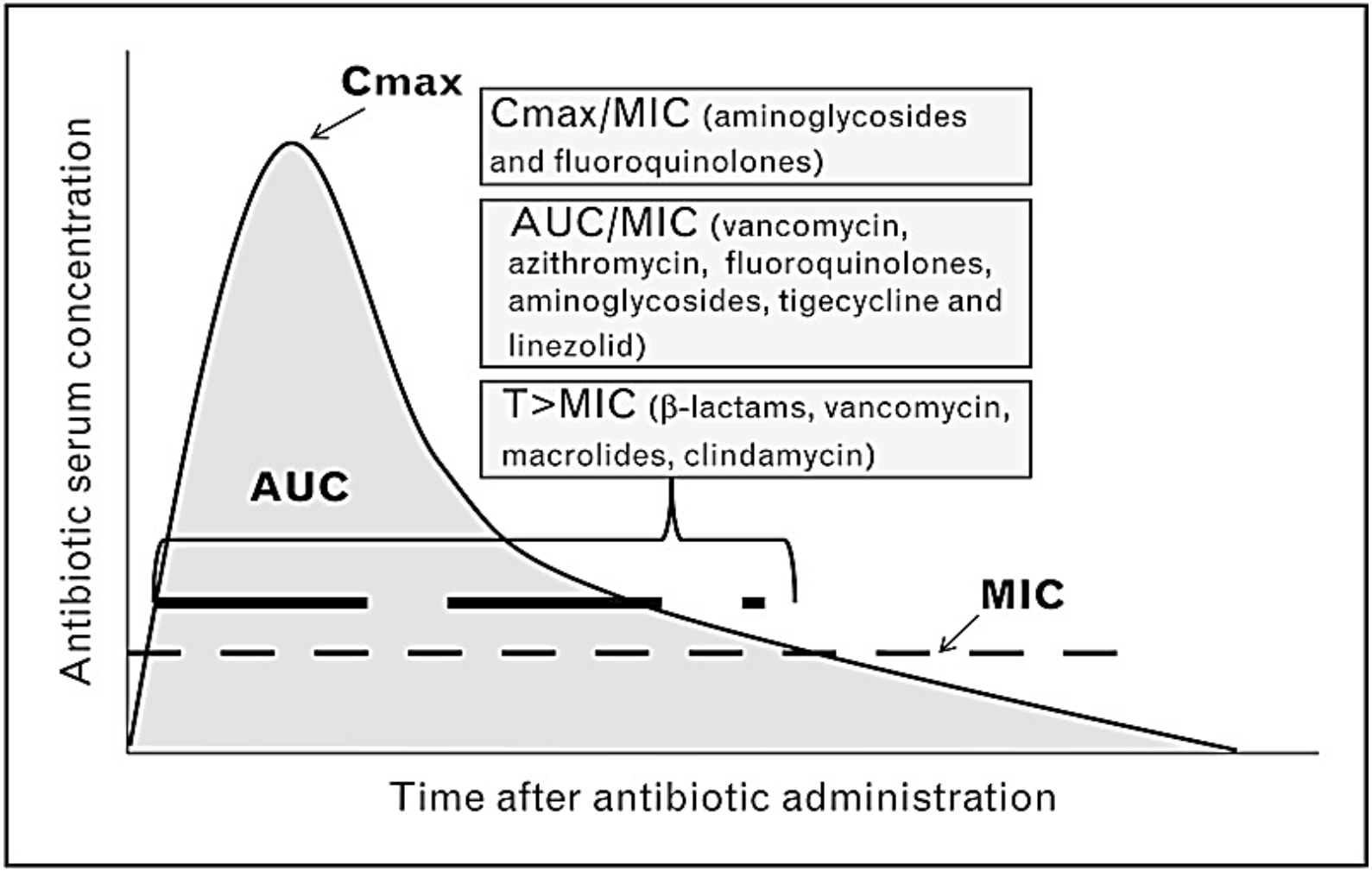
Pai MP. Pharmacotherapy. 2012;32(9):856-68.

