Medication management and pharmacokinetic changes after bariatric surgery

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Abstract
Objective  To identify expected pharmacokinetic changes and provide practical recommendations for the medication management of chronic disease states after bariatric surgery.

Sources of information  MEDLINE, EMBASE, PubMed, Scopus, and the Cochrane Library were searched. The search was limited to studies in human adults. Search terms included obesity, obese, bariatric surgery, gastric bypass, gastrectomy, gastric band, RYGB, roux-en-y, gastrointestinal absorption, medication absorption, drug absorption, bioavailability, dose adjust, drug monitoring, medication adjust, drug change, medication management, and medication dosing. Reference lists of original studies and reviews were also hand searched. Included studies were entered into PubMed and articles under the “Similar articles” heading were also reviewed. Only studies relevant to bariatric surgery types currently available in Canada (ie, Roux-en-Y gastric bypass, sleeve gastrectomy, or gastric banding) were included.

Main message  Pharmacokinetic changes anticipated after bariatric surgery vary by surgery type. There are several guiding principles that might be applied to medication management regimens after bariatric surgery. Practice tips are also presented for medication management of specific chronic disease states.

Conclusion  Changes to long-term medication regimens after bariatric surgery should be anticipated and managed in an appropriate and timely manner. The provided clinical practice recommendations might be used in conjunction with a patient’s clinical picture to adjust chronic medication regimens in an appropriate and evidence-based manner after bariatric surgery.

Obesity is a progressive chronic health condition affecting more than 1 in 4 adult Canadians. Patients who are obese are at an increased risk of many other serious health conditions including type 2 diabetes, hypertension, cardiovascular disease, arthritis, and various types of cancer. Bariatric surgery structurally modifies the gastrointestinal tract to reduce caloric consumption or absorption. The number of bariatric surgeries performed annually in Canada has more than tripled since 2009.

In addition to restricting caloric absorption, bariatric surgeries also have the unintended potential to restrict absorption of other enteral products, including vitamins, minerals, and medications. After surgery, patients typically experience rapid weight loss and might require adjustments to long-term medication regimens owing to changing medication distribution patterns and the effects of weight loss on chronic disease states.

Bariatric surgeries are classified as having restrictive or malabsorptive properties. Restrictive surgeries reduce the volume of food that can be consumed at one time, leading to reduced total caloric intake. Malabsorptive procedures create a diversion around substantial portions of the digestive tract causing reduced absorption of consumed products. Bariatric surgeries currently offered in Canada include Roux-en-Y gastric bypass (RYGB),...
in which a small functional pouch at the top of the stomach is isolated from the rest of the stomach and directly connected to the jejunum, allowing food to pass bypass most of the stomach and the entire duodenum; sleeve gastrectomy, in which approximately 80% of the stomach is removed, leaving a smaller sleevelike stomach; and gastric banding, in which an obstructive band is placed around the proximal stomach, physically restricting the rate at which food can pass into the stomach. Roux-en-Y gastric bypass has both restrictive and malabsorptive properties, while sleeve gastrectomy and gastric banding are primarily restrictive procedures.

Unfortunately, the current literature offers very few clear recommendations regarding specific medication management strategies in patients after bariatric surgery. The objective of this review is to identify expected pharmacokinetic changes and provide practical recommendations for the medication management of chronic disease states after bariatric surgery based on the current available evidence.

**Case description**

A 40-year-old woman is 2 weeks removed from an RYGB procedure and presents to a family medicine clinic with an elevated blood pressure of 158/96 mm Hg. All other vital signs are within normal limits. Her medical history is relevant for class III obesity and stage 1 hypertension, which had previously been well controlled with 10 mg of oral ramipril daily and 60 mg of oral extended-release nifedipine daily. The patient indicates she has adhered to and tolerated her prescribed regimen.

