Long-term pharmacotherapy considerations in the bariatric surgery patient

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Purpose. Pharmacists’ role in optimizing long-term pharmacotherapy for bariatric surgery patients is detailed.

Summary. Bariatric surgery patients provide a difficult challenge in terms of many pharmacotherapy issues, especially in the chronic care setting, where data on long-term effects of bariatric surgery are limited. The most common procedures are Roux-en-Y gastric bypass (RYGB), adjustable gastric banding, and sleeve gastrectomy. Sleeve gastrectomy has become the most common procedure in the United States, primarily because it has less overall chronic malabsorption effects than RYGB. Pharmacotherapy management is complicated by rapid weight loss combined with a number of pharmacokinetic changes, such as decreased absorption of some medications due to altered gastrointestinal tract anatomy and potentially increased concentrations of some medications due to a decreased volume of distribution resulting from weight loss. Nutritional and metabolic supplementation are of the utmost importance in order to limit deficiencies that can lead to a number of conditions. Many chronic diseases, including hypertension, diabetes, gastroesophageal reflux disease, and urinary incontinence, are improved by bariatric surgery but require close monitoring to ensure the effectiveness of maintenance pharmacotherapy and avoidance of adverse effects. Psychotropic medication management is also an important pharmacotherapy concern, as evidenced by antidepressants being the most commonly used medication class among preoperative bariatric surgery patients.

Conclusion. Pharmacists have an increasing role in the chronic management of the bariatric surgery patient due to their knowledge of medication dosage forms and expertise in disease states affected by bariatric surgery.

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Bariatric surgery is one of the fastest-growing elective surgical procedures in the United States. Estimates from the American Society for Metabolic and Bariatric Surgery indicate that 179,000 bariatric surgeries were performed in 2013, representing a 15% increase from 2011. Sleeve gastrectomy is the primary bariatric surgical procedure (42.1% of cases), followed by the Roux-en-Y gastric bypass (RYGB) (34.2%) and gastric banding procedures (14.0%). Much of this growth is due to increased acceptance of bariatric surgery procedures by the medical community and emerging evidence of demonstrated long-term benefits in the treatment of chronic diseases, including diabetes mellitus, hypertension, and obstructive sleep apnea. The anatomical and physiological changes associated with surgery and weight loss create pharmacotherapy concerns that require proactive monitoring and management to maximize the benefits of bariatric surgery procedures and prevent morbidities. Issues of long-term pharmacotherapy management will be discussed in this review. A detailed review of acute perioperative concerns in the bariatric surgery patient can be found in a separate publication.
Pharmacokinetic alterations

Continued chronic disease management is needed after bariatric surgery, and medications should be restarted as soon as feasible to minimize therapy interruptions. Management is complicated by pharmacokinetic changes and rapid, extensive weight loss. While medication-specific data are lacking for most agents, the type of surgical procedure performed can be expected to play a role in medication kinetics. Restrictive procedures, such as adjustable gastric banding and sleeve gastrectomy, reduce the size of the stomach and can be expected to have fewer pharmacokinetic effects than combined procedures.

RYGB and biliopancreatic diversion with duodenal switch (BPD-DS) both reduce the size of the stomach and bypass portions of the small intestine. RYGB is the most commonly performed malabsorptive procedure (i.e., a surgical operation to induce weight loss via gastric malabsorption); in this procedure, the duodenum and 50–70 cm of jejunum are bypassed. In BPD, the entire duodenum and jejunum are bypassed and the stomach is connected directly to the ileum. Due to concerns related to nutrient absorption, BPD is rarely used today. Beyond the anatomic changes that occur as a result of bariatric surgery, physiological changes also can affect medication pharmacokinetics. The rerouting of the gastrointestinal tract increases gastric pH and decreases the effective surface area for medication absorption.

The limited data available for specific agents indicate high interpatient variability, often involving an altered time to maximum plasma drug concentration \( t_{\text{max}} \) and an altered maximum plasma drug concentration, but with area under the drug concentration–time curve (AUC) values similar to those in non–bariatric surgery patients.

Absorption. The partitioning of the stomach with sleeve gastrectomy, adjustable gastric banding, or RYGB can increase gastric pH and shift medication absorption to the more basic small intestine. This overall increase in pH can decrease absorption of weakly acidic medications and increase absorption of basic ones. Medications that require long absorption times, including extended-release agents, are likely to have reduced bioavailability. Bypassed portions of the small intestine also contain efflux transporters, which paradoxically can increase absorption of some agents.

Surgical techniques that promote nutrient malabsorption (e.g., RYGB) are more likely to create medication absorption issues than are restrictive procedures such as sleeve gastrectomy. The primary mechanisms for medication malabsorption are decreased absorptive surface area and altered acidic environment.

The relative changes in pharmacokinetics and pharmacodynamics were compared in 18 RYGB patients and 14 control subjects. A cocktail of probe medications (caffeine, tolbutamide, omeprazole, dextromethorphan, and oral and i.v. midazolam) was administered to estimate the effect of bariatric surgery on five major drug metabolism systems (those mediated by cytochrome P-450 (CYP) isozymes 1A2, 2C9, 2C19, 2D6, and 3A4). Overall, there were no major differences in pharmacokinetic values except for a significantly shorter time to \( t_{\text{max}} \) after administration of some evaluated agents and formulations. Relative to body mass index (BMI)–matched controls, the RYGB group had significantly lower \( t_{\text{max}} \) values for caffeine (0.58 hour versus 2.1 hours, \( p < 0.0001 \)), tolbutamide (1.4 hours versus 2.1 hours, \( p < 0.0001 \)), omeprazole (1.1 hours versus 4.4 hours, \( p < 0.0001 \)), and oral midazolam (0.5 hour versus 0.7 hour, \( p < 0.01 \)). While these data do not describe clinical differences in medication effects, the lower \( t_{\text{max}} \) values suggest that patients who have undergone RYGB could experience more rapid onset of effect with the use of these agents.