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



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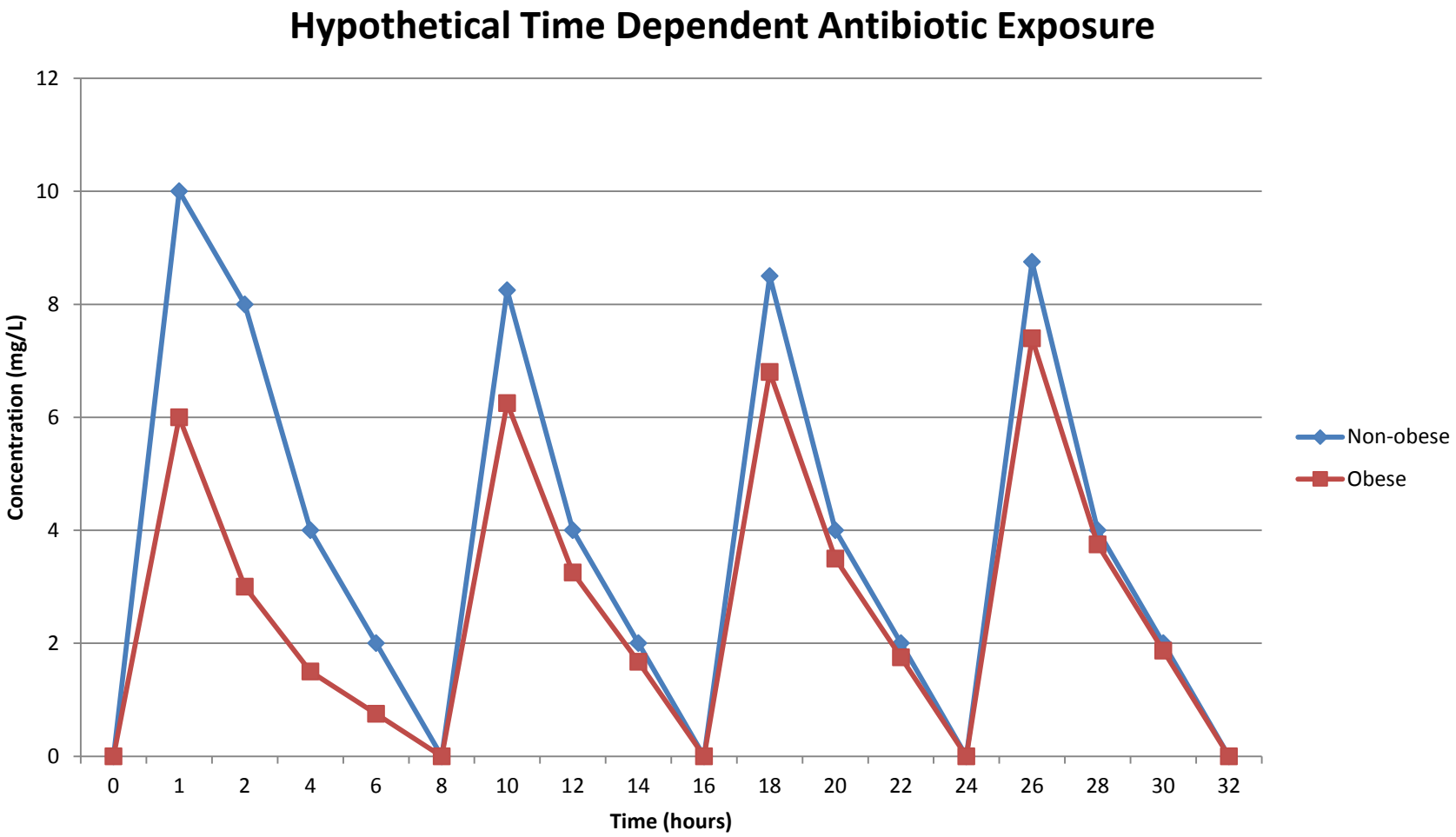
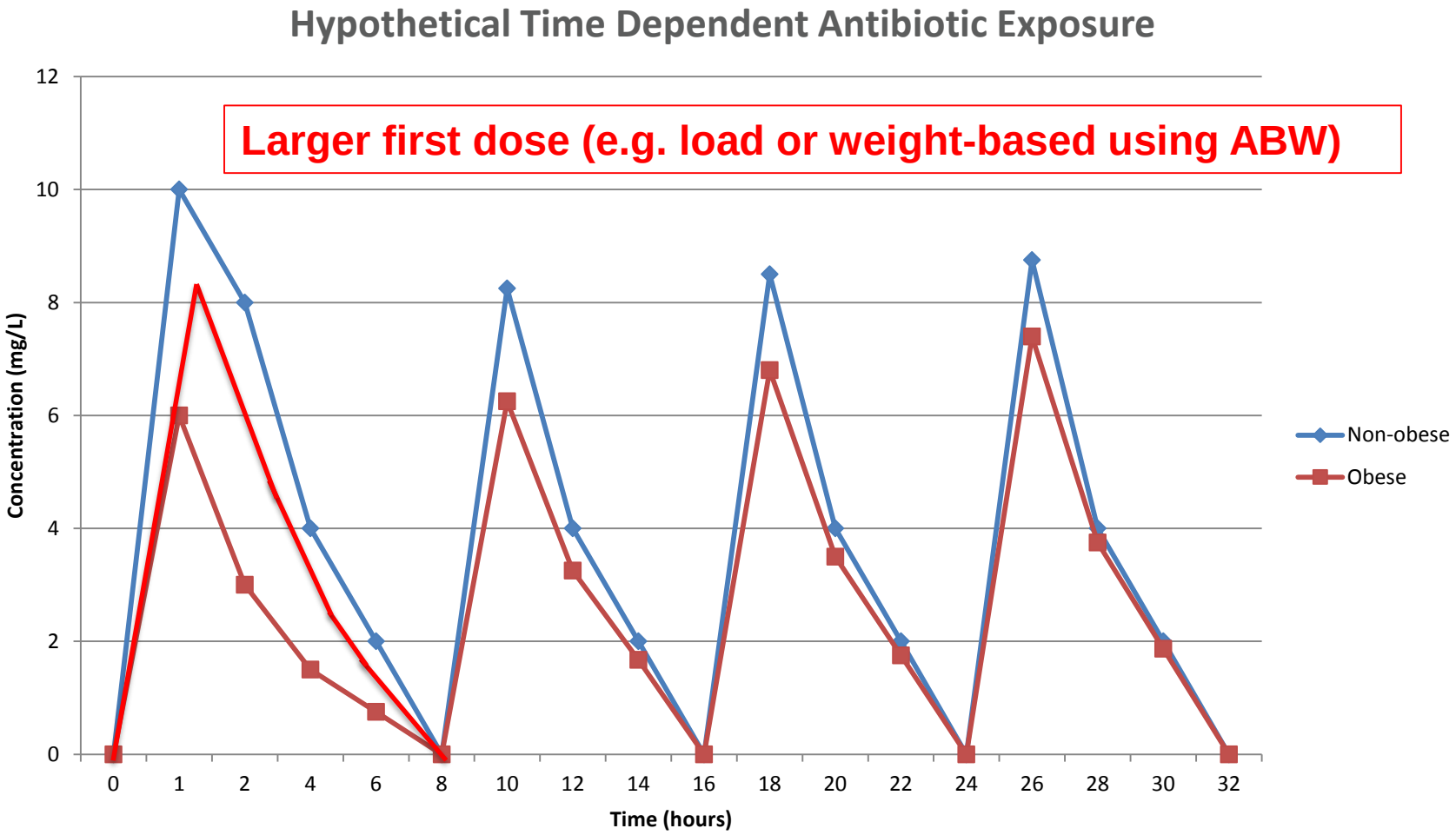
PK/PD Considerations in Obesity