**Sources of information**

**Search strategy.** We searched MEDLINE, EMBASE, PubMed, Scopus, and the Cochrane Library for studies examining the effects of bariatric surgery on either drug absorption or chronic medication management. Search terms included obesity, obese, bariatric surgery, gastric bypass, gastrectomy, gastric band, RYGB, roux-en-y, gastrointestinal absorption, medication absorption, drug absorption, bioavailability, dose adjust, drug monitoring, medication adjust, drug change, medication change, medication management, and medication dosing. A librarian from the University of Alberta in Edmonton assisted with identification of appropriate search terms. Reference lists of original studies and reviews were also hand searched. Included studies were entered into PubMed and articles under the “Similar articles” heading were also reviewed. The search was limited to studies in human adults and is considered up to date as of February 2019.

**Eligibility criteria.** Human case reports, case series, cohort studies, and randomized controlled trials that evaluated or described drug absorption or chronic medication management in patients undergoing bariatric surgery types currently available in Canada (ie, RYGB, sleeve gastrectomy, or gastric banding) were included. We excluded studies examining nutritional supplements such as vitamins and iron preparations.

**Study selection.** Based on the inclusion and exclusion criteria, we independently screened the titles and abstracts of each study to determine eligibility. Both authors independently assessed all full-text articles that were classified as included or unclear for final inclusion. Disagreements were discussed and resolved by consensus.

**Data abstraction.** Using standardized data extraction forms, we independently extracted data on study characteristics (eg, design, country, inclusion and exclusion criteria, funding sources), participants’ clinical characteristics, interventions (eg, medication name, dosage type, dosage amount, surgery type), level of agreement among the evidence, and outcomes. Data not reported in the articles were extracted from supplementary texts where available. Authors were not contacted for missing data.

**Main message**

**General practice tips.** As physiologic and pharmacokinetic changes develop in the days to months after bariatric surgery, it is typically the responsibility of family physicians to modify chronic disease medication regimens in a timely and appropriate fashion. General strategies are available to manage medication regimens after bariatric surgery (Table 1). Strategies to improve medication absorption are not required for all patients; the decision to proactively implement these strategies will depend on many factors, including surgery type and each patient’s long-term medication regimen. In many cases it will be reasonable to monitor patients after surgery and make adjustments if suboptimal medication absorption is suspected.

When reviewing general strategies for medication management after bariatric surgery, it is important to be mindful of these guiding principles:

- Changes to absorption kinetics of drugs after bariatric surgery have high variability among individuals. No single algorithm or practice tool can accurately predict these changes for all patients after bariatric surgery.
- Medication absorption issues might be temporary or permanent; therefore, medication modifications to counteract these issues might also be temporary or permanent.
- Issues with medication absorption and dosage modifications are more likely to occur and persist after malabsorptive procedures.
- When a medication adjustment is made, ensure appropriate monitoring and follow-up is implemented.
- Ensure medication regimens that are dosed by weight are regularly reviewed and adjusted as patients experience weight loss.

**Specific disease state management.** In addition to general management principles, we have identified a number
of strategies to guide medication management for specific chronic disease states after bariatric surgery (Table 2).4-42 Specific medications for which recommendations are made are intended to represent the most commonly prescribed medications in Canada at the time of the literature review.

**Underlying pharmacokinetic changes.** After bariatric surgery, there are multiple pharmacokinetic changes that might occur and that might also explain why patients are not achieving an adequate response to their medications (Table 3).6,43-45 The resultant pharmacokinetic changes might develop within days to months after surgery, vary from patient to patient, and depend on the type of bariatric surgery performed. The changes might either partially or fully reverse as the body heals and adapts to the alterations made from bariatric surgery.

### Table 1. General approaches to medication management after bariatric surgery based on anticipated changes: Based on the anticipated medication and absorption changes after 3 specific procedures: 2 types of restrictive procedures (gastric banding and sleeve gastrectomy) and 1 type with both restrictive and malabsorptive properties (Roux-en-Y gastric bypass).

