

**INVITED REVIEW**

# Oral drug dosing following bariatric surgery: General concepts and specific dosing advice

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Bariatric or weight-loss surgery is a popular option for weight reduction. Depending on the surgical procedure, gastric changes like decreased transit time and volume and increased pH, decreased absorption surface in the small intestine, decreased exposure to bile acids and enterohepatic circulation, and decreased gastrointestinal transit time may be expected. In the years after bariatric surgery, patients will also substantially lose weight. As a result of these changes, the absorption, distribution, metabolism and/or elimination of drugs may be altered. The purpose of this article is to report the general influence of bariatric surgery on oral drug absorption, and to provide guidance for dosing of commonly used drugs in this special population. Upon oral drug administration, the time to maximum concentration is often earlier and this concentration may be higher with less consistent effects on trough concentrations and exposure. Additionally, prescription of liquid formulations to bariatric patients is supported by some reports, even though the high sugar load of these suspensions may be of concern. Studies on extended-release medications result in an unaltered exposure for a substantial number of drugs. Also, studies evaluating the influence of timing after surgery show dynamic absorption profiles. Although for this group specific advice can be proposed for many drugs, we conclude that there is insufficient evidence for general advice for oral drug therapy after bariatric surgery, implying that a risk assessment on a case-by-case basis is required for each drug.

**KEYWORDS**

clinical pharmacology, obesity, nutrition, pharmacokinetics, surgery

## 1 | INTRODUCTION

Obesity (body mass index [BMI] above 30 kg/m<sup>2</sup>) is currently one of the major health issues, with a worldwide prevalence of 13%.<sup>1</sup> Individuals with (morbid) obesity are exposed to an increased risk of

cardiovascular disease, cancer, diabetes mellitus, hypertension, arthritis, sleep apnoea, and other co-morbidities, at higher mortality rates.<sup>2,3</sup>

For patients with morbid obesity (BMI above 40 kg/m<sup>2</sup>) or obesity with a BMI above 35 kg/m<sup>2</sup> with one or more comorbidities

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like type 2 diabetes or hypertension, modification of the gastrointestinal (GI) tract by bariatric surgery is currently the most effective long-term treatment.<sup>4-7</sup> Surgery results in weight loss up to 32 ± 8% after two years and has shown to lead to decreased incidence of diabetes, myocardial infarction, stroke and cancer, and in a reduction in overall long-term mortality.<sup>4,8,9</sup> In addition, obesity has a negative impact on quality of life, which improves significantly after bariatric surgery.<sup>10</sup>

Common techniques used in bariatric surgery include the sleeve gastrectomy (SG) and Roux-en-Y gastric bypass (RYGB).<sup>11</sup> The RYGB is associated with several anatomical and physiological changes. RYGB introduces a small gastric pouch, which results in an increased gastric pH.<sup>12,13</sup> The gastric pouch is connected to the lower part of the intestine, bypassing the small intestine and biliary limb. During the SG procedure, a small longitudinal stomach is created. For both types of surgery, these alterations in the GI tract are known to lead to nutritional deficiencies for which standardized nutritional supplementation is commonly advised.<sup>7</sup> Similarly, it can be anticipated that these changes may alter the absorption of drugs given orally.

Many patients who undergo bariatric surgery use one or more drugs to manage their co-morbid disease(s). Relevant drugs for these patients include cardiovascular (26%) and antidiabetic drugs (26%), analgesics (21%), anti-inflammatory and antirheumatic products (non-steroids) (10%), antidepressants (21%), thyroid therapeutics (12%) and drugs for obstructive airway disease (25%).<sup>14</sup>

In addition to the alterations in oral absorption due to modifications in the digestive tract, there are also changes in distribution, metabolism and/or elimination of drugs as the result of substantial weight loss associated with bariatric surgery.<sup>15,16</sup> The purpose of this article is to provide an overview of how bariatric surgery may influence the process of oral drug absorption and to give specific dosage advice for commonly used drugs in this special patient population.

## 2 | BARIATRIC SURGERY AND ORAL DRUG ABSORPTION

Theoretically, as a result of bariatric surgery, a number of alterations in the process of oral drug absorption may be expected, which may alter the oral pharmacokinetic profiles of prescribed drugs. Table 1 summarizes these alterations, for which a distinction is made between changes occurring upon restrictive procedures, i.e. procedures leading to a limitation in the amount of food in the stomach such as adjustable gastric banding and gastroplasty, or to limited digestive capacity such as SG, versus combined restrictive/malabsorptive procedures that also cause malabsorption of nutrients, such as Roux-en-Y gastric bypass (RYGB). Whether or not these changes ultimately lead to altered pharmacokinetics of a specific drug will depend on individual drug properties. Here we discuss disintegration of the oral drug formulation, dissolution of the drug, gastrointestinal transit time and the role of bile acids as factors of interest for the absorption process of oral drugs.

**TABLE 1** Theoretical changes relevant to oral drug absorption after bariatric surgery related to restrictive and restrictive/malabsorptive procedures

	Restrictive procedures	Restrictive/malabsorptive procedures
Decreased contact time with digestive juices/enzymes	✓	✓
Increased stomach pH	✓	✓
Decreased absorption surface in the small intestine		✓
Decreased exposure to bile acids and enterohepatic circulation		✓

The surgical procedures can be restrictive by limiting the amount of food in the stomach (adjustable gastric banding, gastroplasty), can be restrictive with limited digestive capacity (sleeve gastrectomy [SG]), can be malabsorptive causing malabsorption of nutrients (biliopancreatic diversion-duodenal switch, jejunioleal bypass) or can be a combination of malabsorption and restriction (one-anastomosis gastric bypass or Roux-en-Y gastric bypass [RYGB] and biliopancreatic diversion-duodenal switch, which bypasses the first part of the small intestine).

### 2.1 | Disintegration of the oral drug formulation

The first step in the absorption of solid formulations like tablets and capsules is disintegration in the GI tract. Disintegration is affected by several variables, such as gastric volume and mixing, which can both be diminished after bariatric surgery.<sup>15,16</sup> Due to a reduced gastric volume, tablets may not fully dissolve, resulting in altered exposure of the drug.<sup>17,18</sup> For this reason, administration of oral liquids is often proposed after bariatric surgery, even though hard evidence to support this statement is lacking. A disadvantage of liquid formulations like suspensions is that these formulations may contain sugars, which may, in large amounts, lead to the dumping syndrome.<sup>19</sup>

Montanha et al. investigated the effect of RYGB on the bioavailability of amoxicillin tablets versus suspension.<sup>20</sup> A lower area under the curve (AUC) for tablets (23.10 ± 7.41 mg.h/L) was found as compared to the suspension (27.59 ± 8.32 mg.h/L), corresponding to a relative bioavailability of 83%. The authors also found a higher  $C_{max}$  (8.73 ± 3.26 vs 7.42 ± 2.99 mg/L) and a lower  $T_{max}$  for the suspension compared to tablets (1.7 ± 0.86 vs 2 ± 0.76 h); however, these changes were not statistically significant. While no clinical outcome measures were reported, for both formulations, the time above the minimum inhibitory concentration (MIC) for pathogens with an MIC <4 mg/L was attained, and therefore effectiveness seems to be guaranteed for both oral drug formulations.