- Cmax = dose/Vd
  - Relationship of Vd to body size is most relevant
- AUC = dose/CL
  - Relationship of CL to body size most relevant
- **Vd increase in obesity w/o change in CL will lower Cmax but will not sig. change AUC**
- Time-dependent: CL and Vd both impact time above MIC
  - Increased Cl = decreased time > MIC
  - Increased Vd = decreased time > MIC
  - Often you "catch up" with maintenance doses

Time Dependent Antibiotic Exposure

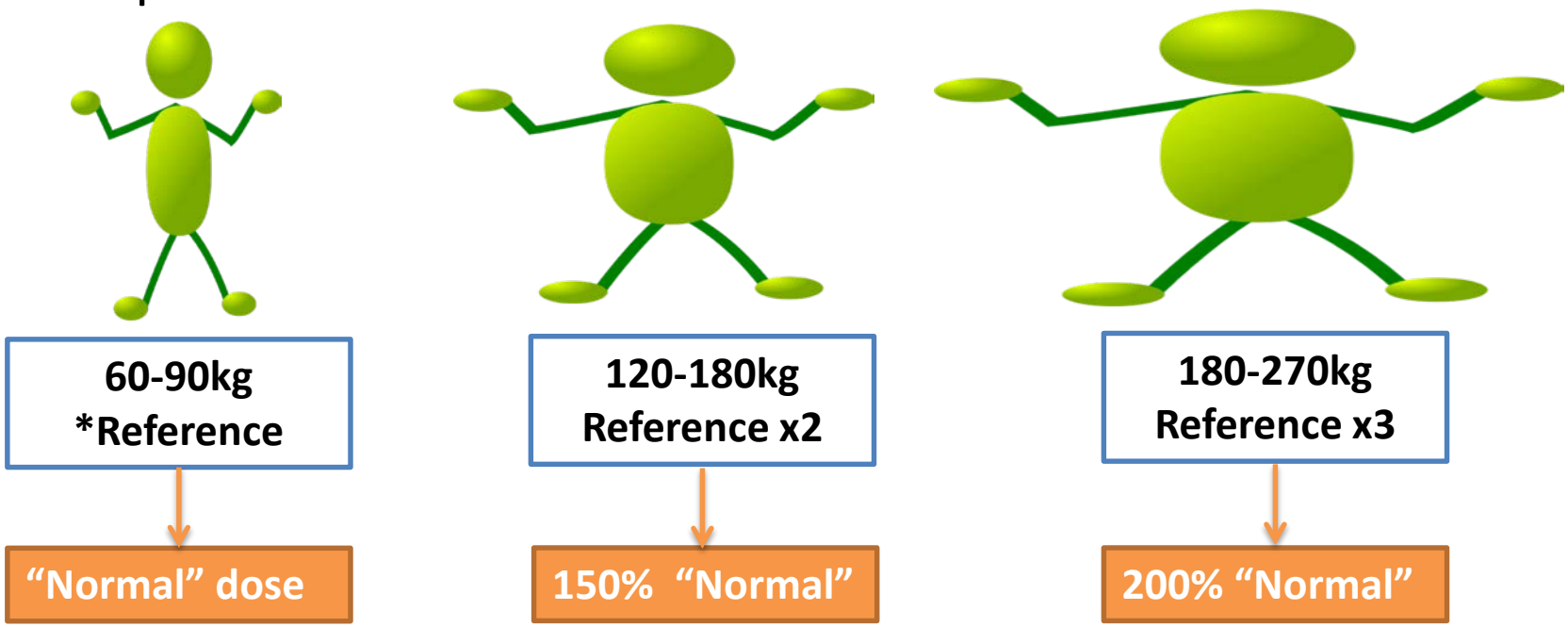


Time Dependent Antibiotic Exposure



Initial Dose in Obesity

- "Allometry"…
- Obese dose = avg. dose (pt wt ÷ avg wt)*β
  - β: 0.5-0.75



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Mahmood I. *J Pharm Sci.* 2010; 99: 2927-2933.

