ACLP How To Guide: Psychopharmacology after Bariatric Surgery

How to Approach Psychopharmacology in the Patient with Bariatric Surgery

Learning Objectives

1. Describe the pharmacokinetic changes that occur after bariatric surgery
2. Translate the pharmacokinetic changes into clinically relevant action steps
3. Identify when to incorporate the action steps with post-surgical patients

Step 1: Understand the types of bariatric surgeries (restrictive vs. malabsorptive mechanism[1] - see Figure)

- Gastric Band - silicone adjustable band tied around antrum of stomach- creates a *restrictive* pouch for less room for food accumulation.
- Sleeve Gastrectomy- roughly 80% of stomach is removed (removes gastric fundus and reduces Ghrelin Cell allotment) - creates a banana-shaped *restrictive* sleeve/tube - less room for food accumulation
- Roux-en-Y Gastric Bypass - stomach size is reduced into a gastric pouch (about the size of an egg) and the intestine is rerouted to bypass distal 2/3 of stomach, entire duodenum, and 20-40 cm of proximal jejunum. *Restrictive* due to the pouch AND *malabsorptive* considering intestinal bypassing. Most literature about psychopharmacology changes.
- Biliopancreatic Diversion with Duodenal Switch - stomach size surgically reduced (can be a pouch or sleeve), bypass the majority of intestine by connecting end portion of intestine to the duodenum near the stomach. Some *restrictive* component due to stomach size change, but mostly (traditionally) focused on *malabsorption.*

Step 2: Identify potential pharmacokinetic changes of all bariatric surgeries[1-4]

- Smaller stomach size and new stomach shape
  - Will shorten timeframe of exposure to the stomach's acidic environment, thus may delay (or cause incomplete) tablet disintegration and dissolution. This may be further exacerbated by a faster gastric emptying rate.
- Perioperative fluid shifts - lithium is especially vulnerable to these changes (lithium is hydrophilic, non-protein bound, renally excreted)
- If successful weight loss
  - Potential for smaller volume of drug distribution due to loss of adipose tissue (particularly lipophilic meds)
  - Improved hepatic function and subsequent metabolism (particularly if the patient had non-alcohol-related fatty liver disease (NAFLD) or non-alcohol-related steatohepatitis (NASH), as these can be reversible with weight loss)
  - Renal drug clearance could be affected from improved renal functioning after significant weight loss

Step 3: Identify potential pharmacokinetic changes of specific Bariatric Surgeries[1,2,5,6,7]

- Restrictive procedures (especially those that make a pouch)
  - Can impede passage of pills >10 mm - painful, delay/irregularities in medication passage, absorption, and subsequent effect
  - Will restrict the amount of available caloric intake in one setting

    - Remember Ziprasidone (500 kcal) and Lurasidone (350 kcal) intake requirements for appropriate absorption (e.g., at 250 kcal, Ziprasidone's absorption can be impaired by up to 90%)
    - In addition, most bariatric surgeries have strict caloric restrictions immediately after surgery with many months required to build up to the final/higher caloric intake (often starting around 200 kcal for multiple weeks)
- Malabsorptive procedures
  - Can have decreased or sporadic absorption
    - Decreased intestinal length, reduced mucosal exposure
    - Altered lipophilic drug solubilization (bypass proximal small intestine where bile salts are present)
  - Could also have supra-therapeutic/toxic drug levels
    - Cytochrome 3A4 – most prevalent CYP in proximal small bowel. When this portion of intestine is removed → less 3A4 metabolism prior to systemic absorption → potential higher serum levels than previously experienced (e.g., aripiprazole, buspirone*, carbamazepine*, citalopram, mirtazapine, quetiapine*, trazodone, vilazodone*. [* indicates 3A4 is the primary CYP responsible for metabolism. In the other examples, 3A4 contributes to metabolism])
    - Cytochrome 1A2 – induced by aromatic hydrocarbons (via smoking). Almost ubiquitously encouraged to stop smoking prior to surgery. Many centers require the patient to stop prior to surgery. Smoking cessation could lead to supra-therapeutic levels and causing more side effects (e.g., clozapine, olanzapine, and clomipramine could result in greater sedating side effects and could impede exercise and recovery involvement)

Step 4: Action Steps- Pre-surgery[1,2,4,8]