Distribution. The changes in the gastrointestinal tract that occur with bariatric surgery generally do not affect medication distribution. However, as weight loss occurs, clinicians should expect a reversal of obesity-related changes in medication distribution, including reduced volumes of distribution secondary to reduced blood volume and adipose tissue. Patients most likely to be affected in this manner are those receiving lipophilic agents, although significant reductions in volume of distribution could occur with many medications, potentially resulting in enhanced therapeutic effects or increased toxicity in a patient previously stabilized on fixed doses of medication prior to surgery.

Metabolism. The small intestine contains many enzymes responsible for medication metabolism; bypassing these regions of the intestine may decrease metabolism. CYP3A4 is the most abundant enzyme in the

**KEY POINTS**

- Data regarding absorption of specific medications after bariatric surgery are limited, requiring vigilant patient monitoring for effectiveness and toxicity.
- Bariatric surgery patients have a high long-term risk of vitamin and mineral deficiency requiring chronic supplementation and monitoring.
- As bariatric surgery can influence the course of a number of chronic diseases (e.g., depression, diabetes, hypertension, gastroesophageal reflux disease), close monitoring of pharmacotherapy is required.
- With their pharmacotherapy expertise, pharmacists are uniquely positioned to ensure appropriate medication management of the bariatric surgery patient in the ambulatory care setting.
Nutritional and metabolic considerations

Beyond considerations of dietary intake of macronutrients, bariatric surgery patients require monitoring and supplementation of vitamins and minerals to prevent and address deficiencies. The reduced size of the stomach, combined with a reduction in intestinal surface area, leaves patients vulnerable to reduced levels of nutrient absorption. As with medication absorption, the risk of deficiencies varies by procedure type. With restrictive procedures, routine monitoring of vitamin levels is not usually needed, and patients only require monitoring in the presence of symptoms of deficiency. However, due to reduced overall nutrition after surgery, many clinicians choose to monitor patients with restrictive procedures initially and then periodically thereafter to ensure there are no deficiencies.

For supplementation in the immediate postoperative period (three to six months after surgery), patients need two chewable adult multivitamins plus mineral supplements daily; chewable or liquid dosage forms are preferred for increasing absorption. While there are commercially available products for bariatric surgery patients, these may come at an increased cost. There is no evidence that these products are superior to inexpensive formulations that are verified by the United States Pharmacopeial Convention. Table 1 provides recommendations on the amounts of vitamins and minerals recommended for supplementation after surgery.

Calcium, vitamin D and phosphate. Patients are at risk for secondary hyperparathyroidism after RYGB, BPD, or BPD-DS due to reduced absorption of calcium and vitamin D. Patients should receive supplementation with calcium citrate (1200–1500 mg of elemental calcium) daily. Calcium citrate is the preferred salt form due to its nonreliance on gastric pH for absorption. Vitamin D should also be supplemented, with at least 3,000 IU taken daily. If vitamin D deficiency (a serum 25-hydroxyvitamin D concentration of <20 ng/mL) occurs, oral doses of vitamin D (or D₃, 50,000 IU once daily to once weekly) may be needed. Vitamin D malabsorption can also lead to hypophosphatemia, which is best corrected through increased vitamin D intake. Oral phosphate supplementation may be given as well. While specific data are unavailable, the use of powdered rather than tablet formulations is the generally preferred method of increasing calcium, vitamin D, and phosphate absorption. Patients may also need dual-energy X-ray absorptiometry scanning for assessment of osteoporosis at approximately two years after surgery.

Iron, folate, and cyanocobalamin. Decreased absorption of iron, folate, and cyanocobalamin can lead to anemia in bariatric surgery patients. Iron supplementation should entail daily administration of at least 45–60 mg of elemental iron, provided either in multivitamins or supplements. Iron is absorbed in the ferrous state (Fe²⁺), but iron is often consumed in the ferric state (Fe³⁺) and reduced in the acidic environment of the stomach. Data on the ideal formulation of iron for supplementation are unavailable, and guidelines recommend supplementation with any form. To help facilitate absorption, clinicians can consider combining iron with ascorbic acid to increase pH. Adequate folate supplementation (400 µg daily) can be achieved through multivitamin and mineral intake. It is especially important to ensure adequate supplementation in women of childbearing age to minimize the risk of neonatal neural tube defects. Cyanocobalamin plays a critical role in the formation of red blood cells, and adequate supplementation must be provided to maintain levels within the normal range. Oral supplementation with 1000 µg

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**Table 1. Recommendations for Vitamin and Mineral Supplementation After Gastric Banding and Gastric Bypass**

<table>
<thead>
<tr>
<th>Vitamin or Mineral</th>
<th>Amount Recommended (as % of Recommended Daily Allowance)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ascorbic acid</td>
<td>200</td>
</tr>
<tr>
<td>Calcium</td>
<td>100</td>
</tr>
<tr>
<td>Copper</td>
<td>50</td>
</tr>
<tr>
<td>Cyanocobalamin</td>
<td>300</td>
</tr>
<tr>
<td>Folate</td>
<td>150</td>
</tr>
<tr>
<td>Iron</td>
<td>50</td>
</tr>
<tr>
<td>Thiamine</td>
<td>150</td>
</tr>
<tr>
<td>Vitamin D</td>
<td>100</td>
</tr>
<tr>
<td>Zinc</td>
<td>33</td>
</tr>
</tbody>
</table>

*Adapted from reference 8.*
of cyanocobalamin daily is recommended if adequate absorption can be confirmed. If oral absorption is inadequate, weekly intranasal cyanocobalamin can be used. Alternatively, cyanocobalamin 1000 µg per month can be administered either intramuscularly or subcutaneously.