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 ÷ CL) so **why do we dose upon weight?**

TABLE 1. New AUC Vancomycin Dosing Chart Based on CrCl Estimated by the (by the Formula of Matzke et al[7]

	Vancomycin AUC Dosing Chart to Initiate Therapy*		
	Complicated Infection‡, Target: $AUC_{24}/MIC \geq 400$§, C_{Trough}: 15–20 mg/L		
$CrCl_{mL/min}$†	High-Dose Regimen	Projected AUC_{24}/MIC‖	Mod
≥175	1250 mg q6h	<671	
135–174	1000 mg q6h	539–670	
100–134	750 mg q6h	520–690	
85–99	750 mg q8h	522–603	
65–84	500 mg q6h	542–690	
45–64	500 mg q8h	524–721	
30–44	500 mg q12h	493–685	

This chart is intended to determine a starting empiric dosing regimen based on vancomycin population

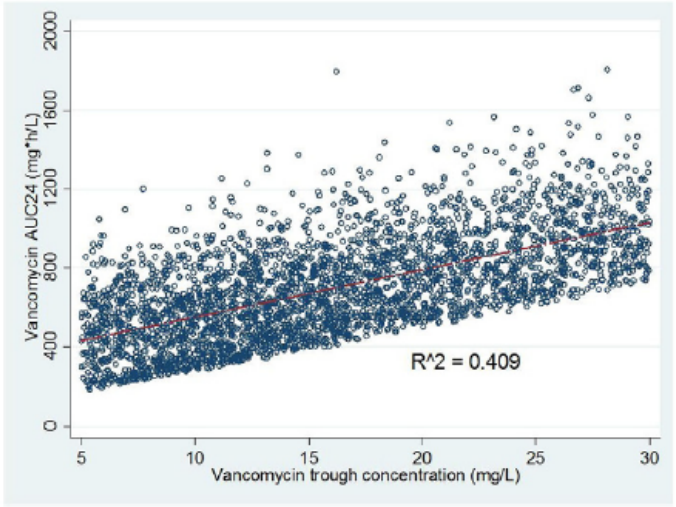

Fig. 2. Scatter and linear fit plot of vancomycin area under the curve over 24 h (AUC24) versus trough vancomycin concentration from 5000 subject Monte Carlo simulation.

1. Davis SL, et al. Pharmacotherapy. 2013;33(12):1256-63
2. Rybak MJ, et al. Pharmacotherapy. 2009;29(11):1275-9.2.
3. http://www.pfizer.com/files/products/uspi_vancomycin_5g_bulk.pdf
4. Pai MP, et al. Adv Drug Deliv Rev. 2014l;20;77:50-7.
5. Brown DL., et al. *Ther Drug Monit.* 2013;35(4):443-9

Estimating Vancomycin Exposure in Obese Patients (n=12)

- Median BMI 45 kg/m^2 (40 - 52)
- Five PK concentrations were measured and 4 pop PK models were used to estimate AUC (AUC_{FULL})
- Data-depleted PK subsets were used to estimate the 24-hour AUC
  - Peak and trough data [AUC_{PT}]
  - Midpoint and trough data [AUC_{MT}]
  - Trough only data [AUC_{T}]
- **AUC_{PT} provided the best approximation of the AUC_{FULL}**
- *AUC_{MT} and AUC_{T} overestimated AUC_{FULL}*

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Carreno JJ, et al. Antimicrob Agents Chemother. 2017 Mar 13. pii: AAC.02478-16.

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[1]
- Voriconazole: should dose on adjusted BW[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[3]
  - Exposure IBW_{Obese} < Exposure $ABW_{Non\text{-}obese}$
- Ganciclovir and Foscarnet: adjusted BW[4]
  - Hydrophilic, risk of nephrotoxicity & bone marrow toxicity

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1. Bhalodi AA, et al. Antimicrob Agents Chemother. 2013;57(3):1144-9.
2. Moriyama B, et al. Pharmacotherapy. 2013 Mar;33(3):e19-22.
3. Turner RB, et al. Antimicrob Agents Chemother. 2016 ;60(3):1830-3.
4. Polso AK, et al. J Clin Pharm Ther. 2014;39(6):584-608.

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/m^2; 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=0.073hr^{-1}, half-life 9.5hours, Cmax 19.5mg/L,

Vd 33.3L (0.25L/kg), **clearance 2.4L/hour (40mL/min)**

On day 2 gram-positive cocci in clusters are recovered from a BAL and the *mecA* PCR test is positive. His 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

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Considerations for weight when we anticoagulate

Nick Zupec, PharmD, BCPS

GMCCP Spring Education Event
May 10th, 2017

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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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1. Schreijer AJ, Cannegieter SC, Doggen CJ, Rosendaal FR. The effect of flight-related behaviour on the risk of venous thrombosis after air travel. *Br J Haematol*. 2009;144(3):425-9.
2. Kahn SR, Lim W, Dunn AS, et al. Prevention of VTE in Nonsurgical Patients. In: Antithrombotic therapy and prevention of thrombosis, 9th ed: American College of Chest Physicians evidence-based clinical practice guidelines . *CHEST*. 2012 February; 141(2): e95S-e226s.