Schulman et al. investigated the effect of RYGB surgery on proton pump inhibitors (PPI) in open capsule (OC) vs intact capsule (IC) form.<sup>21</sup> In this study, 164 patients were included who used high-dose PPI therapy with omeprazole, pantoprazole, esomeprazole or soluble lansoprazole. The authors showed a significantly shorter

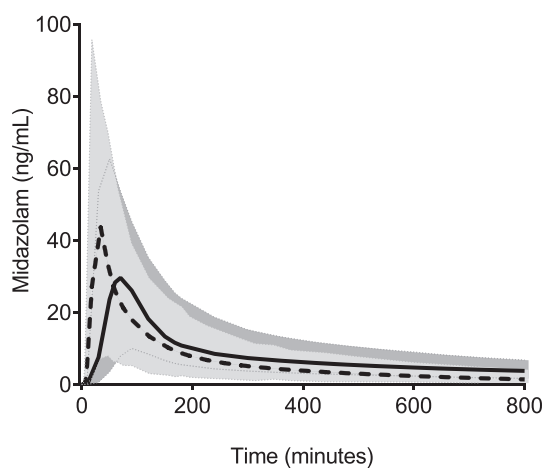
healing time (median healing time of 91 days vs 342 days) in the OC PPI group compared to the IC PPI group. There was, however, a significantly larger percentage of sucralfate use in the OC group and a larger non-significant percentage of non-steroidal anti-inflammatory drug (NSAID) use in the IC group, which may have contributed to the reported difference in effect.<sup>21</sup>

In addition, there are some studies showing that a liquid formulation of levothyroxine improves thyroid-stimulating hormone (TSH) levels post-surgery.<sup>22,23</sup> However, there are many factors involved in levothyroxine tablet absorption.<sup>24</sup> Also, weight loss due to surgery might also improve TSH levels over time.<sup>25</sup>

From these reports, it seems that liquid formulations may possibly lead to a higher exposure but may not always be preferable because of sugar loads, and that open capsules may possibly lead to more effective treatment than intact capsules after RYGB surgery. Therefore prescribers could consider switching to an oral solution or an opened capsule when the expected effect is not observed. However, as shown for amoxicillin suspension, with increased exposure, earlier and higher peak concentrations were observed. Such early and high peak concentrations may be undesirable for certain drugs like morphine, for which use of an oral solution yielded a three-fold increased  $C_{max}$ , lower  $T_{max}$  and increased AUC at 6 months after bariatric surgery.<sup>26</sup> Similarly, for midazolam, an earlier and 1.5-fold higher peak concentration after oral administration was observed (see Figure 1).<sup>27</sup>

## 2.2 | Dissolution of the drug

After disintegration, a drug must become dissolved to be absorbed. This dissolution process is affected by several variables, such as gastric volume, gastric pH and gastric transition time. In healthy subjects, the



**FIGURE 1** Midazolam concentration–time profile after bariatric surgery. Concentration–time profile for 7.5 mg oral midazolam in morbidly obese patients before bariatric surgery (black solid line) and after bariatric surgery (black dotted line). Used with permission (<http://creativecommons.org/licenses/by/4.0/>) from Brill et al. *Pharm Res.* 2015;32(12):3927–3936

stomach is capable of absorbing most acidic drugs and the very weakly basic drugs which are undissociated in the acidic gastric environment.<sup>28</sup> After RYGB surgery, there is limited exposure to acid as a result of a higher gastric pH.<sup>12,13</sup> The studies after SG are conflicting, showing a higher exposure to acid (as a result of a lower pH),<sup>13</sup> while another study showed a rise of 3–4 pH units 1 day after surgery.<sup>29</sup>

In any case, bariatric surgery patients are generally prescribed prophylactic PPIs to reduce the risk of gastrointestinal complications after surgery, such as ulceration or gastrointestinal bleeding during the first months after surgery.<sup>30,31</sup> Due to this rise in gastric pH, the solubility of more basic drugs could decrease since they become less ionized, and the solubility of acidic drugs could increase since they become more ionized.

An example of a drug that is absorbed in the stomach is acetylsalicylic acid (ASA), which is unionized in the acidic environment of the stomach upon which it can be absorbed.<sup>28</sup> Theoretically, because of the higher pH, the absorption and exposure of ASA could be reduced in patients after bariatric surgery. Mitrov-Winkelmoen et al. studied the effect of RYGB on the pharmacokinetics of orally administered ASA before and 6 weeks after RYGB surgery.<sup>32</sup> Instead of a lower AUC, they found a significant increase in AUC (14.1 vs 11.4 mg.h/L), an increased  $C_{max}$  (4.6 vs 3.5 mg/L) and a significantly decreased  $T_{max}$  (0.7 vs 1 h) 6 weeks after RYGB surgery. According to the authors, the higher AUC and  $C_{max}$  suggest that absorption of ASA, even when occurring mainly in ionized form because of the elevated pH, can also take place in the jejunum where it may even exceed absorption in the stomach and duodenum. Regarding these results, it is unknown what the contribution of the higher pH and/or altered gastric emptying and transit time of the GI tract is, as all of these changes occur simultaneously after bariatric surgery. The authors conclude that although the differences were significant, there is no clinical relevance to their findings, since the increased AUC corresponds to an AUC resulting from a dose of 100 mg, which is still within the recommended dosing range of ASA as a platelet aggregation inhibitor.

The weak base posaconazole is another example of a drug where the absorption is related to the residence time in the acidic environment of the stomach. Several studies showed the dependence of posaconazole absorption on the pH, resulting in the avoidance of PPI in patients using posaconazole.<sup>33,34</sup> As in RYGB surgery patients, a higher pH and faster gastric emptying may be expected. Gesquiere et al. performed a single-dose pharmacokinetic study in 12 RYGB surgery patients before and 6–9 months after surgery. After surgery, the  $AUC_{0-\infty}$  was significantly reduced (9.49 vs 4.37  $\mu\text{g.mL/h}$ ,  $P < .05$ ), which was explained by the low solubility of posaconazole, of which the absorption is very sensitive to intraluminal pH and residence time in the stomach.<sup>35</sup> As the decrease in AUC was more extensive than would be expected based on pH-related changes in absorption alone, the authors suggest that the reduced residence time after RYGB surgery contributes to their findings.

From these reports, it seems that the acidic drug ASA is absorbed after RYGB surgery even when the pH in the stomach is decreased. However, the weak base posaconazole is, as expected, not absorbed, resulting in a lower  $AUC_{0-\infty}$  in RYGB surgery patients.

These two results are in contrast to each other, suggesting that the effect of reduced dissolution due to a change in pH may be unpredictable and not applicable to all drugs. Besides a change in stomach pH, where only a small degree of drug absorption takes place, other factors may contribute to these changes in drug absorption like altered gastrointestinal transit time, delayed action of bile salts (see below), altered length of the gastrointestinal tract, altered activity of transporters and/or altered position in the gastrointestinal tract where the drug is absorbed.

### 2.3 | Gastrointestinal transit time

Besides the above-mentioned factors such as pH, gastric volume and gastric transition time, other factors like gastric emptying and gastrointestinal transit time are relevant for absorption. After RYGB, a large proportion of the stomach and intestine is bypassed, which can result in altered gastrointestinal transit time and gastric emptying time. Carswell et al. studied seven obese controls, six obese individuals undergoing adjustable gastric banding, seven subjects undergoing RYGB surgery, and five subjects undergoing biliopancreatic diversion with duodenal switch at 8–29 months post-surgery. The authors found no significant changes in gastrointestinal transit time using a sulphasalazine/sulphapyridine test with sulphapyridine detected at 180 minutes in all four groups.<sup>36</sup> Dirksen et al. measured the transit time of water and solid nutrients through the stomach, small intestine and colon through scintigraphy in 17 RYGB subjects who were at least 12 months post-surgery and in nine non-obese control subjects. In this study, RYGB subjects had faster pouch emptying for water as well for solid nutrients but slower small intestinal transit time and similar colonic transit time in comparison to healthy controls.<sup>37</sup> Nguyen et al. studied the effect of RYGB on gastric emptying and caecal arrival time in ten RYGB subjects who underwent surgery at least 12 months earlier in comparison to healthy subjects.<sup>38</sup> Compared to the healthy controls, gastric emptying and caecal arrival time were substantially faster in RYGB patients. Moreover, gastric emptying was faster when subjects were in a sitting position and tended to be faster after 150 mL in comparison to the 50 mL administration. Lastly, Wang et al. showed rapid gastric emptying in seven RYGB patients 1 year after surgery,<sup>39</sup> where the subjects were their own controls.

The results of these studies on gastric emptying and intestinal and colonic transit time show that gastric emptying is generally faster after bariatric surgery compared to healthy controls and that data on intestinal and colonic transit time is conflicting with more rapid and even slower small intestinal transit or caecal time reported in RYGB surgery patients.