**Thiamine.** After bariatric surgery, patients are at risk for thiamine deficiency that can lead to beriberi, Wernicke's encephalopathy, or Wernicke–Korsakoff syndrome. Short-term signs and symptoms of thiamine deficiency include headache, nausea, fatigue, irritability, depression, and abdominal pain. Beriberi manifests as peripheral neuropathies, cardiomyopathy, edema, and tachycardia. Patients with Wernicke's encephalopathy may develop confusion, cognitive slowing, ataxia, and vision problems; if left untreated, the disease can progress to the Wernicke–Korsakoff syndrome, which is associated with permanent memory loss, inability to form new memories, confabulation, and hallucinations. For routine supplementation, thiamine intake from recommended multivitamins should be adequate. Close monitoring is warranted after bariatric surgery, as nearly 100% of cases of Wernicke–Korsakoff syndrome are diagnosed within six months postoperatively. However, patients with rapid weight loss, vomiting, a need for parenteral nutrition, alcohol abuse, encephalopathy, or heart failure are at increased risk for thiamine deficiency and require screening of thiamine levels; patients presenting with signs and symptoms consistent with Wernicke's encephalopathy also should be screened. Exact repletion regimens for treatment are not well studied, but administration of thiamine 500 mg i.v. daily for three to five days followed by administration of a 250-mg i.v. dose daily for an additional three to five days or until symptom resolution is recommended. Patients who have had Wernicke's encephalopathy should receive additional supplementation indefinitely, with a minimum of 100 mg orally administered daily, and be monitored closely.

**Heavy metals.** Copper and zinc are two heavy metals required in trace amounts for numerous metabolic processes. Zinc deficiency can lead to hair loss, pica, dysgeusia, and (in males) hypogonadism. Copper deficiency can lead to anemia, neutropenia, myeloneuropathy, and impaired wound healing. While routine screening for copper and zinc deficiency after bariatric surgery is not recommended, testing should be performed if a deficiency is suspected. Routine supplementation of both metals can be achieved with recommended multivitamin use. Additional supplementation can be achieved with parenteral or oral formulations. It is important to note that zinc replacement can lead to copper deficiency, and monitoring of copper levels is recommended in conjunction with zinc supplementation.

In summary, vitamin and mineral deficiencies are possible after bariatric surgery, especially malabsorptive procedures. Therefore, patients should receive multivitamin supplementation with two adult multivitamins daily plus additional calcium. Monitoring of symptoms and levels of other vitamins and minerals is necessary, and additional repletion of deficiencies may be required.

**Chronic disease management**

**Hypertension.** Blood pressure should be carefully measured at regular intervals after bariatric surgery, with special attention given to patients receiving antihypertensive medications. Currently, there is no systematic protocol specifying an optimal frequency of blood pressure monitoring postoperatively. Because a decrease in blood pressure as early as one week postoperatively was observed in patients in two studies, we empirically recommend monitoring blood pressure every week for the first month after surgery, followed by monthly monitoring for three months; this recommendation is based on our experience in a multidisciplinary clinical setting with medication adjustments primarily performed by a clinical pharmacist. Ambulatory blood pressure monitoring for this time period may be prudent, but further investigation is required.

Blood pressure may decrease significantly after bariatric surgery. Ahmed et al. observed a mean reduction in systolic blood pressure of 9 mm Hg and a mean reduction in diastolic blood pressure of 7 mm Hg as early as one week postoperatively in a group of 100 patients who underwent laparoscopic RYGB. One year after surgery, mean reductions in systolic and diastolic pressures of 15 and 9 mm Hg, respectively, were observed. Tritsch et al. noted a mean decrease in systolic of 18 mm Hg six months after bariatric surgery after initial adjustments made primarily by a pharmacist. In addition, among patients who were on antihypertensive therapy, the mean number of antihypertensive medications was reduced from 2.4 to 1.7 per patient six months after surgery.

Hypertension and diabetes are the two most common comorbidities seen in bariatric surgery patients. Although “successful” bariatric surgery is often defined as an average weight loss of 50% of excess body weight, modest weight reductions (e.g., 10% of total body weight) can often help reduce blood pressure. In addition to weight loss, other factors contribute to the decreased postoperative blood pressures observed in bariatric surgery patients. Increases in glucagon-like peptide 1 (GLP-1), a common gut hormone, induce natriuresis, thus possibly aiding in the initial lowering of blood pressure. Celik et al. discovered that sodium excretion decreased by 18% postoperatively in bariatric surgery patients yet remained high over a median timeframe of 21 months. Therefore, significant blood pressure reduction after surgery cannot be solely attributed to reduced sodium excretion. Obese patients often exhibit increased levels of renin activity, aldosterone, and angiotensin-converting enzyme, which likely contribute to sodium retention. These hormone inhibitors, ACE inhibitors, and angiotensin receptor blockers are often prescribed in bariatric surgery patients.
concentrations tend to return to normal levels postoperatively, leading to reduced blood pressures.\(^{17}\)

Given the current lack of guidelines on long-term antihypertensive dose modifications after bariatric surgery, practitioners must consider individual patient characteristics and general treatment guidelines when making medication adjustments. Also, it should be considered that patients undergoing bariatric surgery are placed on full liquid diets for one to two weeks preoperatively and postoperatively. The percentage loss of excess body weight must be taken into consideration as well. Initial postoperative dose reductions should be done, first empirically and then as needed. A mean reduction in systolic blood pressure of 8 mm Hg was observed in 71 patients at two weeks after sleeve gastrectomy despite discontinuation of one hypertension medication immediately postoperatively.\(^{11}\)

Initial hypertension medication adjustments should be made on an individual basis.\(^{18}\) The patient’s outpatient blood pressure control and medication adherence should be assessed. In most patients, diuretics should be the first agents discontinued after surgery in an attempt to limit volume depletion, hypotension, and acute kidney injury. However, due to their beneficial effects on hypertension-related morbidity and mortality, diuretics should be reinstituted as soon as possible after bariatric surgery patients are placed on a long-term diet. Beta-blockers should be continued in the immediate perioperative period and chronically in patients with coronary artery disease, heart failure, or myocardial infarction. However, consideration should be given to avoidance of long-term β-blocker therapy in patients with no compelling indication. Angiotensin-converting enzyme inhibitors or angiotensin receptor blockers should be continued indefinitely for their protective renal effects in patients with a diagnosis of chronic kidney disease.\(^{18}\) However, dose reduction or discontinuation may be considered in the immediate postoperative period to decrease the risk of hypotension or acute kidney injury due to potential volume depletion. Calcium channel blockers are excellent perioperative and long-term options due to their lack of effect on volume status and renal function.