Obesity as a risk factor

Obesity versus normal body weight[3]

- 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 weight[4]

The effect is larger at lower ages

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3. Stein PD, Beemath A, Olson RE. Obesity as a risk factor in venous thromboembolism. *Am J Med*. 2005; 118:978–980.
4. Freeman AL, Pendleton RC, Rondina MT. Prevention of venous thromboembolism in obesity. *Expert Rev Cardiovasc Ther*. 2010; 8(12):1711-21.

Box 1. Proposed thrombotic mechanisms in obesity

Enhanced platelet activity

- Adipokinins (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

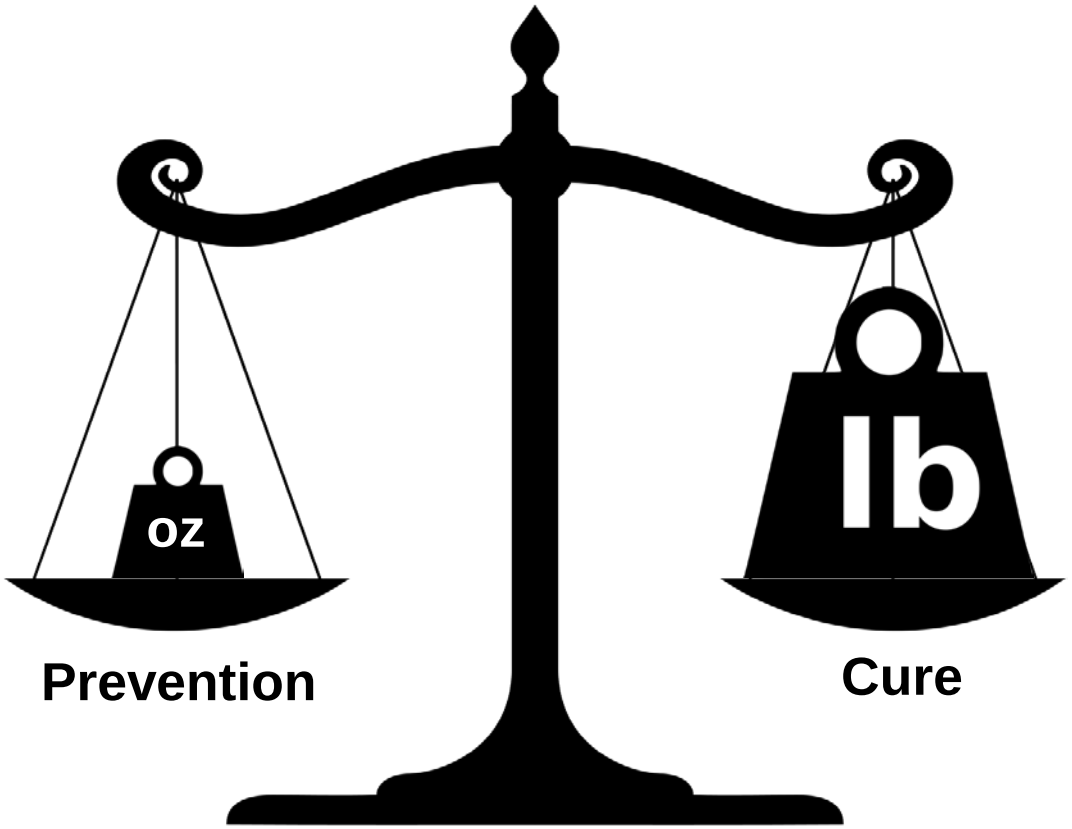
Activation of endothelial cells

- Tissue hypoxia

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

Freeman AL, Pendleton RC, Rondina MT. Prevention of venous thromboembolism in obesity. *Expert Rev Cardiovasc Ther*. 2010; 8(12):1711-21.

Prevention vs. treatment



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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[5]
- Guideline recommendations
  - CHEST Guidelines???
  - American Society for Metabolic and Bariatric Surgery Guidelines???
  - Anyone???

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5. Shepherd MF, Rosborough TK, Schwartz ML. Heparin thromboprophylaxis in gastric bypass surgery. *Obes*. Surg. 2003;13:249–53.

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[6]
- Similar findings in studies with higher incidence of thrombosis in obese patients[7,8]

8.10 Obese Patients[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^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.

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

7. Nutescu EA, Spinler SA, Wittkowsky A, et al. Low-molecular-weight heparins in renal impairment and obesity: available evidence and clinical practice recommendations across medical and surgical settings. *Ann Pharmacother*. 2009;43:1064–83.

8. Rowan BO, Kuhl DA, Lee MD, et al. Anti-Xa levels in bariatric surgery patients receiving prophylactic enoxaparin. Obes Surg. 2008;18:162–166

9. Enoxaparin [package insert]. Bridgewater, NJ: Sanofi-Aventis US LLC; 2013.

High dose thromboprophylaxis

- Large retrospective cohort study with 9241 patients[10]
- Obese = weight >100 kg and BMI ≥ 40 kg/m^2
- High intensity prophylaxis
  - Heparin 7500 mg subcut Q8H
  - Enoxaparin 40 mg subcut Q12H

	Standard prophylaxis	High dose prophylaxis
Rate of VTE	1.48%	0.77% (p=0.047)
Bleeding	8.44%	7.18 % (p=0.15)

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

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10. Wang T, Milligan PE, Wong CA, Deal EN, Thoelke MS, Gage BF. Efficacy and safety of high-dose thromboprophylaxis in morbidly obese inpatients. *Thromb Haemost*. 2014;111(1):88-93.