<table>
<thead>
<tr>
<th>PARAMETER</th>
<th>RECOMMENDATION</th>
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| Suspicion that medications are not being absorbed appropriately | • Switch solid-dose forms to liquid-dose forms, dissolvable or crushable tablets, or capsules that can be opened and sprinkled on food4,5  
• Consider using nonoral dose forms (eg, sublingual, intranasal, rectal, subcutaneous, transdermal)4  
• Switch extended-release formulations to immediate-release formulations4  
• Switch to medications that undergo less first-pass metabolism  
• Consider proactively adjusting medication regimens after malabsorptive procedures when treatment failure might result in a detrimental outcome |
| Medications that increase the risk of upper gastrointestinal irritation, ulceration, and impaired healing | • Minimize use of nonsteroidal anti-inflammatory drugs,5,6 oral bisphosphonates,5 and corticosteroids6 |
| Dumping syndrome | • Avoid liquid formulations that have non-absorbable sugars (eg, mannitol, sorbitol)6 |

### Table 2. Medication management strategies for specific chronic disease states after bariatric surgery: Based on the anticipated medication and absorption changes after 3 specific procedures: 2 types of restrictive procedures (gastric banding and sleeve gastrectomy) and 1 type with both restrictive and malabsorptive properties (RYGB).

<table>
<thead>
<tr>
<th>DISEASE STATE OR MEDICATION CLASS</th>
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| Diabetes                         | • Frequent follow-up and monitoring by a health care provider is required in the postoperative period to ensure ongoing effectiveness and timely modifications of antihyperglycemic medications7  
• While the medication burden might decrease initially after surgery, long-term monitoring is recommended given that diabetes is a progressive disease and can worsen with time in some patients7  
**Drug-specific recommendations for type 2 diabetes**  
Insulin* |  
• Insulin requirements might be volatile and are expected to decrease for at least 12 months after surgery or until weight loss stabilizes, with the most substantial reductions occurring during the first months7,8  
• If the basal insulin dose is <30 units/day before surgery, then discontinue after surgery7-9  
• If the basal insulin dose is ≥30 units/day before surgery, then decrease by 50% to 80% after surgery7-10  
• Short-acting insulin might be used to manage elevated glucose levels7-9 |
| Noninsulin options |  
• In patients taking 1 oral antidiabetic agent before surgery, the agent can be discontinued after surgery8,9  
• If the patient is taking >1 oral medication and ...  
• -HbA1c is <9%, metformin is the preferred single-agent therapy7,10  
• -HbA1c is ≥9%, a second agent can be coupled with metformin, preferably an agent that facilitates CV risk reduction7,11†  
• Avoid oral medications that increase the risk of hypoglycemia7,8,11‡ |
| Anticoagulation                  | • Warfarin is preferred over DOACs in patients who require continuous anticoagulation after bariatric surgery12  
• If considering DOAC therapy after bariatric surgery, then confirm that drug-specific laboratory monitoring is available to ensure levels are within the expected therapeutic range12 |