Information on changes in the gastrointestinal transit time as a result of bariatric surgery may also be deduced from results on studies evaluating the effect of bariatric surgery on the exposure of slow-release vs immediate-release tablets. Yska et al. studied the effect of RYGB surgery on the exposure of **metoprolol** from immediate-release (IR) and controlled-release (CR) tablets in female patient volunteers 1 month before and 6 months after RYGB surgery.<sup>40</sup> The endpoint

was the ratio of the metoprolol  $AUC_{\text{after}}/AUC_{\text{before}}$  surgery. For the IR tablets, no significant changes were observed, albeit with major intraindividual and interindividual variability in AUC (range ratio  $AUC_{0-10 \text{ hours after}}/AUC_{0-10 \text{ hours before}}$ : 0.74–1.98). For the CR tablets, a significantly lower AUC was observed after surgery (range ratio  $AUC_{0-24 \text{ hours after}}/AUC_{0-24 \text{ hours before}}$ : 0.43–0.77). Based on these highly variable results, the authors conclude that RYGB surgery may influence the bioavailability of metoprolol from an IR tablet and that after surgery, the dose of metoprolol CR tablets should be increased according to clinical response.<sup>40</sup> In contrast with these results, another study showed no significant effect on the AUC of metoprolol measured at 6–8 months after RYGB surgery in patients receiving oral metoprolol CR tablets.<sup>41</sup> Also, for IR tablets, no changes in exposure after surgery were found. Because of differences in the volume of water used to swallow the CR tablet influencing pouch emptying and differences between women and men (Yska et al. only included female volunteers) as explanations for the diverging results for CR tablets, it seems too early for conclusions on the use of metoprolol CR tablets after surgery.

For **venlafaxine** administered as CR capsules, Krieger et al. showed no effect on AUC of venlafaxine and its primary metabolite 3–4 months after RYGB.<sup>42</sup> Similarly, Hachon et al. investigated the effect of RYGB surgery on the pharmacokinetics of **morphine** CR tablets in RYGB patients (2 years after surgery) and healthy controls. They found no significant changes in the AUC or other PK parameters between studied groups.<sup>43</sup>

Based on the results of these studies on CR formulations, it seems that a priori, CR formulations may not need to be discouraged in patients after bariatric surgery, even though close monitoring seems warranted.

### 2.4 | Role of bile salts

After bariatric surgery, the influence of digestive content is also altered. Gastric acid secretion is significantly reduced following RYGB surgery, leading to an increase in pH in the stomach.<sup>12,13</sup> The altered GI tract may also lead to a delayed action of bile salts. Bile salts are ionic amphiphilic compounds with a steroid skeleton. One of the most important physiological properties of bile salts is the transport by solubilisation of lipophilic substances through hydrophobic barriers.<sup>44,45</sup> Because bile salts do not reach the GI tract before the jejunum, contact between bile salts and a drug occurs later in comparison to normal subjects. Due to this potentially delayed inlet lipophilic, low soluble drugs might have lower absorption profiles. A drug that has been demonstrated to be dependent on bile salts is **fenofibrate**. Gesquiere et al. performed a single-dose pharmacokinetic study in 12 RYGB surgery patients before and 6–9 months after surgery and surprisingly, the  $AUC_{0-\infty}$ ,  $C_{\text{max}}$  and  $T_{\text{max}}$  of fenofibrate were not altered.<sup>35</sup> The authors hypothesize that these results may be explained by higher fasting total serum bile acid concentration in patients after RYGB and by faster gastric emptying that might compensate for the delayed efflux of bile salts.<sup>35</sup> This study result

suggests that the overall influence of altered timing of bile acids on oral drug absorption may be minor, even though further research on this topic seems warranted.

### 3 | OVERVIEW OF DOSING INFORMATION ON COMMONLY USED DRUGS AFTER BARIATRIC SURGERY

Here we provide an overview of the available literature on dosing of commonly used oral drugs in this special population (for summary, see

Table 2). Literature was searched using a structured approach. We searched in PubMed for available literature, using the keywords 'bariatric surgery' and the drug(s) of interest. Additionally, we checked the reference sections of the articles to find any other relevant literature on the topic of interest.

#### 3.1 | Antibiotics

Obesity is a risk factor for infections, including surgical wound infections and skin infections, urging the need to dose antibiotics

**TABLE 2** Overview of dosing information on commonly used drugs after bariatric surgery

Therapeutic group	Action after bariatric surgery
<b>Antithrombotic Agents</b>	
Direct oral anticoagulant <i>Apixaban, rivaroxaban, dabigatran &amp; edoxaban</i>	Avoid use because of potential insufficient effects and the availability of an alternative therapy (VKAs/LMWH). <sup>46-50</sup>
Platelet aggregation inhibitors <i>Clopidogrel, acetylsalicylic acid, ticagrelor &amp; prasugrel</i>	Current evidence shows that there is no reason to adjust the dose after bariatric surgery even though there is evidence that in obese patients there is increased platelet activation. <sup>30,51-54</sup>
Vitamin K antagonist <i>Warfarin, acenocoumarol, fenprocoumon</i>	Monitor INR frequently post-surgery. The dose after surgery may initially decrease and then normalize to the pre-surgery dose over the following months. <sup>55-58</sup>
<b>Antineoplastic and immunomodulating agents</b>	
Endocrine therapy <i>Tamoxifen</i>	Monitor serum concentration regularly (tamoxifen concentration > 5.9 ng/mL). <sup>59</sup>
<b>Central nervous system</b>	
Serotonin reuptake inhibitors <i>Sertraline, paroxetine, duloxetine, venlafaxine, citalopram &amp; escitalopram</i>	Monitor for therapy failure particularly in the first six months after surgery, consider TDM, and, if necessary, adjust dose accordingly. <sup>60-63</sup>
Lithium	Monitor patients closely after surgery and adjust dose accordingly. <sup>64-66</sup>
<b>Genito urinary system and sex hormones</b>	
Oral contraceptives	Alternative contraceptives should be considered, particularly in the case of chronic diarrhoea. <sup>67-71</sup>
<b>Alimentary tract and metabolism</b>	
Proton pump inhibitors <i>Omeprazole, pantoprazole, esomeprazole</i>	Monitor for signs of therapy failure, if necessary reconsider dose and/or administration of opened capsules. <sup>20,30,72</sup> Take into consideration that PPIs are prone to degradation by the acidic environment of the stomach. <sup>73</sup> Only advise opening when this is allowed according to the SmPC.
<b>Musculoskeletal system</b>	
Anti-inflammatory drugs, non-steroids <i>Ibuprofen, diclofenac, naproxen</i>	First six months: Contra-indicated. After six months: Discourage use. <sup>28,29,74-79</sup>
<b>Anti-infectives for systemic use</b>	
Antibiotics	<p><i>B-lactam (amoxicillin, ampicillin and [phenoxymethyl-]penicillin)</i> No specific dose alteration seems required, consider dosages in the higher range of the normal dosage. There is evidence for lower concentrations compared to normal weight subjects, however these concentrations are judged high enough to treat common pathogens.<sup>20,80-83</sup></p> <p><i>Macrolides (azithromycin and erythromycin)</i> Lower exposure after surgery; discourage use.<sup>84,85</sup></p> <p><i>Fluoroquinolones (ciprofloxacin and moxifloxacin)</i> No specific dose alteration seems required, consider dosages in the higher range of the normal dosage. No relevant decrease in plasma exposure after surgery has been reported.<sup>86,87</sup></p> <p><i>In general</i> Consider the target site of the infection, severity of infection, possibility of other than oral route of administration and toxicity of the antibiotic of choice when selecting the dose. Reduced tissue penetration for instance to the skin has been reported.<sup>88,89</sup> Monitor the effect and possible side effects of antibiotics closely after surgery.</p>

correctly.<sup>88–92</sup> With most studies evaluating antibiotic concentrations in plasma, we emphasize that it seems that an adequate plasma concentration might not always lead to adequate treatment because of potentially reduced perfusion of the antibiotic into the target tissue, as was demonstrated for **cefazolin** and **ciprofloxacin** with respect to skin penetration.<sup>80,81</sup>

### 3.1.1 | Beta-lactam antibiotics (amoxicillin, penicillin and ampicillin)

To date, five studies have been published regarding the pharmacokinetics of oral beta-lactam antibiotics. Two studies, i.e. Terry et al. and Miskowiak et al., describe the pharmacokinetics of oral **phenoxymethylpenicillin** after gastroplasty and jejunioleal bypass, procedures that are currently not often applied.<sup>82,83</sup> Miskowiak et al. reported no significant changes of gastroplasty on the absorption and concentrations of phenoxymethylpenicillin when given as a non-coated tablet or as an aqueous solution (1-week washout) in eight female bariatric surgery patients before and 3 months after gastroplasty surgery.<sup>82</sup> There were also no significant differences in AUC between tablet and aqueous solution. Terry et al. studied the oral absorption of a single administration of 1 g phenoxymethylpenicillin in three subjects before and 3 months after jejunioleal bypass and in five subjects 3 months after jejunioleal bypass.<sup>83</sup> In the group with AUC measurements before and after surgery, a substantially increased AUC after surgery ( $176.8 \pm 98.1$  vs  $17.1 \pm 5.9$  units/mL\*h) was demonstrated. Peak serum concentration also increased significantly. The authors explained the enhanced absorption of penicillin by the lack of degradation, which generally occurs in acid gastric contents.