Enoxaparin

- Different approaches[4,7,8,10,11]

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

11. Scholten DJ, Hoedema RM, Scholten SE. A comparison of two different prophylactic dose regimens of low molecular weight heparin in bariatric surgery. *Obes Surg*. 2002;12:19–24.

Enoxaparin

- Scholten, et al.[11]
- 481 bariatric surgery patients

	30 mg Q12H (n=92)	40 mg Q12H (n=389)	P values
BMI	51.7	50.3	NS
VTE incidence	1.4% (n=5)	0.6% (n=2)	$p < 0.01$
Clinically relevant bleeding	1.09% (n=1)	0.26% (n=1)	NS

11. Scholten DJ, Hoedema RM, Scholten SE. A comparison of two different prophylactic dose regimens of low molecular weight heparin in bariatric surgery. *Obes Surg*. 2002;12:19–24.

Thromboprophylaxis controversies

- What about BMI 30-40 kg/m^2?
- What about BMI ≥ 50 kg/m^2?
- 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)[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[13,14]
- Obese patients often take longer to get to therapeutic range[15]
- Controversy: Should we use dose capping?

12. Raschke RA, Reilly BM, Guidry JR, Fontana JR, Srinivas S. The weight-based heparin dosing nomogram compared with a "standard care" nomogram. A randomized controlled trial. *Ann Intern Med*. 1993;119(9):874-81.
13. Hull RD, Raskob GE, Rosenbloom D, et al. Optimal therapeutic level of heparin therapy in patients with venous thrombosis. *Arch Intern Med*. 1992;152:1589–95.
14. Garcia DA, Baglin TP, Weitz JI, Samama MM. Parenteral Anticoagulants. In: Antithrombotic therapy and prevention of thrombosis, 9th ed: American College of Chest Physicians evidence-based clinical practice guidelines. *CHEST*. 2012 February; 141(2): e24S-e43s
15. Hurewitz AN, Khan SU, Groth ML, Patrick PA, Brand DA. Dosing of Unfractionated Heparin in Obese Patients with Venous Thromboembolism. *J Gen Intern Med*. 2010;26(5):487-91.

Unfractionated heparin

- Studies have shown that non-capped heparin protocols based on actual body weight help patients achieve therapeutic PTT faster[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

16. Bauer SR, Ou NN, Dreesman BJ, et al. Effect of body mass index on bleeding frequency and activated partial thromboplastin time in weight based dosing of unfractionated heparin: a retrospective cohort study. *Mayo Clin Proc*. 2009;84:1073–1078.

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[9]

- 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.[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 ~190 kg have not been represented in clinical trials
- In patients ≥ 190 kg, factor Xa monitoring is recommended[18]

17. Spinier SA, Inverso SM, Cohen M, et al. Safety and efficacy of unfractionated heparin versus enoxaparin in patients who are obese and patients with severe renal impairment: analysis from the ESSENCE and TIMI 11B studies. *Am Heart*. 2003;146:33-41.
18. Nutescu EA, Spinler SA, Wittkowsky A, Dager WE. Low-molecular weight heparins in renal impairment and obesity: Available evidence and clinical practive recommendations across medical and surgical settings. *Ann Pharmacother*. 2009;43:1064-83.

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 by monitored[19,20]
  - 3-**4** hours after dose for BID dosing
  - **4**-6 hours after dose for once daily dosing

4 hours is safe for both

- Should check after **3rd**, 4th, or 5th dose for BID dosing, after 2nd or **3rd** dose for daily dosing[20,21]
- Twice daily dosing is preferred

After the 3rd dose is safe for both

Regimen	Reference Range
Twice daily treatment dosing	**0.6-1 IU/mL**
Once daily treatment dosing	1-2 IU/mL
Prophylactic dosing*	0.2-0.5 IU/mL
* Anti-Xa monitoring not generally recommended for prophylactic dosing, even in obesity	

19. Bounameaux H, de Moerloose P. Is laboratory monitoring of low-molecular-weight heparin therapy necessary? *No. J. Thromb Haemost*. 2004;2:551–4.

20. Lim W. Using low molecular weight heparin in special patient populations. *J Thromb Thrombolysis*. 2010; 29:233–40.

21. Bazinet A, Almanric K, Brunet C, et al. Dosage of enoxaparin among obese and renal impairment patients. *Thrombosis Research.* 2005;116:41-50.

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]

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

22. Monagle P, Michelson AD, Bovill E, Andrew M. Antithrombotic therapy in children. *Chest.* 2001;119(1 suppl):344S-370S.

Assessment question #3

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[23]

	Therapeutic INR at discharge	Time to therapeutic INR	Average daily dose at discharge (therapeutic patients)
Normal body weight	71.1%	6 days	5 mg
Obese	42.3%	8 days	6.6 mg
Morbidly obese	38%	10 days	7.6 mg

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

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23. Wallace JL, Reaves AB, Tolley EA et al. Comparison of initial warfarin response in obese patients versus non-obese patients. *J Thromb Thromb*, 2013; 36:96–101.