**Hyperlipidemia.** Hyperlipidemia is a common comorbidity associated with obesity and thus in patients undergoing bariatric surgery. The effect of bariatric surgery on various lipid components has varied among studies as well as the type of surgical procedure. A single-center study demonstrated a statistically significant increase in the mean postoperative high-density lipoprotein (HDL) concentration (from 48.10 to 52.47 mg/dL) at 2 months but no significant difference at 12 months in 250 patients undergoing RYGB, sleeve gastrectomy, or gastric band placement.\(^{19}\) Another single-center study comparing medical therapy and bariatric surgery for diabetes management evaluated lipid changes as a secondary outcome.\(^{20}\) While low-density lipoprotein (LDL) concentrations at 12 months were not reported, at 36 months the concentrations in the RYGB and sleeve gastrectomy groups had increased 16.9% and 14.5%, respectively (those changes were not statistically different from those documented with medical therapy). HDL concentrations were significantly higher, by nearly 35%, in both the RYGB and sleeve gastrectomy patients at 12 and 36 months postoperatively, as compared with HDL levels in the medical therapy group. A recent review of 29 published studies of outcomes in bariatric surgery patients (total \(n = 7971\)) found only 3 studies that reported long-term effects, with only 1 examining lipid concentrations.\(^{21}\) Remission of hyperlipidemia (defined as improvement to a total cholesterol concentration of <200 mg/dL, a triglyceride concentration of <200 mg/dL, and HDL and LDL cholesterol concentrations of >40 and <160 mg/dL, respectively) was achieved in 60.4% of RYGB patients and 22.7% of gastric band patients. More prospective studies are needed to definitively determine the effect of bariatric surgery on lipid profiles, absorption of hyperlipidemia-targeted medications, and, ultimately, cardiovascular outcomes.

**Anticoagulation.** A primary complication after bariatric surgery is venous thromboembolism (VTE), which can be due to several factors, such as lack of mobility, obesity, and surgery. Obesity is a known risk factor for atrial fibrillation, with many patients already receiving chronic anticoagulation therapy requiring temporary cessation or “bridging” of oral therapy depending on stroke risk. Patients should be evaluated on a case-by-case basis to develop an optimal anticoagulation plan based on assessment of stroke and bleeding risks using validated risk assessment instruments.

Traditional treatment of VTE involves the use of i.v. unfractionated heparin or subcutaneous low-molecular-weight heparin, with subsequent transition to warfarin therapy. Limitations of low-molecular-weight heparin include a paucity of data on its use in patients weighing more than 130 kg, who account for a significant portion of the bariatric surgery population; this makes unfractionated heparin potentially more useful in this setting despite the requirement for monitoring of activated partial thromboplastin time in order to have an accurate real-time measure of anticoagulation for acute VTE, as many facilities currently do not perform real-time anti–factor Xa monitoring in patients receiving low-molecular-weight heparins.

Warfarin therapy in the bariatric surgery patient presents a number of challenges. Patients generally ingest much less vitamin K in the weeks after bariatric surgery due to a clear-liquid or full-liquid diet. Results of a recent study revealed that warfarin dosing requirements decreased significantly in the weeks after bariatric surgery but returned to normal at approximately six months.\(^{22}\) Absorption of warfarin...
and other medications could be altered after bariatric surgery, especially after malabsorptive procedures. The effects of malabsorptive procedures on the absorption of many medications are largely unknown and require further investigation. Therefore, International Normalized Ratio (INR) values should be monitored closely in patients receiving warfarin during the early postoperative period (for dosage decreases) and for long-term management. It may be prudent to empirically withhold warfarin therapy or decrease the dosage in the early postoperative period until the patient is on solid foods.

With the availability of novel anticoagulants, there is interest in using these agents to treat VTE after bariatric surgery because they do not require therapeutic monitoring or vitamin K diet consistency. Currently available Food and Drug Administration (FDA)–approved agents for VTE or atrial fibrillation (or both) include the factor Xa inhibitors apixaban, rivaroxaban, and edoxaban as well as the direct thrombin inhibitor dabigatran. Edoxaban is absorbed primarily in the proximal small intestine, which could be affected by RYGB; rivaroxaban is also largely absorbed proximally. Apixaban is absorbed significantly in the colon; thus, it can be inferred that its absorption is not likely to be greatly affected by bariatric surgery. Dabigatran is not an ideal agent for use in bariatric surgery patients given the high frequency of gastrointestinal adverse effects, including dyspepsia and esophagitis, reported in clinical studies.

Currently, there are minimal clinical data on novel anticoagulants specific to the bariatric surgery population. The only relevant published report pertained to a single patient with VTE who was treated with rivaroxaban. The patient had peak plasma rivaroxaban concentrations similar to the expected range (based on published data), but the initiation of rivaroxaban did not occur until several months after surgery following warfarin reversal due to INR values above the therapeutic range. Rivaroxaban should be taken with food to increase bioavailability (by approximately 20%) when doses exceed 10 mg daily, which could be difficult in patients receiving long-term anticoagulation therapy with this agent. It is also not recommended to be administered via nasojejunal tube. At this point, no novel anticoagulant can be routinely recommended in the bariatric surgery population until further studies demonstrate both safety and effectiveness.

Diabetes mellitus. The mechanisms of bariatric surgery’s beneficial effect on glycemic control are multifaceted but not yet fully elucidated. In addition to long-term weight loss, other effects include decreased hepatic insulin resistance, improved insulin secretion, and increased GLP-1 concentrations. These effects often occur immediately after surgery, and, in addition to decreased postoperative glucose intake, place the bariatric surgery patient at high risk for hypoglycemia.