The pharmacokinetics of oral amoxicillin after RYGB surgery was studied by Rocha et al. and Montanha et al.<sup>20,84</sup> Rocha et al. studied eight obese subjects receiving an amoxicillin 500 mg capsule before and 2 months after RYGB surgery.<sup>84</sup> They found a large and significant rise in AUC ( $7.21 \pm 5.13$  vs  $2.03 \pm 0.77$   $\mu\text{g}\cdot\text{h}/\text{ml}$ ) and  $C_{\text{max}}$  ( $1.77 \pm 1.19$  vs  $0.62 \pm 0.22$ ) after surgery, whereas  $T_{\text{max}}$  and  $t_{1/2}$  were not significantly altered. All of these values were, however, substantially lower compared to non-obese subjects who had  $\text{AUC}_{0-\text{tlast}}$  values of 12.44–12.05  $\mu\text{g}\cdot\text{h}/\text{mL}$  and a  $C_{\text{max}}$  ranging from 4.94 to 5.31  $\mu\text{g}/\text{mL}$ .

As previously stated, Montanha et al. reported a higher AUC for amoxicillin suspension compared to amoxicillin tablets in 20 RYGB surgery patients.<sup>20</sup> This higher AUC was predominantly explained by the higher  $C_{\text{max}}$  observed after the suspension. When comparing these results to amoxicillin absorption rates in non-bariatric and non-obese subjects, the total absorbed amount of amoxicillin appeared 40% lower in the suspension group and 50% lower for the tablets. Even though no clinical outcome measures were reported, for both formulations, the time above the MIC for pathogens with a MIC <4 mg/L was attained in the study of Montanha et al. Therefore, it seems that oral amoxicillin can be used in post RYGB surgery patients, despite the fact that the AUC is lower in comparison to normal weight subjects.

Kampmann studied oral absorption of **ampicillin** in six patients with morbid obesity undergoing jejunioleostomy.<sup>85</sup> Before surgery

and 1–2 weeks, 6 months and 12 months postoperatively, patients received 500 mg ampicillin intravenously and 700 mg of oral pivampicillin (the pivaloylmethylester of ampicillin) on separate days. A significant decrease in bioavailability was reported at 1–2 weeks ( $65 \pm 18\%$ ), 6 months ( $66 \pm 36\%$ ) and at 12 months ( $41 \pm 30\%$ ) after surgery compared to preoperative bioavailability ( $109 \pm 44\%$ ). However, as the bioavailability in healthy normal-weight subjects was 50%, these lower values might not have implications for antibiotic therapy. The authors suggest that the impeded absorption compared to pre-surgery in morbidly obese patients may have several explanations including: a change in bile acid metabolism; an increased number of enterobacteriae; premature splitting of the lipophilic part of pivampicillin; and/or an elevated mucosal enzyme level participating in the hydrolysis of pivampicillin.<sup>85</sup> No explanations were given for the higher bioavailability of pivampicillin in morbidly obese patients before surgery compared to healthy volunteers (109 vs 50%).

### 3.1.2 | Macrolide antibiotics (azithromycin and erythromycin)

Two studies investigating macrolide antibiotics have been published.

Prince et al. studied seven patients with morbid obesity receiving a single dose of 250 mg **erythromycin** within 3 days before and 6 weeks after surgery (one gastric bypass, six gastroplasty).<sup>86</sup> Mean weight-corrected AUC was reduced by 41% compared to pre-surgery values, with two patients having no detectable serum concentration after surgery. Mean peak concentration decreased from 1.04 to 0.5  $\mu\text{g}/\text{mL}$ , and  $T_{\text{max}}$  increased from  $3.9 \pm 1.5$  to  $6.7 \pm 2.8$  hours.<sup>86</sup>

Padwal and colleagues studied **azithromycin** pharmacokinetics in 14 female RYGB surgery patients, and 14 BMI matched controls.<sup>87</sup> Subjects were administered two 250 mg azithromycin tablets at least 3 months after surgery. AUC was reduced in the RYGB subjects by 31%;  $C_{\text{max}}$  and  $T_{\text{max}}$  were not significantly altered.<sup>87</sup>

Since both studies showed a reduction in exposure after surgery, it seems that the use of macrolide antibiotics should be discouraged after bariatric surgery.

### 3.1.3 | Fluoroquinolone antibiotics (ciprofloxacin and moxifloxacin)

To date, there are two studies published investigating the effect of bariatric surgery on oral fluoroquinolone antibiotics.

De Smet and colleagues studied the oral bioavailability of **moxifloxacin** in 12 individuals after RYGB surgery.<sup>93</sup> Each subject received two single doses of 400 mg oral or intravenous moxifloxacin with a washout period of 7 days at least 6 months after surgery. While mean oral bioavailability was 88%, oral and intravenous exposures were 50% higher than those described for subjects without gastric bypass.<sup>93</sup> The authors suggest that differences in the percentage of men and women or a higher enterohepatic recirculation of moxifloxacin after gastric bypass may contribute to this finding.

Rivas et al. evaluated the pharmacokinetic parameters of ciprofloxacin in 17 RYGB patients before, 1 month, and 6 months after surgery compared to 17 matched controls.<sup>59</sup> AUC was  $9737.2 \pm 2717.6$  h.ng/mL in the control and  $9141.3 \pm 1774.0$  h.ng/mL at baseline in the surgery group. One month after surgery, AUC decreased to  $7581.4 \pm 1511.1$  h.ng/mL and returned to presurgical baseline values at 6 months after surgery ( $9067.6 \pm 3880.2$  h.ng/mL).

### 3.1.4 | Failure of oral antibiotic therapy after bariatric surgery

Roy et al. investigated the association between the history of RYGB and increased treatment failure in patients who received oral antibiotics.<sup>94</sup> Treatment failure was defined as any prescription change that resulted in an increased daily dose, frequency or duration of current oral antibiotics, substitution or addition of another oral, intramuscular or intravenous antibiotic for the same indication, any surgical intervention for current infection, emergency room or outpatient visit for current infection and hospitalization for current infection. In their study, 186 patients were included (58 RYGB patients and 128 controls). There was no significant difference in composite therapeutic failure rates by time since RYGB surgery (24.1%,  $n = 14$ ) compared to the control group (15.6%  $n = 20$ ). However, in the subgroup treated with fluoroquinolones (31.6 vs 7.1%,  $n = 6$  and 2 respectively) and with sulfamethoxazole/trimethoprim (40 vs 7.1%,  $n = 4$  and 2 respectively), more therapeutic failure rates were reported compared to controls.

### 3.1.5 | Summary

Summarizing, for beta-lactam antibiotics, similar, increased or decreased exposure can be anticipated after surgery; however, as concentrations seem overall high enough to achieve therapeutic levels, these antibiotics can generally be applied. For macrolide antibiotics, a reduced exposure up to 30–40% after surgery has been reported and therefore the use of these antibiotics should be discouraged. While fluoroquinolones did show some reduction in exposure after surgery, the overall bioavailability seems adequate. In general, it seems that bariatric surgery patients treated with oral antibiotics should be monitored closely for therapy failure and side effects, particularly because of potentially reduced penetration into the target tissue. When prescribing antibiotics to bariatric surgery patients, several factors should be considered, including the site and severity of infection, route of administration and potential toxicity.

