**Special Populations: Obesity**

**Advanced Clinical Pharmacokinetics (P-313)**

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**Required Reading:**

Miller AD, Smith KM. Medication and nutrient administration considerations after bariatric surgery. *Am J Health-Syst Pharm* 2006:63:1852-7.

**Chapter 3:** Applied Clinical Pharmacokinetics. Larry A. Bauer, 2nd edition, 2008, pp. 81-2.

**Chapter 154:** Pharmacotherapy: A Pathophysiologic Approach, eds. DiPiro et al., 8th edition, 2011. (Not responsible for treatment section)

**Learning Objectives:**

1. Identify medications that can contribute to weight gain.
2. Describe the medical risks and disease states associated with overweight populations.
3. Discuss commonly used equations or measurements to define overweight and obesity and the potential limitations for drug dosing.
4. Explain the effect of obesity on absorption, distribution, metabolism, and elimination.
5. Summarize pharmacokinetic changes in specific drugs and drug classes post-bariatric surgery.
6. Provide recommendations for drug administration in bariatric surgery patients.

**Facts and Figures of Obesity**

**WHO has designated obesity as a disease AND its prevalence to be of epidemic proportion.**

Obesity is a major and visible public health problem in the US as well as worldwide.

65% of the world’s population lives in countries where overweight (OW) and obesity kills more people than underweight.

Worldwide obesity has nearly doubled since 1980.

* Overweight and obesity are the fifth leading cause of global deaths
* 2.8 million adults die each year as a result of being OW or obese

Adult Obesity Rates in the US (2012 data)

* Louisiana 34.7%
* Colorado 20.5%
* Pennsylvania 29.1%
* Delaware 26.9%
* New Jersey 24.6%
* New York 23.6%

The average American is more than 24 pounds heavier today than in 1960.

“Obesity rates tripled in the past 30 years, a trend that means, for the first time in our history, American children may face a shorter expected lifespan than their parents.”

-www.letsmove.gov

WHO: Obesity is preventable.

**Causes of Obesity**

The development and prevalence of obesity is complex and involves many factors:

* Lifestyle/Environmental
  + Reduced physical activity
  + Portion distortion
  + “Super-size” meals
  + More reliance on take out and eating in restaurants
  + Other factors
* Genetics
  + Parents vs. children
  + Siblings
  + Obesity genes
  + Inherited syndromes
* Medical Conditions
  + Obesity may occur secondary to a medical condition
  + Cushing’s disease, growth hormone deficiency, insulinoma, leptin deficiency, depression, binge-eating disorder, schizophrenia
* Medications

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| ***Medications Associated with Weight Gain*** | |
| Atypical antipsychotics  Clozapine, olanzapine, quetiapine, risperidone | Conventional antipsychotics  Chlorpromazine, haloperidol |
| Antidepressants  TCA, mirtazapine | Oral hypoglycemic agents  Sulfonureas, thiazolidinediones |
| Anticonvulsants  *Carbamazepine, gabapentin, valproic* | Hormones  Corticosteroids, insulin, oral contraceptives |

**Costs of Obesity: Financial and Health Impact**

* Up to 35% of Americans resolve to lose weight each year ($30-50 billion/yr)
* Obesity is associated with significant morbidity and mortality, increased health care costs, and reduced quality of life
* Obesity is a major risk factor for coronary heart disease \*\**second leading cause of preventable death in the US after tobacco use\*\**
* Risk of co-morbid disease is linked to the degree of obesity

**All fat is not created equal…**

* Intraabdominal or visceral fat
  + Central obesity pattern
  + Apple vs. pear
  + Apple: weight above waist = bad (HTN, DM, Heart)
  + pear: weight below waist = less risk
* Subcutaneous fat
  + Can affect the metabolic processes of insulin to varying degrees

**Defining Overweight or Obesity** (See Table 154-3 in Pharmacotherapy text)

* Obesity: an excessively high amount of body fat or adipose tissue in relation to lean body mass
* Overweight: refers to increased body weight in relation to height, when compared to a standard of acceptable weight
* Body Mass Index (BMI)
  + Expression of an individual’s weight in relation to height
  + Most valid and practical indicator of overweight and obesity
* Waist Circumference (WC) = *narrowest circumference measured between the last rib and the top of the iliac crest*
  + Most practical method of determining central/visceral adiposity
  + ↑ WC also a marker for ↑ risk even if normal weight
  + Men: > 40 inches Women: > 35 inches
* Other methods
  + Whole body immersion, computed tomography (CT), magnetic resonance imaging (MRI)]