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<thead>
<tr>
<th>DISEASE STATE OR MEDICATION CLASS</th>
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<tbody>
<tr>
<td>Anticoagulation</td>
<td>Drug-specific recommendations</td>
</tr>
<tr>
<td>Warfarin</td>
<td>Warfarin doses should typically decrease in the immediate postoperative period (about 3–4 wk) and then increase further out from surgery.12–14</td>
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<td></td>
<td>To reduce bleeding risk, decrease the warfarin dose after surgery and adjust it based on the INR results, similar to a new warfarin start</td>
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<tr>
<td>Apixaban, rivaroxaban</td>
<td>Limited evidence suggests that rivaroxaban and apixaban do not require dose adjustment after bariatric surgery.15,16</td>
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<td></td>
<td>Drug-specific laboratory monitoring is recommended to ensure levels are within the expected therapeutic range.12</td>
</tr>
<tr>
<td>Dabigatran, edoxaban</td>
<td>Literature outlining the pharmacokinetic changes to dabigatran and edoxaban after bariatric surgery is lacking.12</td>
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<tr>
<td>Antiplatelet therapy</td>
<td>Antiplatelet therapy might increase the risk of gastrointestinal bleeding5,6</td>
</tr>
<tr>
<td></td>
<td>-Antiplatelet medication for primary prevention of CV events should be reassessed</td>
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<tr>
<td></td>
<td>-Continuing antiplatelet therapy in patients who are at high risk of future CV events is appropriate at the lowest indicated dosage</td>
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<tr>
<td>Dyslipidemia</td>
<td>Lipid levels might decrease with weight loss; consider monitoring every 3 mo until weight loss stabilizes and discontinue therapy if appropriate.17–19</td>
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<td>In patients who are taking dyslipidemia therapy for secondary prevention of CV events, the dose might be determined by the previous event rather than postoperative laboratory values</td>
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<tr>
<td>Hypertension</td>
<td>The need to use antihypertensive medications typically decreases after surgery. This decrease might begin immediately after surgery and continue for up to 2 y.10–22</td>
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<td></td>
<td>-Patients should have frequent follow-up with a general practitioner</td>
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<td></td>
<td>-Patients should monitor their blood pressure daily until it stabilizes</td>
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<td></td>
<td>—Results should be recorded and assessed by a health care professional to support medication changes</td>
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<td></td>
<td>—Patients should be reminded of the correct self-monitoring technique</td>
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<tr>
<td></td>
<td>Consider discontinuing or changing diuretic therapy if patients develop dehydration8</td>
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<tr>
<td></td>
<td>In patients with diabetes it might be preferable to continue an ACEI or ARB owing to their renoprotective effects8</td>
</tr>
<tr>
<td>Depression and anxiety</td>
<td>Close monitoring for psychiatric symptom relapse after surgery is recommended.23</td>
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<td></td>
<td>-Patients should be aware of the signs and symptoms of worsening psychiatric illness and be advised of whom to contact if this occurs</td>
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<td></td>
<td>-If relapse occurs, adjust psychiatric medications as quickly as possible owing to the anticipated lengthy response time associated with changing regimens</td>
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<td></td>
<td>The literature suggests that the concentration of SSRIs might drop initially and then rebound within a few months; dose adjustments occurring in the immediate postoperative period might be temporary.23,24</td>
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<td></td>
<td>Switching to a formulation that is absorbed more readily (eg, liquids, crushed pills, immediate-release preparations, tablets that dissolve orally) might be necessary</td>
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**Drug-specific recommendations for medications that do not have an immediate-release version available in Canada**

Venlafaxine

- The literature suggests that RYGB does not substantially alter the absorption of extended-release venlafaxine or its active metabolite25