## 3.2 | Antihormones

**Tamoxifen** is widely used in the treatment of oestrogen receptor-positive breast cancer and is known for its inter-individual variability in pharmacokinetics. Previously, a minimal concentration threshold of

5.9 mg/mL of the active metabolite (Z)-endoxifen for the recurrence of breast cancer has been identified.<sup>95</sup> Therefore, therapeutic drug monitoring (TDM) has been recommended for tamoxifen to prevent undertreatment based on the (Z)-endoxifen concentration.<sup>96,97</sup>

In patients after RYGB surgery, reduced absorption of tamoxifen has been described in three women after RYGB<sup>98</sup> with tamoxifen blood concentrations below the therapeutic level of 5.9 mg/mL. For one patient, the time between RYGB and measured tamoxifen concentration was described and was 4 years. Because of the established relation between (Z)-endoxifen and the recurrence of breast cancer, particularly for patients after bariatric surgery, it seems advisable to apply TDM of (Z)-endoxifen over time after bariatric surgery. The monitoring of side effects can be included in determining the effectiveness/absorption of the therapy; however, because hot flashes are not predictive of serum concentrations of tamoxifen and its metabolites,<sup>99</sup> it cannot replace TDM. To the best of our knowledge, there are no known data from other antihormones in patients with bariatric surgery. Tamoxifen seems to be the preferred antihormone therapy because of routine TDM.

## 3.3 | Direct acting anticoagulants (DOACs)

In recent years, direct-acting anticoagulants (DOACs) have emerged as alternatives for vitamin K antagonists to be used for stroke prevention in atrial fibrillation and for the prevention and treatment of venous thromboembolism. In the general population, these drugs have a predictable pharmacokinetic profile, which enables fixed dosing without routine coagulation additional monitoring and, consequently, DOACs may have a profound benefit over the vitamin K antagonists (VKAs).<sup>100</sup> However, in patients undergoing bariatric surgery, these pharmacokinetic profiles may be aberrant. This may particularly apply to **rivaroxaban** whose oral absorption is linear until a dose of 15 mg, while in higher doses the bioavailability is reduced and becomes dependent on co-administration with food.<sup>100</sup> For rivaroxaban 20 mg tablets, AUC and  $C_{max}$  were reported to increase by 39% and 76% when administered with food, respectively.<sup>101</sup> Also, **dabigatran**, which requires an acid environment for absorption for which tartaric acid is added to the capsule, the reduced volume for gastric acid secretion leading to a more alkaline pH in the gastric pouch, may be subject to altered absorption.<sup>46,102</sup> Since all DOACs are absorbed in the first part of the gastrointestinal tract, surgery-related changes in the absorptive surface could alter the absorption of all these drugs.<sup>47</sup>

Only limited information is available about the absorption of DOACs after bariatric surgery. Kröll et al. measured the rivaroxaban AUC after a single dose of 10 mg rivaroxaban in 12 patients with obesity 1 day before and 3 days after RYGB/SG surgery.<sup>48</sup> In this study, no significant changes in pharmacokinetic profile were reported. In an extension study, Kröll and colleagues investigated a single dose of 10 mg oral rivaroxaban 6–8 months after SG or RYGB.<sup>49</sup> While the AUC and  $T_{1/2}$  were not significantly altered 6–8 months after surgery,  $T_{max}$  was increased after RYGB and SG, and  $C_{max}$  was lower and not altered in RYGB and SG patients, respectively.<sup>48,49</sup> Given the known

nonlinear absorption of rivaroxaban, it is unknown whether these results can be extrapolated to 15 or 20 mg tablets.

Rottenstreich et al. matched 18 patients who underwent bariatric surgery (12 SG, four adjustable bands, and two RYGB) to 18 obese control subjects. They were receiving DOACs (9 apixaban 5 mg BID, 7 rivaroxaban 15 mg OD and 20 mg OD and 2 dabigatran 110 mg and 150 mg BID) for atrial fibrillation, pulmonary embolism or deep vein thrombosis. The median time elapsed from surgery until study inclusion was 4.9 years. Peak concentrations were within the normal range in all apixaban and dabigatran patients; however, five of the seven patients receiving rivaroxaban had significantly lower peak concentrations than the control group.<sup>50</sup> The authors conclude that all DOACs, particularly rivaroxaban, should be used cautiously after bariatric surgery if used at all given that VKAs can be easily monitored. In two case reports, thromboembolic events related to possible impaired dabigatran absorption have been published.<sup>103,104</sup>

Based on the above reports, it seems that until more data on DOAC use is available, VKAs or low molecular weight heparins are to be preferred over DOACs. Measuring DOAC<sup>105-107</sup> or anti-Xa<sup>108,109</sup> concentrations has been suggested when applied in special patient groups; however, as there is no hard evidence on the relation between peak, trough or AUC of these measures with outcome, it seems too early to use TDM as guidance for DOAC use in post-bariatric surgery patients. In another special patient population (i.e., children), anti-Xa measurement for monitoring of the effect of rivaroxaban was regarded as inferior compared to measurement of rivaroxaban concentration. The reason for this conclusion is that the anti-Xa assay result may be falsely high or low because the assay can be influenced by pre-processing procedures (e.g., blood draw technique, extended time until measurement).<sup>110</sup>

### 3.4 | Non-steroidal anti-inflammatory drugs (NSAIDs)

The most common postoperative complications of bariatric surgery are related to the GI tract, such as bleeding and ulceration.<sup>74,111</sup> Depending on the definition, the reported incidence of ulceration ranges from 1 to 20%.<sup>75-78,111-115</sup> It has been demonstrated that the use of NSAIDs is an independent risk factor for the development of ulcerations.<sup>79,116,117</sup> Although NSAIDs after bariatric surgery are often proclaimed to be life-long contraindicated,<sup>30,31</sup> NSAIDs are commonly used in bariatric surgery patients.<sup>67,116-118</sup> Studies show that the majority of the ulcerations occur within the first year after surgery,<sup>76,112,114</sup> and therefore it can be speculated that the risk might thereafter be the same for bariatric surgery patients and other subjects. For now, it seems reasonable to conclude that NSAIDs are contraindicated in the first 6 months after bariatric surgery and that until there is more evidence, after these 6 months, the use of NSAIDs should be discouraged. There are no studies on the pharmacokinetics of NSAIDs before vs after bariatric surgery.

### 3.5 | Oral contraceptives

Obesity is associated with infertility in women by various mechanisms,<sup>119</sup> which seems to be (totally or partially) reversible after bariatric surgery due to weight loss.<sup>120</sup> As reproductive-aged women are advised to avoid pregnancy 12-24 months after bariatric surgery, contraceptives are recommended.<sup>68,121,122</sup> An anticipated reduction in absorption area, residence time and enterohepatic circulation after bariatric surgery may potentially decrease the reliability of oral contraceptives. There is, however, limited information on the use of oral contraceptives after bariatric surgery. Current guidelines recommend replacing oral contraceptives after RYGB by nonoral contraceptives due to conflicting data regarding pharmacokinetic and clinical outcomes in this population.<sup>69</sup> Victor et al. showed that **norethisterone** and **levonorgestrel** levels were lower after jejunoileal bypass at 1-8 hours after ingestion even though at 24 hours there was no difference.<sup>70</sup> Ciangura et al. showed reduced norgestrel levels 6 months after RYGB; however, these values were considered sufficiently high for a contraceptive effect.<sup>71</sup> De Brito et al. showed no significantly reduced levonorgestrel and **ethinylestradiol** levels at least 12 months after RYGB with a mean of 3.8 years, in 20 women compared to matched controlled non-bariatric women.<sup>123</sup> Besides evaluation of the pharmacokinetics, evaluation of clinical outcomes after a period of prolonged treatment with oral contraceptives is important. Furthermore, a reduced effect of oral contraceptives after biliopancreatic bypass was described by Gerrits et al.<sup>124</sup> Two of the nine patients who used oral contraceptives postoperatively were unexpectedly pregnant. These two patients suffered from chronic diarrhoea. No unexpected pregnancies were reported among users of non-oral contraceptives.<sup>124</sup>