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| |  | | --- | | Table 154-3 Classification of Overweight and Obesity by Body Mass Index (BMI), Waist Circumference, and Associated Disease Risk | |
| |  |  |  | **Disease Risk*a* (Relative to Normal Weight and Waist Circumference)** | | | --- | --- | --- | --- | --- | |  | **BMI (kg/m2)** | **Obesity Class** | **Men http://www.accesspharmacy.com/images/special/lesserorequal.gif40 inches Women http://www.accesspharmacy.com/images/special/lesserorequal.gif35 inches** | **Men > 40 inches Women > 35 inches** | | Underweight | <18.5 |  | – | – | | Normal weight*b* | 18.5–24.9 |  | – | High | | Overweight | 25.0–29.9 |  | Increased | High | | Obesity | 30.0–34.9 | I | High | Very high | |  | 35.0–39.9 | II | Very high | Very high | | Extreme obesity | http://www.accesspharmacy.com/images/special/greaterorequal.gif40 | III | Extremely high | Extremely high | |
| *a*Disease risk for type 2 diabetes, [hypertension](javascript:PopupGlossaryTerm(2752286);), and cardiovascular disease.  *b*Increased waist circumference can also be a marker for increased risk even in persons of normal weight.  *Adapted from Preventing and Managing the Global* [*Epidemic*](javascript:PopupGlossaryTerm(2752252);) *of Obesity. Report of the World Health Organization Consultation on Obesity. Geneva: World Health Organization, 1997. National Institutes of Health, National Heart, Lung and Blood Institute, [http://www.nhlbi.nih.gov/guidelines/obesity/ob\_home.htm](http://www.nhlbi.nih.gov/guidelines/obesity/ob_home.htm" \t "_blank).* |

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**Which weight is appropriate for dosing calculations?**

* Total body weight (TBW)

*If drug gets distributed in fat, use TBW*

* Ideal body weight (IBW)

Men: 50 kg + [2.3 kg X (ht in inches – 60)]

Women: 45 kg + [2.3 kg X (ht in inches – 60)]

* Dosing weight or adjusted body weight

Use if drug gets distributed in muscle

DWOB = IBW + (CF)(TBW – IBW)

Drug dosing may be based on TBW, IBW or on an adjusted body weight in between these two values, depending on the drug’s properties.

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| **Physiologic Changes in Obesity** | **Pharmacokinetic Implications** |
| Absorption | No significant effect on rate or extent of absorption |
| Distribution   * Higher % of body fat * Lower % of lean tissue and body water | Vd : Effect of obesity on Vd is highly variable and dependent on lipid solubility  ***Lipid solubility*** *= most important variable in predicting effect of obesity on drug distribution*  High lipid solubility 🡪 distribute into adipose tissue 🡪 Vd in obesity dramatically larger than non-obese  \*\*May affect t½ and duration of drug effect  Hydrophilic drugs 🡪 little to no distribution into adipose tissue 🡪 no significant difference in Vd in obese vs non-obese  Protein binding:  Albumin: unchanged in obesity  AAG: conflicting evidence |
| Metabolism   * Higher cardiac output * ↔ Hepatic blood flow * Enlarged liver with histologic changes | Influence of obesity on hepatic clearance is not well understood  Hepatic clearance: dependent on the metabolic pathway of a given drug |
| Elimination/Excretion   * Increased renal blood flow * Higher glomerular filtration rate | ↑ Renal elimination  ↑ Kidney size  Studies found higher absolute clearance values for drugs dependent on glomerular filtration in obese vs. non-obese |

Applied Pharmacokinetics and Pharmacodynamics: Principles of Therapeutic Drug Monitoring. ME Burton. 4th ed. 2006

**Predicting renal clearance**

* Creatinine clearance in obesity
  + - TBW 🡪 overestimate CrCl
    - IBW 🡪 underestimate CrCl
    - Salazar and Corcoran (1988) – unverified method for obese patients (wt in kg & ht in meters)

Clcr (males) = [137-age] x [(0.285 x wt) + (12.1 x ht2)]

(51)(SCr)

Clcr (females) = [146-age] x [(0.287 x wt) + (9.74 x ht2)]

(60)(SCr)

* + - For BMI >30, calculate adjusted body weight
    - TUSP: 40% correction factor for adjusted body weight

DWOB = IBW + (CF)(TBW – IBW)

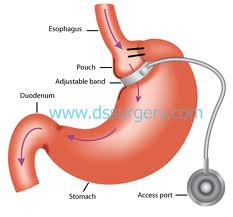
* Weight for Clcr may be different from dosing weight

**Pharmacodynamic Effects in Obese Patients**

* Changes in target tissue sensitivity
* Increased sensitivity *(glipizide, glyburide, prednisolone, triazolam)*
* Decreased sensitivity *(verapamil, atracurium)*
* Changes in receptor expression or affinity

*PD effects: poorly predictable*

**Pharmacokinetic Medication Changes after Bariatric Surgery**

* Issues surrounding drug therapy for obesity
  + Modest weight loss
  + Various adverse effects (steatorrhea, oily spotting, CV side effects)
* Prevalence of bariatric surgery in US
  + 1993: 16,000 annually
  + 2003: 103,000 annually
  + 2008: 800,000 annually
* Cosmetic vs. health benefits
  + Remission of disease
  + Increased risk of hospital admission in first year after surgery
  + Most remain clinically obese and regain weight