One of the most common reasons patients undergo bariatric surgery is to attenuate or “cure” diabetes mellitus. Patients with diabetes who have a BMI of ≥35 kg/m² are considered eligible for bariatric surgery per national guidelines. Results of a recent prospective study showed that both sleeve gastrectomy and RYGB patients were much more likely to have a glycated hemoglobin concentration of ≤6.0% 1 year after surgery than patients who underwent intensive medical therapy alone. A long-term observational study showed that 15 years after bariatric surgery, 30.4% of patients were in diabetes remission (defined as having a fasting blood glucose concentration of <110 mg/dL and receiving no diabetes medication), as compared with only 6.5% of control patients (p < 0.001). Microvascular and macrovascular complications were also less likely in the surgical patients at 15 years.

Published protocols on systematic medication adjustments for diabetes, as well as long-term data on medication effectiveness and safety, remain limited. Initial changes immediately after surgery should be focused on maximizing patient safety by discontinuing sulfonlureas if patients are receiving these agents to reduce the risk of hypoglycemia. Insulin dosages should be decreased by 50–75% immediately after surgery to decrease the risk of hypoglycemia. A recent single-site study found that insulin dose reductions performed by a pharmacist immediately after sleeve gastrectomy averaged approximately 25 units, with reductions maintained for up to six months after surgery. Thiazolidinediones should be avoided after bariatric surgery, if possible, due to weight gain as a potential adverse effect. Metformin is ideal after bariatric surgery due to its weight-neutral or weight loss–promoting properties and the lack of hypoglycemia associated with metformin monotherapy. A drawback is metformin’s potential to cause diarrhea, which may be enhanced in the post–bariatric surgery population. Whether GLP-1 agonists or dipeptidyl peptidase-4 inhibitors might be effective in bariatric surgery patients is unknown due to the increased GLP-1 levels resulting from bariatric surgery. There are no safety or efficacy data pertaining to the use of sodium–glucose cotransporter 2 inhibitors in bariatric surgery patients.

Gastrointestinal considerations

Bariatric surgical interventions are the most effective treatment modalities for weight loss and avoidance of long-term complications related to morbid obesity. However, bariatric surgeries create major anatomic and functional changes in the gastrointestinal tract that may either have a beneficial effect (e.g., a sense of satiety, extensive weight loss) or result in unintended consequences. Potential gastrointestinal adverse consequences of bariatric surgical interventions include gastroesophageal reflux, medication malabsorption, and dumping syndrome.
Gastroesophageal reflux disease (GERD). Obesity is a common risk factor for GERD in the general population; depending on the type of bariatric procedure planned, the potential for development of GERD may be a consideration. Although weight loss is generally associated with decreased GERD symptoms in patients not receiving bariatric surgery, the effect of bariatric surgery on GERD can vary by surgery type. 29 A systematic review of outcomes data on various bariatric surgery procedures indicated that RYGB was superior to gastric banding for improving GERD symptoms; sleeve gastrectomy was the procedure most likely to be associated with an increase in GERD symptoms or to have no effect, whereas mixed positive, neutral, and negative effects were noted with laparoscopic adjustable gastric banding procedures. 30

In one notable registry-based study of patients undergoing bariatric surgery (n = 10,766) during the period January 2006–October 2012, postprocedural use of acid suppressive therapy (AST) agents—proton pump inhibitors (PPIs) or histamine H2-receptor blockers—after various bariatric surgery procedures was evaluated at one year via patient surveys. 31 Overall, AST use decreased from 37.7% at baseline to 29.6% one year after surgery (p < 0.001). Only a small proportion of patients who were not already taking an AST agent at baseline were taking one at follow-up, with rates of AST use varying by surgery type as follows: gastric banding, 13.9%; RYGB, 19.2%; sleeve gastrectomy, 21.6%; and BPD-DS, 42.1%. The proportion of patients discontinuing AST was highest after RYGB (56.2%), followed by gastric banding (55.6%), sleeve gastrectomy (37.3%), and BPD-DS (42.1%).

In recent years, significant associations between PPI use and hypomagnesemia and osteoporosis have been described. 32 As a result, prescribing information warns of the potential for hypomagnesemia and osteoporosis with long-term use of PPIs. However, few studies have examined the effects of PPIs on serum magnesium levels in bariatric surgery patients. In one study, the mean serum magnesium concentration increased by approximately 11%, from 1.9 to 2.1 mg/dL, at one year after surgery in patients undergoing RYGB relative to matched morbidly obese controls. 33 This study was performed in 2009, before the association between hypomagnesemia and PPIs was documented, and the investigators did not report on the proportion of patients taking PPIs at one year after surgery. Long-term use of PPIs could also worsen changes in bone metabolism known to occur postoperatively, possibly increasing the risk of osteoporosis-related fractures (see related information on calcium and vitamin D supplementation above).

Dumping syndrome. Dumping syndrome is defined as uncomfortable gastrointestinal and vasomotor symptoms that can be attributed to rapid gastric emptying or rapid exposure of the small intestine to nutrients. 34 Dumping syndrome occurs most commonly after surgical techniques involving partial or complete gastrectomy (e.g., RYGB). Symptoms are triggered by ingestion of meals and often categorized as early and late manifestations, as described in Table 2. Most patients develop only early symptoms or experience both early and late symptoms. After gastric bypass, approximately 40–70% of patients experience symptoms of dumping syndrome.

Initial therapy for dumping syndrome involves strict implementation of dietary measures. Patients are instructed to eat smaller, more frequent meals (up to six per day) and to avoid drinking with meals and for two hours postprandially. Adjunctive measures, including the use of viscous food additives such as pectin, can be implemented to slow gastric emptying. Many patients find these additives to be unpalatable, however, lessening their utility.