Duloxetine

- RYGB might decrease patients’ exposure to duloxetine and this might persist for at least 12 mo after surgery.26
  - If therapy appears to be ineffective after surgery, then an increased dose or alternative therapy might be required
<table>
<thead>
<tr>
<th>DISEASE STATE OR MEDICATION CLASS</th>
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| **Depression and anxiety**       | Desvenlafaxine  
  • If therapy appears to be ineffective after surgery, then an increased dose or alternative therapy might be required  
  Bupropion  
  • If therapy appears to be ineffective after surgery, consider the following:  
    - Continuing or changing to SR bupropion  
    - SR formulation is easier to crush than the extended-release formulation  
    - Crush tablets and administer with water; this is expected to provide effects similar to the immediate-release tablets available outside of Canada  
    - Divide total daily dosage in 3 to 4 daily doses. Maximum single dose should not exceed 150 mg, and maximum total daily dose should not exceed 450 mg²⁷ |
| **Migraine**                     | Migraine or headache frequency might decrease after surgery²⁸,²⁹  
  • Average time to medication reduction was about 5.6 mo after surgery (range 1 to 36 mo)²⁸  
  • If initial migraines began after obesity onset, there is a greater probability that migraines will resolve postoperatively²⁸ |
| **Epilepsy or seizures**         | Seizures should be well controlled with medications before surgery  
  • Consider empirically switching to a liquid formulation, crushable tablets, or capsules that can be opened before malabsorptive procedures  
  • Where indicated, drug monitoring during the early postoperative period is recommended to ensure therapeutic drug levels |
| **Asthma**                       | Patients with asthma might require less medication after surgery³⁰,³¹  
  • If patients report decreased rescue medication use, then consider reducing or discontinuing maintenance therapy |
| **Psoriasis**                    | Patients with psoriasis might require less medication after surgery³²,³³  
  • If patients report decreased psoriasis severity, consider reducing or discontinuing therapy |
| **Pain**                         | Avoid NSAIDs after bariatric surgery owing to increased risk of gastric injury (eg, marginal ulcers)³⁴,³⁵  
  • For patients undergoing malabsorptive surgery and who are taking extended-release medications or high-dose opioid therapy, consider changing to immediate-release formulations or alternate routes of administration before surgery  
  • Liquid acetaminophen contains sorbitol, which increases the risk of dumping syndrome³⁶ |
| **Transplant**                   | If the patient is receiving transplant medications, consider stabilizing medication levels using a liquid formulation before surgery  
  • Increased levels of tacrolimus and mycophenolate have been observed after sleeve gastrectomy³⁷  
  • Where indicated, monitor drug levels postoperatively and adjust the dose as appropriate |
| **Ulcer prevention and GERD**    | Rapid-dissolve tablets or capsules that can be opened and sprinkled on food might have greater absorption and efficacy for patients after bariatric surgery  
  • Patients who experienced postoperative ulceration healed significantly faster (P < .001) while taking opened and dispersed proton pump inhibitor capsules compared with those taking whole capsules or tablets³⁸  
  • Prescriber should specify “no substitution” when prescribing dispersible or open capsules |
| **HIV**                          | Sleeve gastrectomy does not appear to negatively affect CD4 counts and viral load, and appears to be safe in individuals living with HIV³⁹,⁴⁰  
  • Substantially decreased absorption has been observed with raltegravir and atazanavir after sleeve gastrectomy³⁹-⁴¹  
  • Suggest replacing raltegravir and atazanavir with alternative HIV therapy before bariatric surgery³⁹  
  • If replacing raltegravir and atazanavir is not possible, then ensure postoperative pharmacokinetic monitoring is performed and adjust medication doses accordingly³⁹ |
| **Contraception**                | Rocha et al³⁹ and Curtis et al⁴⁰ indicate that for women who have undergone a ...  
  • malabsorptive procedure, oral contraceptives are not recommended owing to a theoretical risk of decreased drug absorption resulting in reduced contraceptive efficacy³⁹  
  • restrictive procedure, all contraceptive methods are acceptable³⁹,⁴⁰ |

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<table>
<thead>
<tr>
<th>DISEASE STATE OR MEDICATION CLASS</th>
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<tbody>
<tr>
<td>Contraception</td>
<td>• Caution is recommended in all cases. Ensure the patient understands the potential risks of using oral contraception and that secondary methods (eg, male or female condoms, diaphragms) should be employed</td>
</tr>
</tbody>
</table>

**Drug-specific considerations**

Effective after restrictive procedures only

- Combined oral contraceptive
- Progestin-only pill

Effective after both procedures, but might be less effective in women weighing ≥ 90 kg (≥ 198 lb)\(^4\)

- Ethinyl estradiol and norelgestromin patch

Effective after both procedures, but effectiveness in women who are obese is not well studied\(^4\)

- Ethinyl estradiol and etonogestrel vaginal ring

Effective after both malabsorptive and restrictive procedures

- Subcutaneous or intramuscular injection of medroxyprogesterone
- Levonorgestrel intrauterine device
- Copper intrauterine device


*Insulin recommendations are based on current published evidence for the treatment of type 2 diabetes mellitus after bariatric surgery. Specific recommendations for type 1 diabetes mellitus were not identified in the current literature, although decreased insulin requirements after surgery have been observed.

†Examples of drugs that facilitate CV risk reduction include empagliflozin, canagliflozin, liraglutide, and semaglutide.\(^1\)

‡Examples of drugs that increase the risk of hypoglycemia include glipizide, glimepiride, glyburide, and repaglinide.\(^2\)

**Table 3. Anticipated pharmacokinetic changes after bariatric surgery:** Based on the anticipated medication and absorption changes after 3 specific procedures: 2 types of restrictive procedures (gastric banding and sleeve gastrectomy) and 1 type with both restrictive and malabsorptive properties (RYGB).