Types of Bariatric Surgery – **categorized by surgical technique**

* Restrictive Procedures:

*Stomach is reduced to a small pouch*

*Weight loss is achieved through reducing food intake*

* + Gastric banding
  + Vertical-banded gastroplasty
  + Sleeve gastrectomy
* Malabsorptive Procedures:

*Portions of the small intestine are bypassed*

*Weight loss is achieved through reducing food absorption*

* + Biliopancreatic diversion
  + Duodenal switch
* Combination Procedures:
  + Roux-en-Y gastric bypass

Drug Pharmacokinetics after Bariatric Surgery

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| ***Physiologic change*** | ***Possible effect on medications*** |
| **Smaller stomach size** | **Smaller stomach size** |
| Less gastric mixing | Reduced drug disintegration |
| Increases gastric pH  **(Normal stomach has pH 1-3)** | ↓ absorption of acidic meds **(ketoconazole, digoxin, rifampin)** |
| Slower gastric emptying | Reduced rate of absorption  **(not reduced extent of abs)** |
| **Intestinal diversion** | **Intestinal diversion** |
| Less surface area for absorption | Reduced absorption of many drugs |
| Limited bile acid resins | Reduced F of lipophilic drugs and  those undergoing enterohepatic  recirculation **(cyclosporine, phenytoin, rifampin, levothyroxine)** |
| Reduced metabolic enzymes or  transporters in intestinal wall | Altered levels of drugs which are  substrates of these enzymes or  transporters |

Clinical Implications

* Drugs exhibiting decreased bioavailability

1. cyclosporine and tacrolimus
2. levothyroxine
3. phenytoin
4. rifampin

* Drugs exhibiting NO changes post-bariatric surgery
  1. isoniazid
  2. ethambutol
  3. ranitidine
  4. haloperidol
* Drug properties with the greatest potential for decreased absorption
* **Poorly absorbed**
* **lipophilic**
* **undergoing enterohepatic recirculation**

Considerations for commonly used drugs & drug classes post-bariatric surgery

Oral Contraceptives

* Increased risk for unplanned pregnancies
  + Obesity is linked to infertility
  + Decreased absorption of OCs
* Recommendation: increase dose of oral contraceptives

NSAIDS and salicylates

* Increased risk of GI ulceration due to the smaller stomach
* Recognize that pain syndromes may improve post-operatively with weight loss
* Recommendation:

Oral bisphosphonates

* Increased risk of GI ulceration due to reduced stomach size
* Risk for osteoporosis due to ↓ calcium absorption after bariatric surgery
* Recommendation:

Insulin

* Potential for decreased insulin needs post-operatively
  + Significant reductions in caloric intake initially
  + Rapid weight loss 🡪 increased insulin sensitivity
    - RYGB ~ 10-15 lb weight loss per month during the first 6 months
  + Increased levels of GLP-1 and GIP 🡪 Induces insulin secretion
  + Resolution of DMII may occur within days
* *Recommendation: use sliding scale and increase BG monitoring*

Warfarin

* No evidence of decreased warfarin effects after bariatric surgery
* Well-absorbed from the stomach and proximal small intestine
* Recommendation:

Vitamin and Mineral Considerations

Calcium

* Increased risk for bone loss and secondary hyperparathyroidism
* Bariatric surgery results in a decrease in hydrochloric acid production 🡪 affecting the absorption of calcium
* Absorption can be increased by using different salt forms
* Recommendation: Calcium citrate (not Ca carbonate b/c it requires acidic environment to absorb. Bariatric surgery, produce less acid)

Iron

* Increased risk of iron deficiency anemia
* Bariatric surgery results in a decrease in hydrochloric acid production 🡪 affecting the absorption of iron
* We consume iron in ferric state (Fe3+), it gets reduced to ferrous state (Fe2+) in the acidic stomach, and then absorbed in the duodenum
* Duodenum is the primary site for iron absorption 🡪 duodenum is bypassed in bariatric surgery procedures, thus significantly impacting iron absorption
* Recommendation: Give iron with Vit C to decrease stomach pH for absorption

Vitamin B12

* B12 deficiency 🡪 pernicious anemia, irreversible peripheral neuropathy
* Absorption is dependent on:
  + Intrinsic factor which is made in the parietal cells of the stomach
  + Hydrochloric acid to cleave vitamin B12 from stomach proteins
* Recommendation: B12 injection qmonth

General recommendations in the bariatric patient

* Avoid ER, DR, EC
  + Consider immediate release or crushable/liquid formulations
* Increased monitoring for therapeutic effect may be necessary for efficacy
* Remember to consider nutrient supplementation
  + Daily MVI (possibly liquid form) indefinitely for all patients!
  + Calcium citrate
  + Bone mineral density testing
  + Iron + vitamin C
  + B12 supplementation