- Action steps are from a psychopharmacology standpoint. They are not a comprehensive description of the presurgical psychosocial assessment.
- Get a Baseline:
  - Mental Status + most prominent and target psychiatric symptoms
  - Use standardized rating scales to assess severity of psychiatric disorder; having a baseline measurement can help with trending symptom severity perioperatively
  - Consider getting plasma drug levels if available
- Investigate:
  - Type of surgery (restrictive vs malabsorptive vs combination)
  - Current Mediations: Site of absorption? Alternate formulations? Lipophilic? Caloric requirements? Vulnerable to fluid shifts? Pill size? CYP 3A4 or 1A2 metabolic pathways?
- Educate Patient on any potential for:
  - Malabsorption
  - Withdrawal symptoms vs symptom recurrence/exacerbation
  - Increased side effects
- The only currently agreed upon proactive psychopharmacology intervention:
  - Change from controlled release, modified release, enteric coating, extended release, etc. to immediate release (IR) form if available
  - Other than the IR consideration DO NOT make major changes to the patient's regimen if they are stable prior to surgery. There is no guarantee that a change will be necessary nor

is there an absolute way to know if they will have malabsorption or side effects from the procedure.

Step 5: Action Steps - Immediately Post Surgery up to 1 year[1,2,5,6]

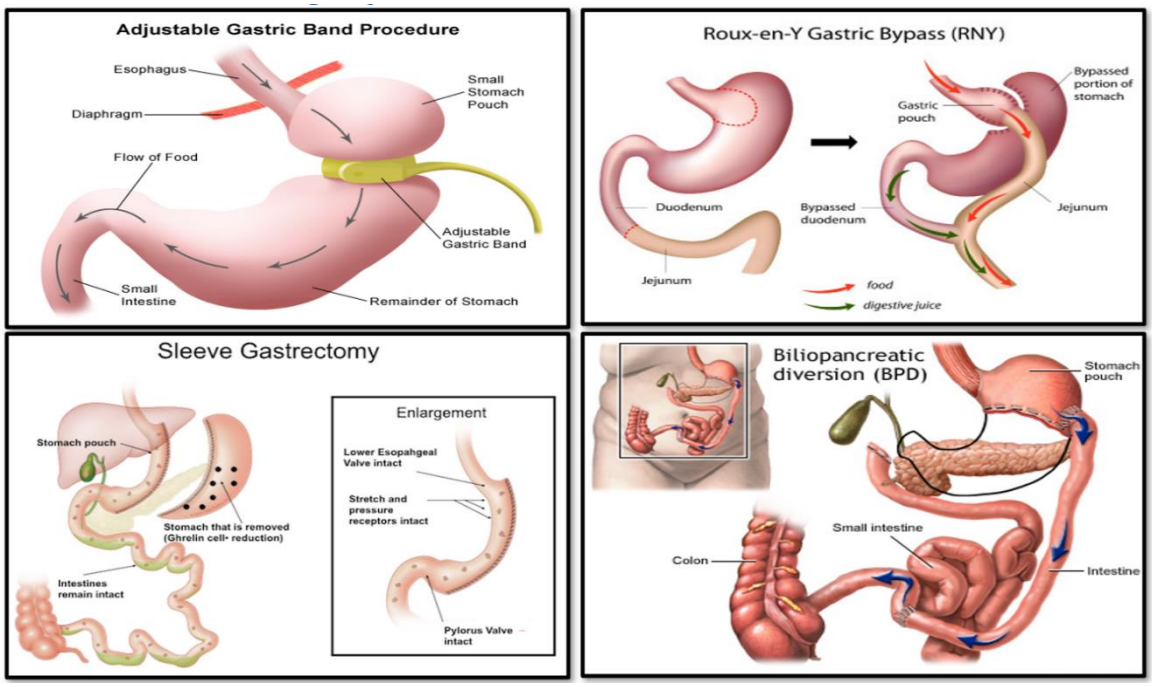
- Use the clinical interview to evaluate for worsening symptoms vs. withdrawal symptoms vs. side effects.
- Trend plasma drug levels, validated rating scales, and symptom logs that patients have been asked to fill out in order to track disease course, symptom timing, and severity.
- Malabsorption concerns (consider these to be incremental steps: "try this, then do this")
  - Use an IR form (if not already done proactively)
  - Increase or divide the dose of the current medication
  - Consider crushing the pill, using oral disintegrating tablet or liquid form (if available)
    - This will at least bypass tablet disintegration and dissolution phase
    - Remember, just because the med dissolves in the mouth does not mean that it is absorbed in the mouth
  - Use an alternate route of administration, a.k.a. "bypass the bypass" (if available)
    - Transdermal, intravenous, intramuscular, inhaled, rectal, sublingual
    - Compounding pharmacies may be able to help
  - Switch to a new medication (potentially one that can fulfill any of the above steps)
    - Switching is often preferred over augmentation or combination strategies to avoid meds with high metabolic burden (e.g., atypical antipsychotics, valproic acid, mirtazapine, etc.)
    - However, if medications with high metabolic burden are needed for stability, they should be considered. Remember to identify the patient's preference of treatment in risk vs benefit discussions.
- Side effects
  - If pill discomfort - can see if smaller pill sizes are available (or crush the pill if appropriate)
  - Decrease the dose if med is a substrate of 3A4 or 1A2 or is subject to fluid shifts
  - Check labs/tests for toxicities (Cr/TSH, ANC, LFT/Plt, EKG, etc.)
  - If medication toxicity, reduce or hold medication. Depending on severity consider restarting at a lower dose
- Ensure appropriate risk vs benefit conversations with patients to appropriately align with their goals!