Direct oral anticoagulants (DOACs)

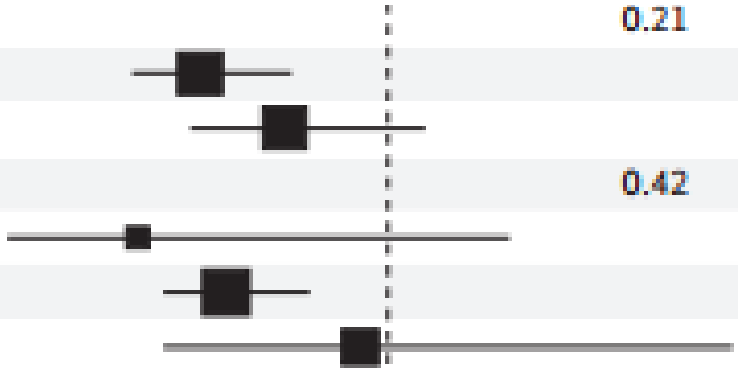
- Direct thrombin inhibitors
  - Dabigatran

- Factor Xa Inhibitors
  - Rivaroxaban
  - Apixaban
  - Edoxaban

Dabigatran

- No recommendations for dose adjustments in obesity (not even listed under special populations in the PI)[24]
- RELY trial did not exclude patients based on weight[25]
  - Mean weight ~82 kg

Subgroup	Patients *total no.*	Dabigatran 110 mg *% per yr*	Dabigatran 150 mg *% per yr*	Warfarin	Hazard Ratio with Dabigatran, 150 mg (95% CI)	P Value for Interaction
Body-mass index						0.21
<28	9,131	1.78	1.17	2.01		
≥28	8,962	1.28	1.04	1.34		
Weight						0.42
<50 kg	376	2.58	2.24	5.04		
50–99 kg	14,629	1.66	1.14	1.77		
≥100 kg	3,099	0.80	0.87	0.94		



24. Pradaxa [package insert]. Ridgefield, CT: Boehringer Ingelheim Pharmaceuticals Inc; 2015.
25. Connolly SJ, Ezekowitz MD, Yusuf S, et al. Dabigatran versus warfarin in patients with atrial fibrillation. *N Engl J Med.* 2009;361:1139-51.

Dabigatran

- Subgroup analysis of RELY trial[25]

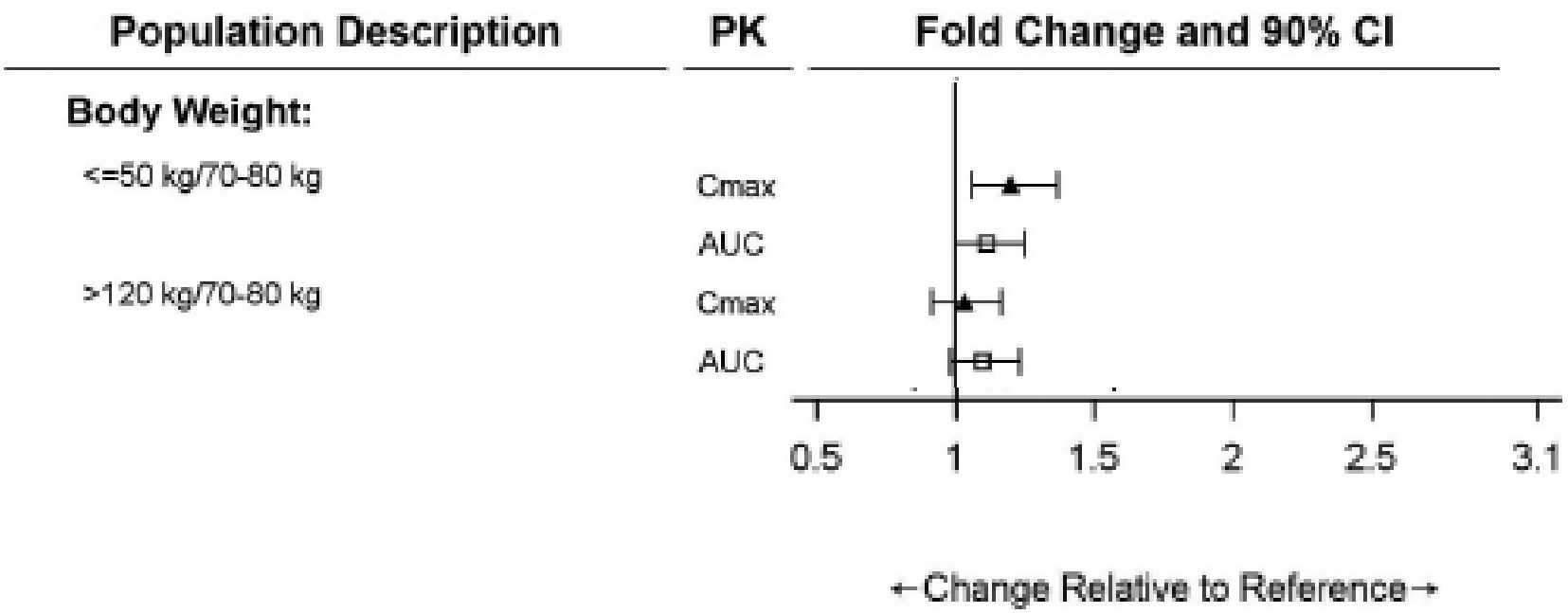
Weight group	Mean dose normalized dabigatran trough level (ng/mL per mg)
< 50 kg	0.998
50-100 kg	0.824
> 100 kg	0.652

- 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[26]
  - 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)

26. Breuer L, Ringwald J, Schwab S, Köhrmann M. Ischemic stroke in an obese patient receiving dabigatran. *N Engl J Med*. 2013; 368(25) 2440-2.