Few studies have evaluated the effectiveness of acarbose in the treatment of dumping syndrome. Acarbose, which is indicated for controlling diabetes mellitus, effectively slows carbohydrate absorption through intestinal α-glucosidase inhibition. In one small study of 8 RYGB patients, 7 patients (88%) had complete resolution of symptoms of dumping syndrome after initiation of acarbose 50–100 mg three times daily for six weeks. 35 Patients also underwent continuous interstitial glucose (IG) monitoring via a wearable device (CGMS System Gold, Medtronic MiniMed, Northridge, CA) before and after acarbose was initiated. Continuous glucose monitoring measures glucose levels in the fluid surrounding cells and can be calibrated to approximate plasma glucose levels. On average, after RYGB there was a significant increase in the time to peak IG levels. The frequency of hypoglycemia (defined as an IG concentration of <60 mg/dL) was significantly decreased, and the minimal IG concentration was significantly increased from baseline. In a separate study, Valderas et al. 36 evaluated the effect of acarbose on glucose, insulin, and GLP-1 in 8 consecutive RYGB patients. The patients received a standardized meal containing 50 g of carbohydrates with and without acarbose. After eating the meal without acarbose, 5 patients (63%) developed asymptomatic hypoglycemia (i.e., a glucose concentration of <50 mg/dL), with inappropriately high insulin levels and an exaggerated GLP-1 response. After eating the meal without acarbose, 5 patients (63%) developed asymptomatic hypoglycemia (i.e., a glucose concentration of <50 mg/dL), with inappropriately high insulin levels and an exaggerated GLP-1 response. After eating the meal without acarbose, 5 patients (63%) developed asymptomatic hypoglycemia (i.e., a glucose concentration of <50 mg/dL), with inappropriately high insulin levels and an exaggerated GLP-1 response. After eating the meal without acarbose, 5 patients (63%) developed asymptomatic hypoglycemia (i.e., a glucose concentration of <50 mg/dL), with inappropriately high insulin levels and an exaggerated GLP-1 response. After eating the meal without acarbose, 5 patients (63%) developed asymptomatic hypoglycemia (i.e., a glucose concentration of <50 mg/dL), with inappropriately high insulin levels and an exaggerated GLP-1 response.


flatulence, bloating, and diarrhea due to carbohydrate malabsorption, usually limit patient acceptance. Adherence to postsurgery dietary instructions, acarbose dose adjustment, and use of the minimal effective dose may minimize acarbose adverse events.

If other measures fail, somatostatin analogs such as octreotide can be considered. These are considered the most effective treatment options for dumping syndrome, with demonstrated effectiveness in addressing both early and late symptoms. Octreotide has several proposed mechanisms of action that are beneficial in dumping syndrome, including promotion of delayed initial gastric emptying, slower small intestine transit time, and inhibition of splanchnic vasoconstriction and postprandial vasodilation. Although effective, these agents are generally reserved due to increased treatment costs and (in the case of octreotide) the need for thrice-daily subcutaneous injections. Initially, octreotide 50–100 mg can be administered subcutaneously three times daily to assess tolerability and effectiveness; patients with a good response can be transitioned to a slow-release depot injection.

Patients who do not respond to medical therapies for dumping syndrome may require surgical revision or reversal (if possible). In these difficult cases, a gastric reservoir can be created, or a restrictive intervention (e.g., placement of a band around the stomach pouch) can be performed to help slow or regulate the release of nutrients to the small intestine.

Contraception

Rapid weight loss after bariatric surgery results in improved fertility, which increases the risk of unplanned pregnancy. Contraception is a primary need for women after bariatric surgery, as current guidelines recommend against pregnancy for 12–18 months to avoid potential maternal and fetal harm due to vitamin and mineral deficiencies associated with bariatric surgery, especially RYGB. Despite these recommendations, surveys have demonstrated poor adherence with contraception recommendations after bariatric surgery, with up to 35% of women reporting no contraceptive use in the first 12 months postoperatively.

There is a theoretical risk of decreased absorption of oral contraceptives after bariatric surgery, potentially leading to an increased risk of pregnancy. Oral estrogen is absorbed primarily in the upper gastrointestinal tract, which would be of primary concern with the use of most estrogen preparations, especially after RYGB. Pharmacokinetic and outcomes data regarding serum levels of both estrogens and progestins have not been published to date. More research is needed before endorsing oral contraceptive use in bariatric surgery patients.

Transdermal patches and subdermal implants are potential options for contraception in this population. Increased amounts of flaccid skin may impede patch adherence. Insertion of a contraceptive implant into a suitable area may be difficult after surgery. Another concern with implants is the potential for weight gain associated with this method of contraception.

Diaphragms, female condoms, and vaginal rings are difficult to insert in obese patients, leading to poor adherence. Also, even minor weight changes require diaphragm users to visit their healthcare provider for device adjustments, making this method cumbersome after bariatric surgery.

The use of a copper or levonorgestrel intrauterine device (IUD) remains the most recommended method of contraception after bariatric surgery. This method avoids potential decreased medication absorption associated with oral contraceptives as well as weight gain associated with hormonal implants. Until further data demonstrating therapeutic postsurgery levels of contraceptive hormones with oral or transdermal dosage forms are available, IUDs will remain the standard of care to prevent pregnancy in the bariatric surgery patient.

Urinary symptoms

Urinary symptoms are common in obesity, with many patients experiencing increased urinary frequency and urgency as well as stress incontinence. Nearly 50% of morbidly obese patients develop stress incontinence. Therefore, many bariatric surgery patients are prescribed various therapies for symptom control, including α-antagonists, anticholinergics, and topical estrogen therapy.

Part of the etiology of urinary symptoms involves the pannus resting directly on the bladder. After bariatric surgery, patients may have fewer
urinary symptoms and may no longer require medication therapy. Results of a recent study revealed a decreased frequency of urinary symptoms after sleeve gastrectomy.\textsuperscript{40} Another study, focusing on female patients, demonstrated that 62.4% of those with a preexisting diagnosis of urinary incontinence no longer had that diagnosis up to three years after surgery, as compared with 42.1% of patients in a cohort not treated via bariatric surgery ($p = 0.0009$); this suggests an indirect benefit of bariatric surgery in addition to the resultant weight loss.

Patients receiving anticholinergic therapy for urinary symptoms should be monitored closely after surgery for hypotension and anticholinergic adverse effects. Growing evidence (as mentioned above\textsuperscript{41}) demonstrates the potential for cessation of medication use for urinary symptoms after bariatric surgery; thus, a trial of therapy discontinuation is reasonable once significant weight loss has occurred.