Step 6: Action Steps - Post Surgery > 1 year[1,2,8,9]

- If dosing or frequency changes were made - consider retrial of the pre-surgery regimen
  - Many homeostatic corrections occur. For example, hepatic cytochrome P450s will eventually compensate for the 3A4 loss, and patients may go back to smoking (thus re-inducing 1A2)
- If changes due to stomach size were made (smaller pill size, crushing the pill, disintegrating or liquid forms, caloric restrictions)
  - Depending on eating habits, the stomach may stretch back out (to some degree) and potentially allow a reassessment of the changes that were made.
- If weight regain
  - Remember above pharmacokinetic points (from "Step 2") regarding:

    - Drug distribution and adipose tissue (especially lipophilic meds)
    - Hepatic function and subsequent metabolism (particularly with NAFLD or NASH)
    - Renal drug clearance changes
  - Attempt to keep the metabolic burden of the medication regimen as low as possible.
  - Remember that weight gain can be emotionally difficult for patients; a non-judgmental, empathetic approach is recommended in order to be effective
- If new neuropsychiatric symptoms arise
  - Consider exploring additional aspects beyond the surgery, medications, and pharmacokinetics in this timeframe
  - The rate of new onset alcohol use disorder after bariatric surgery is approximately 7%-8%
  - Bariatric surgery often calls for major life change. Adjusting to lifestyle changes can be stressful, especially if there is weight regain or if eating was a coping strategy to deal with life stressors.
  - Many psychiatric disorders are chronic, and it is not unusual to have to change medication regimens during the course of treatment (with or without bariatric surgery).

Figure: Types of Bariatric Surgeries



Pictures from: https://obesitycenter.org/weightlosssurgery/adjustable-gastric-banding.php; https://hospital.uillinois.edu/primary-and-specialty-care/surgical-services/bariatric-surgery-program/our-services/roux-en-y-gastric-bypass-rygb; https://drvpareek.com/laparoscopic-sleeve-gastrectomy-procedure-and-outcomes/; https://www.princetonhcs.org/care-services/institute-for-surgical-care/the-center-for-bariatric-surgery-and-metabolic-medicine/surgical-procedure-options/biliopancreatic-diversion

References

1. Padwal, R., Brocks, D., & Sharma, A. M. A systematic review of drug absorption following bariatric surgery and its theoretical implications. *Obes Rev;* 2010. *11*(1), 41-50.
2. Roerig, J. L., & Steffen, K. Psychopharmacology and Bariatric Surgery. *European Eating Disorders Review;* 2015. *23*(6), 463-469.
3. Seaman, J. S., Bowers, S. P., Dixon, P., & Schindler, L. Dissolution of common psychiatric medications in a Roux-en-Y gastric bypass model. *Psychosomatics;* 2005. *46*(3), 250-253.
4. Macgregor, A. M., & Boggs, L. Drug Distribution in Obesity and following Bariatric Surgery: A Literature Review. *Obes Surg;* 1996. *6*(1), 17-27.
5. Bingham, K., Hawa, R., & Sockalingam, S. SSRI discontinuation syndrome following bariatric surgery: a case report and focused literature review. *Psychosomatics;* 2014. *55*(6), 692-697.
6. Hamad, G. G., Helsel, J. C., Perel, J. M., Kozak, G. M., McShea, M. C., Hughes, C.,. Wisner, K. L. The effect of gastric bypass on the pharmacokinetics of serotonin reuptake inhibitors. *Am J Psychiatry;* 2012. *169*(3), 256-263.
7. Rosenbaum, J. F., Fava, M., Hoog, S. L., Ascroft, R. C., & Krebs, W. B. Selective serotonin reuptake inhibitor discontinuation syndrome: a randomized clinical trial. *Biological Psychiatry;* 1998. *44*(2), 77-87.
8. Tandra, S., et. Al. Pharmacokinetic and pharmacodynamic alterations in the Roux-en-Y gastric bypass recipients. *Ann Surg;* 2013 *258*(2), 262-269.
9. King WC, Chen JY, Mitchell JE, Kalarchian MA, Steffen KJ, Engel SG, Courcoulas AP, Pories WJ, Yanovski SZ. Prevalence of alcohol use disorders before and after bariatric surgery. Jama. 2012;307:2516-2525.