<table>
<thead>
<tr>
<th>PHARMACOKINETIC PARAMETER</th>
<th>POTENTIAL PHARMACOKINETIC PARAMETER CHANGES</th>
<th>POTENTIAL THERAPEUTIC IMPLICATIONS FOR ORAL MEDICATIONS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gastric motility</td>
<td>Might be impaired(^6,43)</td>
<td>Disintegration and dissolution of oral medications might decrease(^6)</td>
</tr>
<tr>
<td>Gastric volume</td>
<td>Decreased, thereby decreasing the amount of fluids in the stomach available to act as solvents(^6)</td>
<td></td>
</tr>
<tr>
<td>Gastric pH</td>
<td>Typically becomes more basic after bariatric surgery(^6,43)</td>
<td>Solubility of basic drugs might decrease whereas solubility of acidic drugs might increase(^4,43)</td>
</tr>
<tr>
<td>Surface area</td>
<td>Sleeve gastrectomy will decrease stomach surface area(^6)</td>
<td>Dissolution and absorption(^6) of oral medications might decrease</td>
</tr>
<tr>
<td>Bile secretions (eg, P-glycoprotein)</td>
<td>NA</td>
<td>Medications will have less contact with bile secretions(^5,43)</td>
</tr>
<tr>
<td>Hepatic CYP enzyme activity</td>
<td>NA</td>
<td>The proximal small intestine has a high concentration of CY3A4 enzymes(^6)</td>
</tr>
<tr>
<td>First-pass metabolism</td>
<td>NA</td>
<td></td>
</tr>
</tbody>
</table>

CYP—cytochrome, NA—not applicable, RYGB—Roux-en-Y gastric bypass.
Case resolution

This patient’s hypertension has become poorly controlled after RYGB, most likely as a result of decreased absorption and efficacy of extended-release nifedipine. Extended-release oral nifedipine tablets use an osmotic gradient mechanism to control the release of medication, faster gastric transit time might result in incomplete emptying of tablets and thus incomplete absorption of medication. The family physician discontinues nifedipine and initiates 10 mg of oral amlopidine daily, while continuing ramipril as previously prescribed. Amlopidine and nifedipine have the same mechanism of action; however, amlopidine is available in a small immediate-release tablet and is less likely to be absorbed differently after bariatric surgery. The patient returns to the clinic 2 weeks later and presents with blood pressure at target, 136/84 mm Hg. In-clinic follow-up is planned for every 2 to 4 weeks until the patient’s weight loss stabilizes, and she is encouraged to monitor her blood pressure at home between appointments.

Conclusion

Owing to alterations in the gastrointestinal tract after bariatric surgery, there is an intuitive presumption that the absorption, and therefore effectiveness, of medications will change. This review describes changes to the absorption of medications that can be anticipated after bariatric surgery and provides clinical guidance for management of these changes. There is a paucity of previous high-quality literature to support medication management decisions after bariatric surgery. This review closes this gap and provides clinical guidance to practitioners by consolidating the best available evidence. Clinical guidance provided here must always be considered in conjunction with each patient’s clinical picture when adjusting medication regimens. To provide the best care to future bariatric surgery patients, further clinical studies are needed to reveal the effects of bariatric surgeries on drug absorption and to understand the underlying mechanisms. Awareness of this important issue must be stressed and it will be incumbent on prescribers to remain informed of new evidence in this area and adjust their practices accordingly.

Dr Lorico is a pharmacist completing a pharmacy residency at the Red Deer Regional Hospital Centre within Alberta Health Services. Mr Colton is a University of Alberta librarian. Dr Lorico identified all articles that met the search criteria. Dr Lorico and Mr Colton independently reviewed all titles and abstracts to determine which articles to include; discrepancies were resolved with discussion. Dr Lorico initially read the included articles and recorded pertinent results in a data collection spreadsheet; Mr Colton then read the articles to confirm the information and add to the data collection spreadsheet as required. Dr Lorico wrote most of the initial draft of the manuscript; Mr Colton proofread and edited it. All writing and editing was agreed upon by both authors. Consensus was achieved via discussion for all disputes.

Competing interests

None declared

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References


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