### Psychotropic medication management

The prevalence of psychiatric illness in individuals seeking bariatric surgery is high, estimated to be 27–69% in preoperative patients.\textsuperscript{42-45} In one large-scale U.S. study of 23,000 bariatric surgery patients, 41% reported a diagnosis of depression, with 15% reporting anxiety, 2.1% reporting bipolar disorder, 0.7% reporting substance abuse disorder, and 2.7% reporting other psychiatric disorders.\textsuperscript{46} Smaller studies of psychopathology in bariatric surgery patients have found remarkably high rates of bipolar spectrum disorders, ranging from 3.3% to as high as 89%, as compared with rates of about 1.8% in community samples.\textsuperscript{47,48}

The impact of bariatric surgery on psychiatric pharmacotherapy has received very little attention. Indeed, the most recent iteration of the clinical practice guidelines for the perioperative management of bariatric surgery patients fails to address postsurgery psychiatric pharmacotherapy management.\textsuperscript{9} More than a third of bariatric surgery patients take psychotropic medications preoperatively, with nearly half using antidepressants.\textsuperscript{46,49,50} Mitchell and colleagues\textsuperscript{44} found that the most common medication class used preoperatively by a sample ($n = 199$) of bariatric surgery patients was antidepressants. Forty-two percent of the sample had been prescribed an antidepressant within 90 days of the psychological evaluation; women were more likely than men to be taking antidepressant medications (44% versus 26%).

The use of psychiatric medication combinations by bariatric surgery patients is common and frequently involves the use of an antidepressant combined with a mood stabilizer, anxiolytic, or atypical antipsychotic, with most of these medications contributing to weight gain. Research on the impact of continued use of weight gain–inducing psychotropic medications after bariatric surgery is lacking. One recent study of weight loss patterns after gastric bypass in patients with multiple psychiatric comorbidities showed that participants with two or more psychiatric conditions at the time of surgery were six times more likely than those with one or no psychiatric problems to stop losing weight, or even regain weight, after the first postoperative year.\textsuperscript{51} Consensus recommendations for managing medication-induced weight gain in psychiatric patients advise that the offending medication(s) be switched out for a drug in the same class that is more weight neutral. If use of the offending medication(s) must be maintained for optimal therapeutic benefit, the lowest effective dose should be used.\textsuperscript{52,53} Without specific guidance for bariatric surgery patients, this recommendation should be followed when adjusting a patient's postsurgery medications.

An exacerbation of depressive symptoms and manic or hypomanic states, as well as suicide attempts, has been reported in some patients after bariatric surgery, but the reasons why this occurs are unclear.\textsuperscript{54-56} Although psychosocial factors likely play a role in some postsurgery psychiatric complications, decreased medication absorption may be an important cause of psychiatric instability after malabsorptive procedures. For example, postsurgery complications of nausea and hyperemesis, dehydration, or problems swallowing oral medications after surgery may necessitate alternative liquid, depot, or intraoral dissolvable formulations to ensure that therapeutic levels are maintained.\textsuperscript{50-53} It is also possible that long-term alterations in psychotropic medication bioavailability weigh into an exacerbation of psychiatric symptomatology after bariatric surgery. The wall of the duodenum that is partially bypassed contains CYP isozymes, several of which (e.g., CYP1A2, CYP3A4, CYP3A5, CYP2D6) are known to metabolize a variety of psychoactive medications in the following classes: selective serotonin reuptake inhibitors, selective serotonin–norepinephrine reuptake inhibitors, norepinephrine–dopamine inhibitors, tricyclic antidepressants, first- and second-generation antipsychotics, antiepileptics, mood-stabilizing agents, and benzodiazepines. There is a paucity of research addressing postsurgery changes in medication concentrations and subsequent clinical management in patients receiving these agents.

To date, only two studies have examined the bioavailability of psychiatric medications after gastric bypass. In the first study, Roerig et al.\textsuperscript{54} examined changes in sertraline levels approximately one year after RYGB using a single-dose probe. Plasma sertraline concentrations in the 10 hours after ingestion of a 100-mg tablet were lower in RYGB patients than in nonsurgical controls matched for BMI, age, and gender. Maximum plasma sertraline concentrations in the bariatric surgery patients were, on average, only 39% of those in the control group. In a related study by the same team, plas-
ma duloxetine concentrations over a 72-hour period after administration of a 60-mg dose of duloxetine were compared in RYGB patients (approximately one year after surgery) and age-, gender-, and BMI-matched controls. They found that the bioavailability of duloxetine through the 72-hour study period was substantially less (57%) in the RYGB patients, as compared with the controls; peak plasma duloxetine concentrations were lower, and clearance times were shorter. The authors speculated that this finding may have been associated with the loss of duodenal absorptive surface area and rapid movement of the medication through the jejunum.

It should be noted that data on the bioavailability of psychotropic medications after mainly restrictive bariatric procedures, such as the vertical sleeve gastrectomy and gastric banding, are absent from the scientific literature. One might assume that post-surgery medication complications are less likely to occur with primarily restrictive bariatric procedures. However, a case report described a patient with bipolar disorder and a history of lithium use who underwent a gastric banding procedure and developed lithium-induced nephrogenic diabetes insipidus (LINDI) with altered mental status, agitation, and polydipsia during the postoperative period. LINDI persisted in this patient despite discontinuation of lithium use four years prior to surgery, a phenomenon which has been documented in other patients.

Absent specific best-practice guidelines, pharmacologic management of bariatric surgery patients taking psychotropic medications obliges good communication between the bariatric team and the patient's psychiatric prescriber before and after surgery to optimize pharmacotherapy and mitigate adverse reactions. Reassessment of medication dosing and compliance should be performed before surgery to help ensure steady therapeutic levels after surgery. A variety of problems ranging from physical complications to dehydration to malabsorption can occur after bariatric surgery. Many psychiatrists and other prescribers are unfamiliar with these potential complications, and they will benefit from education and collaboration with a clinical pharmacist. Prescribers should be encouraged to monitor patients monthly for an exacerbation of symptoms in the first six postoperative months. In addition, the patient and involved family members should be educated on potential psychiatric complications after surgery to ensure that the family promotes patient safety and timely intervention when aberrant behaviors or altered mental status is observed.