In conclusion, the absorption of oral contraceptives may be reduced, particularly in the event of chronic diarrhoea following restrictive and malabsorptive bariatric surgery. Oral contraceptives should be discouraged, or alternative nonoral contraception should be used. However, as seen in the study by de Brito et al., oral contraceptives could be considered in patients (weight variation smaller than 5% within 3 months). Of note, Damhof et al. showed that 16% of the women undergoing bariatric surgery are using potentially unsafe contraception postoperatively, warranting the attention of health care professionals for this problem.<sup>125</sup>

### 3.6 | Platelet aggregation inhibitors

Platelet aggregation inhibitors such as ASA, **clopidogrel**, **prasugrel** and **ticagrelor** are frequently prescribed for the prevention of (recurrent) thrombotic disease in high-risk patients. Clopidogrel and prasugrel, both thienopyridines, and ticagrelor, a cyclopentyltriazolopyrimidine, are oral P2Y<sub>12</sub> receptor antagonists. While clopidogrel and prasugrel both need metabolic activation, ticagrelor acts directly on the P2Y<sub>12</sub> receptor. ASA, which is also a prodrug, exerts its effects by irreversible COX inhibition, which in turn leads to a reduction in the production of prostaglandin thromboxane A<sub>2</sub> and inhibition of platelet aggregation.



Several studies have shown that elevated body weight results in higher platelet reactivity, and therefore altered regimens for ASA<sup>51,52,126–129</sup> and clopidogrel<sup>53,54,126,130</sup> have been explored that might provide a more optimal platelet inhibition in obese patients. The relevance of the higher platelet reactivity in obese patients and its consequence for dosing of platelet inhibitors is unknown.

To date, four studies have investigated the effect of bariatric surgery on the pharmacokinetic profile of platelet aggregation inhibitors. Three studies describe the effect of bariatric surgery on ASA.<sup>32,128,131</sup> The other study investigates the effect of surgery on the pharmacodynamics of ticagrelor.<sup>132</sup>

As previously described, in an open-label longitudinal repeated-measure study, Mitrov-Winkelmolen et al. studied the effect of RYGB on ASA pharmacokinetics. In their study,  $T_{max}$  was shorter, and both  $C_{max}$  and  $AUC_{0-24}$  (14.1 and 11.4 mg/L, respectively,  $P < .001$ ) were higher after surgery. Although statistically significant, the authors argue that there are no clinically relevant changes in ASA pharmacokinetics, since the changes are still within the recommended dosing range for platelet aggregation inhibition.<sup>32</sup>

Norgard and colleagues studied the effect of bariatric surgery on the aspirin-induced platelet inhibition and subsequent platelet aggregability.<sup>128</sup> Ten patients undergoing bariatric surgery (8 RYGB and 2 SG) were administered two 7-day courses of ASA, before and 3 months after surgery. After the last dose, platelet reactivity expressed as aspirin reaction units (ARU) was tested and compared to data of normal-weighted subjects. They showed that before surgery, the platelet reactivity was significantly higher in patients with obesity compared to normal-weight subjects ( $469 \pm 60$  vs  $419 \pm 52$  ARU,  $P = .016$ ) when using ASA. After surgery, the platelet reactivity was significantly reduced ( $432 \pm 143$  vs  $469 \pm 60$  ARU,  $P = .03$ ), which was also seen in RYGB patients who did not use ASA ( $602 \pm 59$  vs  $531 \pm 78$  ARU,  $P = .035$ ). This shows that the reduced reactivity after surgery compared to preoperative values may not be solely related to ASA.<sup>128</sup>

The safety of low-dose ASA was studied by Kang and colleagues.<sup>131</sup> They followed a group of 1016 patients undergoing RYGB surgery, of whom 145 used ASA. The incidence of ulceration was not significantly different between the two treatment groups. Although it was a small study, the authors conclude that patients were not at increased bleeding risk when using low-dose ASA.<sup>131</sup> In contrast, Caruana et al. reported an overall rate of upper gastrointestinal bleeding of four of 11 bariatric surgery patients within 2–3.5 weeks after starting clopidogrel (25–234 days after surgery).<sup>133</sup> As such, it seems that prophylactic PPIs are indicated for at least 6 months after bariatric surgery when platelet inhibitors are given.

Ma and Norgard measured the influence of ticagrelor on whole blood impedance platelet aggregability induced by adenosine in obese patients undergoing bariatric surgery and in healthy normal-weight control subjects.<sup>132</sup> The half-maximal inhibitory concentration ( $IC_{50}$ ) value was 34.0 nM 6 weeks before bariatric surgery, which reduced to 23.1 nM 12 weeks after surgery, whereas in controls, the  $IC_{50}$  level of ticagrelor was 14.5 nM. This suggests that bariatric surgery

improves the ticagrelor pharmacodynamic response that was blunted by obesity, which is also shown in the study by Norgard described above.<sup>128</sup>

In conclusion, although obese patients seem to differ from non-obese patients with respect to platelet activity, it seems that platelet aggregation inhibitors do exert an effect after bariatric surgery. However, it is difficult to distinguish between the influence of the reduction of obesity vs the effect of the platelet inhibitor. From the available results, it seems that there is no indication for dose adjustments of platelet inhibitors after bariatric surgery.

### 3.7 | Proton pump inhibitors (PPIs)

According to many local protocols, PPIs are frequently prescribed after bariatric surgery for the prevention of ulceration, even though the duration of prophylactic PPI use seems to vary. In an internet-based survey among members of the International Federation for the Surgery of Obesity and Metabolic Disorders (IFSO) on the management of anastomotic ulcers after RYGB surgery, 88% of the 189 participants reported the prescription of prophylactic medication of which 91% preferred proton pump inhibitors.<sup>72</sup> The prophylactic medication was prescribed for a period of 1 month in 25% of the cases, for a period of 3 months in 37% of the cases, for a period of 6 months in 28% of the cases, for more than 6 months in 4% of the cases and lifelong for 5% of the cases, with a median of 3 months.<sup>72</sup> Even though the majority (~75%) of ulceration appears to occur in the first year after surgery, with the steepest increase in the first 6 months (~60%),<sup>112</sup> the available literature regarding this subject is not conclusive on the duration of prophylaxis in this population.<sup>73,76,78,112,113,115</sup>

Since the prescription and usage of PPIs is widespread, information on the absorption and dose is of relevance. Mitrov-Winkelmolen et al. studied the pharmacokinetics of omeprazole in 34 patients with morbid obesity 3 months–2 weeks before and more than 6 weeks after RYGB.  $T_{max}$  after surgery was 0.9 hours compared to 2.1 hours before surgery,  $C_{max}$  was higher ( $958.6 \pm 300.8$   $\mu\text{g/L}$  vs  $731.1 \pm 339.0$   $\mu\text{g/L}$ ) and  $AUC_{0-12}$  was lower ( $2834.1 \pm 1560.4$  vs  $3737.4 \pm 21932$   $\mu\text{g.h/L}$ ) after surgery.<sup>32</sup> Another study in 18 RYGB subjects 1 year after surgery also showed a reduced  $T_{max}$  (0.75 h vs 4 h) but no alterations in other PK parameters compared to matched controls.<sup>134</sup> This discrepancy might be explained by differences in study design (matched vs repeated measure design) and/or large interindividual variability in omeprazole PK. Also, the timing of the study in relation to surgery, can be relevant.

Another factor that might contribute to therapy failure of PPIs is the dissolution of the capsule, which was investigated by Schulman et al., reporting shorter healing time when the capsule was opened (as described in Section 2.1).<sup>21</sup> Therefore, in case an inadequate response is observed, opening the PPI capsule can be advised provided that PPIs do not get in contact with acid to prevent degradation.<sup>135</sup> Therefore, PPI capsules can only be opened when this is allowed according to the SmPC.