Rivaroxaban

- No recommendations for dose adjustments in obesity (not even listed under special populations in the PI)[27]



27. Xarelto [package insert]. Titusville, NJ: Janssen Pharmaceuticals, Inc; 2011.

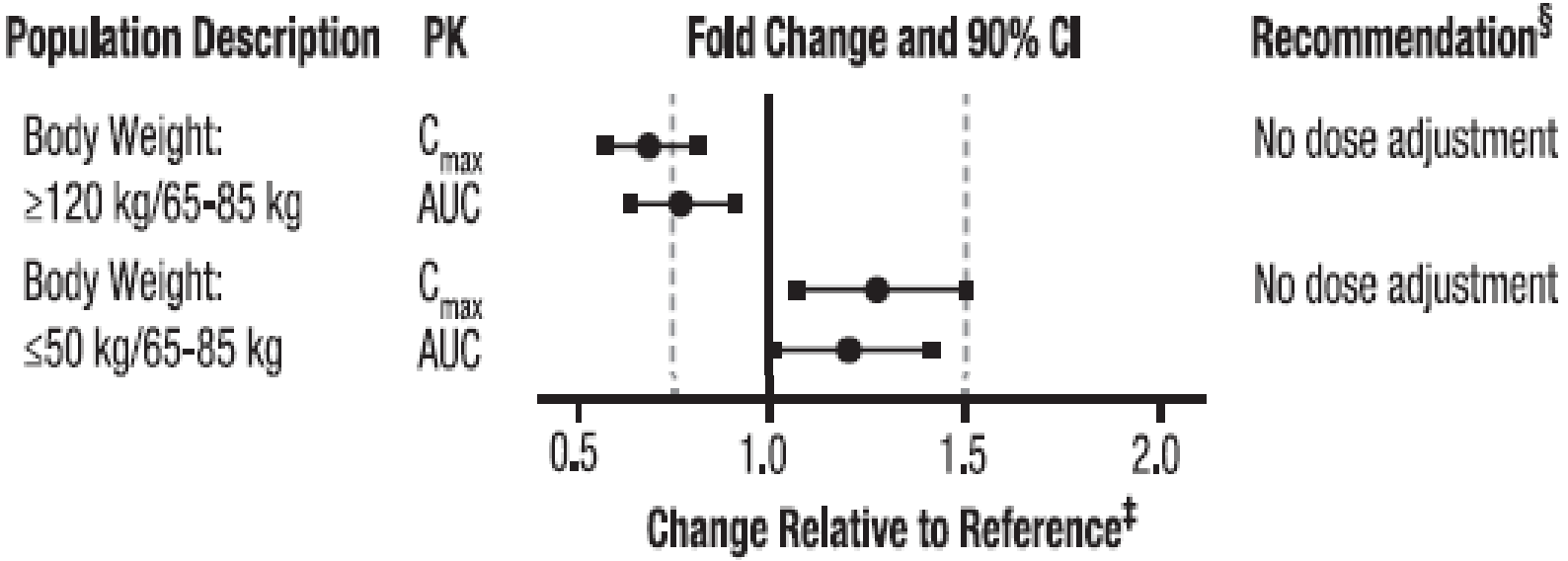
Rivaroxaban

- EINSTEIN DVT/PE trial did not exclude patients based on weight[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[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

28. Buller HR, Prins MH, Lensin AW, et al. Oral rivaroxaban for the treatment of symptomatic pulmonary embolism. *N Engl J Med*. 2012; 366:1287-97.
29. Domienik-Karlowicz J, Pruszczyk P. The use of anticoagulants in morbidly obese patients. *Cardiology Journal*. 2016;23(1):12-16.

Apixaban

- No recommendations for dose adjustments in obesity (not even listed under special populations in the PI)[30]



- Significant differences in Cmax and AUC based on body weight

30. Eliquis [package insert]. Princeton, NJ: Bristol-Myers Squibb Company; 2016.

Apixaban

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

31. Upreti VV, Wang J, Barrett YC, et al. Effect of extremes of body weight on the pharmacokinetics, pharmacodynamics, safety, and tolerability of apixaban in healthy subjects. *Br J Clin Pharmacol*. 2013;76(6):908-16.

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

32. Savaysa [package insert]. Parsippany, NJ: Daiichi Sankyo, Inc.; 2015
33. Büller HR, Décousus H, Grosso MA, et al. Edoxaban versus warfarin for the treatment of symptomatic venous thromboembolism. *N Engl J Med*. 2013;369:1406–15.

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

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