A word should be said about the vulnerability of bariatric patients to developing alcohol use disorders after surgery. New-onset alcohol misuse and abuse are most commonly seen in RYGB patients, likely due to quicker absorption after surgery, but also can occur in patients who have undergone the mainly restrictive sleeve gastrectomy or vertical banded gastropasty procedures. Large studies have shown that although alcohol consumption often decreased from presurgery levels in the first postoperative year, consumption increased in the second and subsequent postoperative years, with alcohol abuse often manifesting within two to three years of surgery. A family history of substance abuse has been associated with the development of postsurgery alcohol misuse, as have presurgical problems with food addiction. There does not appear to be a strong correlation between heavy alcohol consumption prior to surgery and postsurgical alcohol abuse. Given the profound negative consequences that can occur with the development of alcohol use disorders in the bariatric surgery patient, the clinician team needs to be vigilant—not just in the first year after surgery but especially in the subsequent three to five years, a time when many bariatric patients become lax in their commitment to healthful eating and regular exercise.

**Oral chemotherapy**

The past two decades have seen a significant increase in the development of new oral chemotherapeutic agents, with over 50 FDA-approved agents currently available. Relative to parenteral therapy, oral therapy offers patient convenience and, often, improved quality of life. Despite these advantages, these medicines are associated with significant toxicity and many drug–drug and drug–food interactions. There are limited data on the use of chemotherapy agents, specifically oral agents, in the obese population. In 2012 the American Society of Clinical Oncology released guidelines on use of oral and parenteral chemotherapeutic agents in obese patients. An expert panel recommended full weight-based dosing and the same toxicity-based dose reductions in obese and nonobese patients.

In post–bariatric surgery patients, controlled caloric intake and optimal nutrition are paramount. Segal et al. reported that of the 58 oral chemotherapeutic agents they investigated, 9 require administration with food and 20 are to be taken on an empty stomach. Additionally, 9 agents have pH-dependent absorption, and 4 agents have significant lactose content. Moreover, many of these agents have associated gastrointestinal toxicities, including significant gastritis, nausea, vomiting, and diarrhea, although rates of toxicity appear similar in obese and nonobese patients. Because strategies to mitigate these adverse effects may be in contradicition to conventional diet recommendations after bariatric surgery, careful consultation with dieticians and oncology pharmacists is recommended.

Interpatient pharmacokinetic variability with the use of oral chemotherapeutic agents is to be expected, and several strategies to mitigate the variability have been suggested; although pertinent data specific to post–bariatric surgery patients are not available, it is reasonable to expect similar pharmacokinetic variability in this population. McLeod and Evans
suggested that therapeutic drug monitoring may be considered at the initiation of oral chemotherapy to help optimize patient-specific dosing. While this approach has many limitations, including financial constraints, issues of commercial availability of monitoring tests, and the need for expert interpretation of test results, it may be considered in post–bariatric surgery patients. Another strategy often employed with use of chemotherapy agents is dose adjustment when toxicity occurs; as described above, many of these toxicities may be gastrointestinal in origin and should be carefully monitored in post–bariatric surgery patients.

Drug–drug interactions are common with the use of oral chemotherapy agents. While many post–bariatric surgery patients are appropriate candidates for discontinuation of some maintenance medications, many patients still require some medications for chronic and acute conditions, including diabetes, hypertension, infections, and depression. Approximately 70% of oral chemotherapy agents are substrates of the CYP isozyme system, with an additional 31% also being substrates of P-glycoprotein. Enzymatic changes after bariatric surgery, including altered levels of small-bowel and hepatic enzymes, may be expected; thus, careful assessment of drug–drug interactions and response to therapy is required. Based on the available evidence, pharmacokinetic data specific to the obese population are needed and should be a target of future investigations.

Role of the pharmacist

The pharmacist has an increasingly important role in the chronic management of the bariatric surgery patient. Cumulative evidence demonstrating beneficial cardiovascular and endocrine outcomes in long-term studies, coupled with the expanding roles of pharmacists in the ambulatory care setting, provides a ripe opportunity for pharmacist involvement in the bariatric surgery population. The potential exists for the creation of “bariatric pharmacist” positions that enable pharmacists to comprehensively address bariatric surgery patients’ pharmacotherapy needs, weight-loss medication management, and weight-based dosing and medication adjustment.

Counseling regarding appropriate nutritional and exercise needs is important to give postoperative patients the best opportunity for maintaining weight loss. Encouraging patients to ingest multiple small meals incorporating 60 g of protein and five servings of fruit and vegetables daily is essential. Exercise recommendations should include 30 minutes of moderate aerobic physical activity five days weekly; this can be increased to a goal of 300 minutes weekly along with resistance training two or three times weekly.

Patients undergoing malabsorptive procedures should demonstrate compliance with the required regimens of vitamin and mineral supplementation. Patients receiving medications that may interact with divalent cations within vitamins, such as fluoroquinolone antibiotics, should be counseled appropriately to time ingestion of these medications to avoid decreased absorption. Pharmacists should ensure that a patient receiving a malabsorptive procedure has all medication dosage forms converted to the appropriate formulation (e.g., extended-release tablets versus immediate-release tablets after RYGB) and assess tolerability after conversion.

Patients should be consistently reassessed for the appropriateness of each medication, with particular attention to the need for continued use of medications for hypertension, diabetes mellitus, hyperlipidemia, and urinary incontinence. Many medications may require dosage decreases or even cessation in the first postoperative year, depending on the response to surgery and adherence to diet and exercise recommendations.

Pharmacists should give appropriate counseling to patients after surgery regarding smoking cessation. In addition, alcohol intake should be limited, as there is growing evidence of an increased risk of developing an alcohol use disorder after bariatric surgery.

Conclusion

Pharmacists have an increasing role in the chronic management of the bariatric surgery patient due to their knowledge of medication dosage forms and expertise in disease states affected by bariatric surgery.

Disclosures

The authors have declared no potential conflicts of interest.

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