### 3.8 | Psychotropic drugs

Morbid obesity has been linked to different psychiatric disorders. Depression is the most common psychiatric disorder in the obese population with reported odds ratios (OR) ranging from 1.21 to 5.8 with a stronger association in women.<sup>64</sup> There is also a higher risk of anxiety disorders in the obese population (OR 1.27–1.40).<sup>64</sup> The prescription of psychotropic drugs is, therefore, relatively common in the bariatric surgery population.

In an in-vitro model studying the dissolution of common psychotropic drugs, ten of 22 psychiatric drugs had a significantly lower dissolution fraction and two (i.e., **lithium** and **bupropion**) had significantly higher dissolution after RYGB compared to preoperatively.<sup>65</sup> This might explain the lithium toxicity reported in many papers.<sup>60,61,66</sup> We therefore strongly recommend closely monitoring patients who are using lithium after surgery and adjusting the dose accordingly.

Hamad et al. investigated the effect of RYGB on the pharmacokinetics of serotonin reuptake inhibitors (SRI). Patients were taking venlafaxine ( $n = 5$ ), **citalopram** ( $n = 2$ ), **escitalopram** ( $n = 2$ ), **sertraline** ( $n = 2$ ) or **duloxetine** ( $n = 1$ ).<sup>62</sup> AUC values decreased by an average of 54% (36–80%), mainly in the SSRI group, 1 month after surgery in comparison with preoperative levels. In most patients, AUC values returned to baseline or exceeded baseline at 6 months after surgery.<sup>62</sup>

Marzinke et al. measured escitalopram plasma levels in four subjects 2 weeks before vs 2 and 6 weeks after RYGB. Two weeks after surgery, escitalopram plasma levels decreased significantly by 33% (4–71%). Samples collected 6 weeks after surgery showed a further decrease of 16–19%.<sup>63</sup> Although the decrease was significant, the study size was rather small.

Roerig et al. measured the AUC of duloxetine and sertraline in RYGB patients and matched controls.<sup>135,136</sup> For sertraline, both the  $AUC_{0-10.5}$  ( $124.4 \pm 55.5$  ng.hr/mL vs  $314.8 \pm 129.6$  ng.hr/mL) and  $C_{max}$  ( $19.0 \pm 7.8$  ng/mL vs  $48.7 \pm 19.1$  ng/mL) were significantly lower 9–15 months after RYGB surgery.<sup>55</sup> For duloxetine,  $AUC_{0-\infty}$  ( $646.74 \pm 79.7$  vs  $1119.91 \pm 593.40$ ) and  $T_{max}$  ( $2.2 \pm 0.86$  vs  $6.0 \pm 2.17$ ) were significantly lower in the RYGB group 9–15 months after surgery.<sup>56</sup>

These studies suggest that healthcare professionals should be aware of decreased serum concentrations when prescribing antidepressants and antipsychotic drugs to bariatric surgery patients, especially in the first few weeks and months after surgery.<sup>55,56,62,63</sup> Although no information was provided on the mental status of patients in the above-mentioned reports, prescribers should monitor patients for signs of therapy failure, particularly in the first year after bariatric surgery.

### 3.9 | Vitamin K antagonists (VKAs)

VKAs, such as **acenocoumarol**, **phenprocoumon** and **warfarin**, inhibit the carboxylation of the vitamin K-dependent coagulation factors II, VII, IX and X in the liver necessary for coagulation and thus indirectly

inhibit the coagulation process. VKAs are used for the prophylaxis and treatment of venous thromboembolism (VTE) and stroke prevention in atrial fibrillation. As VKAs are absorbed in the proximal intestine, bariatric surgery could have an impact on the absorption of VKAs.

Several studies investigated the effect of bariatric surgery on the daily dose of warfarin.<sup>57,58,136,137</sup> All studies demonstrated that the warfarin dose was significantly reduced after RYGB surgery, especially in the 6 months postoperatively. After the direct postoperative phase, the required dose tended to gradually go back up to pre-surgical levels at 6 months to 1 year after surgery.<sup>57,58,136,137</sup> It is not yet entirely clear why a lower dose is needed shortly after the operation. While it can be hypothesized that absorption may be increased because of crushing the tablets by patients directly after surgery, another explanation may lie in the changes that are associated with bariatric surgery that are to date not fully understood, such as metabolic changes.<sup>4</sup> Also changes in diet during the first months after surgery may play a role. Similar to the results of platelet aggregation inhibitors, it seems that bariatric surgery may improve the response to VKAs compared to obese subjects, especially in the first months after surgery.<sup>57,58</sup> It is known that compared to normal weight patients, obese patients require a higher average daily dose and also require more time to achieve therapeutic international normalized ratio (INR).<sup>138</sup> While no studies have been conducted on acenocoumarol and fenprocoumon after bariatric surgery, it may seem that these results also apply to these drugs. Overall, more frequent monitoring of the INR seems appropriate in the first year after bariatric surgery.

## 4 | DISCUSSION

Because of the increasing number of bariatric surgery procedures that are being performed, healthcare professionals will be increasingly confronted with the care of these patients. Since during this procedure, alterations to the gastrointestinal tract are being made which results in substantial weight loss over time, changes in the absorption, distribution, metabolism and elimination of drugs can be expected, and special considerations, particularly regarding the dosing of oral drugs, may apply. In this review, we report on the influence of bariatric surgery on the different steps of the process of oral drug absorption and give practical dosing considerations for several commonly used drugs for patients with a history of bariatric surgery based on a review of the available literature.

In general, the pharmacokinetic profile of orally administered drugs seems to change after bariatric surgery; the  $T_{max}$  can be earlier and  $C_{max}$  higher, with less consistent results on the AUC, which can be similar,<sup>20,42,43,48,49</sup> lower<sup>20,35,55,59,62,87</sup> or higher<sup>32,83,84</sup> after surgery. Many reports compare the pharmacokinetics in patients after bariatric surgery to the pharmacokinetics before surgery, while some studies also consider the pharmacokinetics in non-obese individuals for comparison. The latter may be of particular relevance for drugs for which altered pharmacokinetics in obese patients compared to non-obese patients have been reported, or when the pharmacodynamics are different in obese individuals as is the case for VKAs or platelet

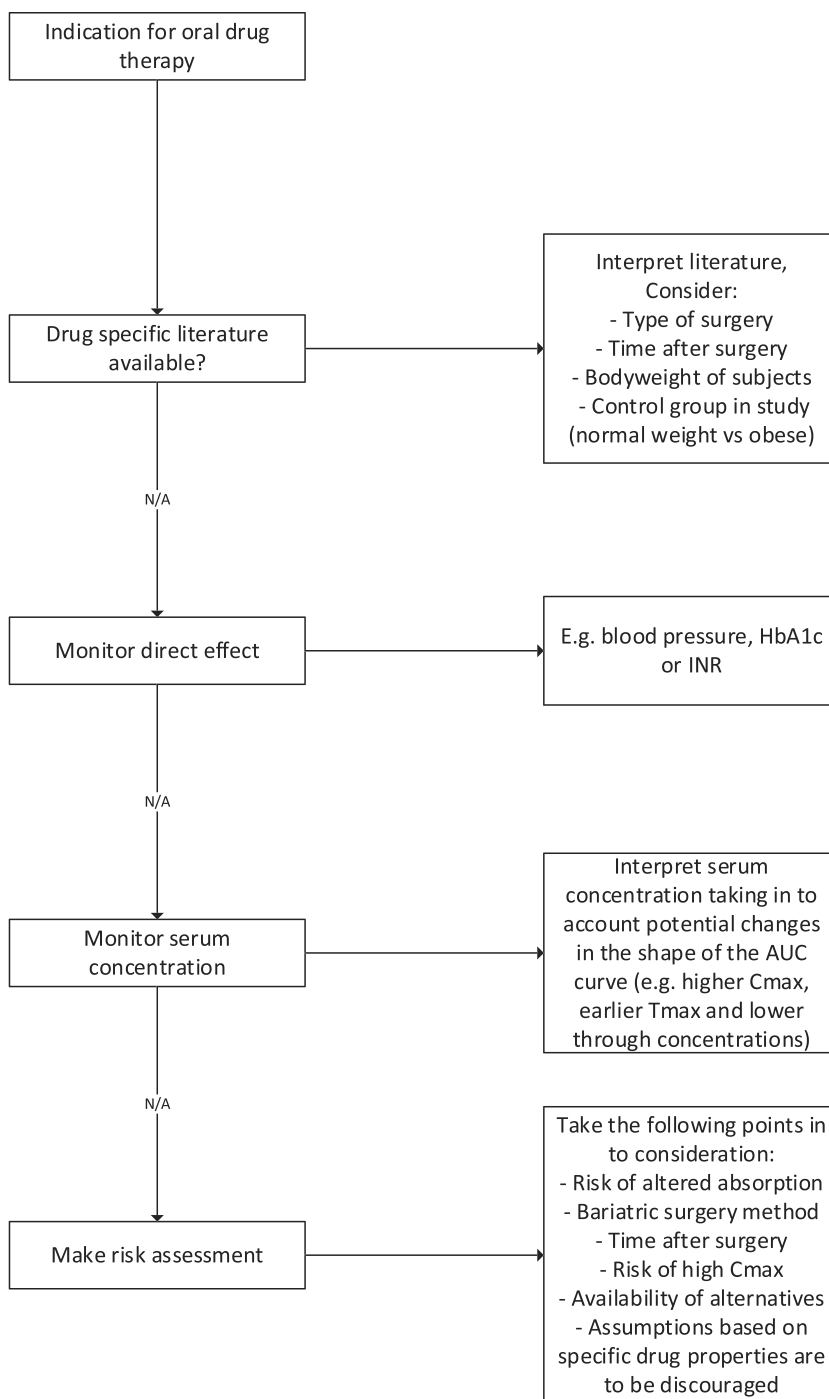
inhibitors. We note that even for similar drugs, different results may be observed, as shown for phenoxymethylpenicillin.<sup>82,83</sup> Also for controlled-release formulations, conflicting results were obtained in different studies.<sup>40,41</sup> While these differences may result from large inter- and intraindividual variability known in oral drug dosing, they may also result from different surgical techniques and formulations.

Another important issue to consider is that the shape of the pharmacokinetic profile of orally administered drugs may change substantially over time (e.g., with psychotropic drugs). Although conclusions like earlier and higher concentration peaks seem applicable, general

predictions on oral absorption after bariatric surgery are difficult to ascertain.

As such, advice regarding oral drug use after bariatric surgery should be given on a case-by-case basis.

Figure 2 shows some guidance on oral drug advice after bariatric surgery. Firstly, available literature on the drug before and after surgery should be considered. Predictions based on drug properties such as the Log *P*, the location of absorption in the gastrointestinal tract or BCS classification are to be discouraged because they did not prove to predict post-bariatric surgery bioavailability.<sup>17</sup> For drugs where a



**FIGURE 2** Flowchart for oral drug therapy after bariatric surgery

direct effect can be measured (e.g., blood pressure, INR, blood glucose, T3, T4 and TSH), this can be monitored and the dose be adjusted accordingly. Another possibility is to measure serum concentrations of the specific drug through TDM. When measuring a trough concentration, the shape of the concentration–time curve may have changed after surgery (see Figure 1).<sup>32</sup> In such a case, a lower trough concentration may not be reflective of a lower AUC and therefore conclusions based on a trough sample alone may not be predictive of the ultimate effect of the drug. This phenomenon may be relevant for drugs that exert their pharmacodynamic effects based on the AUC<sub>0–24h</sub> (e.g., some antibiotics, DOACs, pain killers). For drugs dependent on time above a certain concentration such as antibiotics, these considerations are less relevant, as long as the peak concentration does not result in potential safety issues, as may be the case for oral morphine<sup>26</sup> or midazolam.<sup>27</sup>

In addition, a risk assessment for the drug of interest can be made when prescribing oral drugs to post-bariatric surgery patients. During this assessment, the risk of reduced absorption and therapy failure and overdosing is weighed. If this risk is high (i.e., severe toxicity upon overdosing or increased morbidity and mortality upon underdosing), another therapy should be proposed. An example of such a drug are DOACs for which VKAs are a proposed alternative. For drugs where it is known that earlier and higher peaks may occur, for example morphine and midazolam, adjusted doses or additional monitoring may be

**TABLE 3** General considerations regarding oral absorption in bariatric surgery patients

Administration form/ specific drug properties	Advice after bariatric surgery
<b>Disintegration</b>	
<i>Large tablets</i>	Consider the switch to an oral solution; however, be aware of dumping syndrome by sugars which can be present in the oral solution <sup>82</sup> and of early and higher peaks that may occur for high-risk drugs (like midazolam and morphine). <sup>25,26</sup>
<i>Capsules</i>	Consider administering open capsules, if this is allowed according to the SmPC. <sup>20</sup>
<b>Dissolution</b>	
<i>Weak base or acidic drugs that are absorbed in the stomach</i>	Be aware of the potential loss of absorption; when possible, monitor direct effect or serum concentration. <sup>30,39</sup>
<b>Oral caecal transit time</b>	
<i>Controlled-release tablets</i>	There is no structural evidence for altered efficacy for controlled release tablets. Monitor for reduced absorption and therapy failure. When this occurs, switch to alternative therapy or prescribe immediate-release tablets, but beware of early and higher peaks. <sup>38–41</sup>

proposed. In this respect, also the type of surgery and period of time after bariatric surgery should be taken into consideration.

Different surgical techniques may lead to differences in alterations in the gastrointestinal tract. In this paper we have focused on the most commonly performed surgeries, the SG and RYGB. The One Anastomosis Gastric Bypass (OAGB) is a procedure that is gaining popularity, and is the most common type of surgery in some parts of the world.<sup>139</sup> For the OAGB, the stomach is dissected to create a long narrow gastric pouch; a loop of the small bowel is connected at the end of this pouch.<sup>140</sup> It is important to note that this procedure seems to be related to more malabsorptive problems compared to RYGB, and thus it is expected that the effect on oral drug absorption might also be more profound when patients undergo this type of surgery.<sup>140</sup> In addition, the period of time after bariatric surgery is also relevant since there is evidence that pharmacokinetic changes might change over time (e.g., VKAs and psychotropic drugs). Here also the formulation needs to be considered, as studies on oral suspensions, open capsules and direct release and controlled-release tablets have generally shown conflicting results (see Table 3).

## 5 | CONCLUSIONS

Bariatric surgery is increasingly employed for (morbid) obesity because it improves long-term morbidity and mortality. As a result of changes in the gastrointestinal tract that subsequently result in major weight loss, the pharmacokinetics of drugs in patients after bariatric surgery may be subject to alterations in the absorption, distribution, metabolism, and/or elimination. Due to an increased absorption rate after bariatric surgery, the time to maximum concentration is often earlier and the maximum concentration may be higher with less consistent effects on trough concentrations and exposure or area under the curve upon oral drug administration. Additionally, the use of liquid formulations instead of tablets for bariatric surgery patients is supported by some reports, but prescribers should be cautious about the high sugar load the suspension may contain. Studies on extended-release medication result in an unaltered exposure for some drugs, suggesting no need to avoid these formulations, especially when clinical effects (e.g., blood pressure) can be monitored. Also, studies evaluating the influence of the time after surgery show that absorption profiles may change over time. We conclude that, based on the current literature, advice can be proposed in many cases, but also that there is insufficient evidence for general dosing recommendations for oral drug therapy after bariatric surgery, implying a risk assessment on a case-by-case basis.

### 5.1 | Nomenclature of targets and ligands

Key protein targets and ligands in this article are hyperlinked to corresponding entries in <http://www.guidetopharmacology.org>, and are permanently archived in the Concise Guide to PHARMACOLOGY 2019/20.<sup>141</sup>

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## COMPETING INTERESTS

The authors state that there are no conflicts of interest to report.

## CONTRIBUTORS

J.S.K., D.M.T.B., V.M.M. and C.A.J.K. conceptualized the study and drafted the paper. All authors contributed to writing and revision of the paper. J.S.K., D.M.T.B. and C.A.J.K. critically revised the prefinal version. All authors revised the paper draft and approved the final version.

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