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REVIEW

Bioavailability of Orally Administered Drugs After Bariatric Surgery

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Abstract

Purpose of Review Oral drug absorption after bariatric surgery is likely to be altered, but the impact of different bariatric surgery procedures on individual drugs is not uniform. The aim of this article is to describe factors influencing the bioavailability of orally administered drugs after bariatric surgery and to provide readers with practical recommendations for drug dosing. We also discuss the medications that may be harmful after bariatric surgery.

Recent Findings The fundamental factors for enteral drug absorption are the production of gastric acid; the preserved length of the intestine, i.e., the size of the absorption surface and/or the preserved enterohepatic circulation; and the length of common loop where food and drugs are mixed with digestive enzymes and bile acids. Bypassing of metabolizing enzymes or efflux pumps and changes in intestinal motility can also play an important role. Significant changes of drug absorption early after the anatomic alteration may also be gradually ameliorated due to gradual intestinal adaptation. The most affected drugs are those with low or variable bioavailability and those undergoing enterohepatic circulation. Attention should also be paid to oral drug formulations, especially in the early postoperative period, when immediate-release and liquid formulations are preferred.

Summary The changes in oral bioavailability are especially clinically meaningful in patients treated with drugs possessing narrow therapeutic index (e.g., oral anticoagulants, levothyroxine, and anticonvulsants) or in acute conditions (e.g., anti-infectives); nevertheless, it may also influence the therapeutic value of chronic therapy (e.g., antidepressants. antihypertensives, antiplatelets, statins, PPIs, contraceptives, and analgesics); therapeutic effect of chronic therapy is further influenced by pharmacokinetic alterations resulting from weight loss. Therapeutic drug monitoring, periodical clinical evaluation, and adequate dose adjustments are necessary. Due to safety reasons, patients should avoid oral bisphosphonates, regular use of non-steroidal anti-inflammatory drugs, and, if possible, corticosteroids after bariatric surgery.

Keywords Drug absorption · Drug dosing · Pharmacokinetics · Roux-en-Y bypass · Sleeve gastrectomy

Introduction

Surgical procedures on the gastrointestinal tract (GIT) are an integral part of current obesity treatment algorithms. They may cause a significant reduction of food intake, reduction of intestinal absorption of nutrients by shortening GIT functional length, or a combination of both principles. From this point of view, bariatric methods are considered restrictive (gastric plication, sleeve gastrectomy), malabsorptive (biliopancreatic diversion), or combined (gastric bypasses, single anastomosis duodeno-ileal bypass with sleeve gastrectomy) (Fig. 1) [1]. Predominant site of absorption of most drugs after oral administration is the proximal part of the small intestine, due to its large absorption surface (200 m^2), large blood supply, and optimal pH (6–6.5) [2]. Bariatric surgery (BS), especially procedures bypassing the proximal part of GIT, may therefore largely influence the bioavailability (BAV) of some orally administered drugs [3••, 4]. Moreover, BS may influence not only drug absorption into the systemic circulation, but also the release of drug from its pharmaceutical formulation (liberation). As a result of these changes, the amount of absorbed drug can decrease, remain unaltered,

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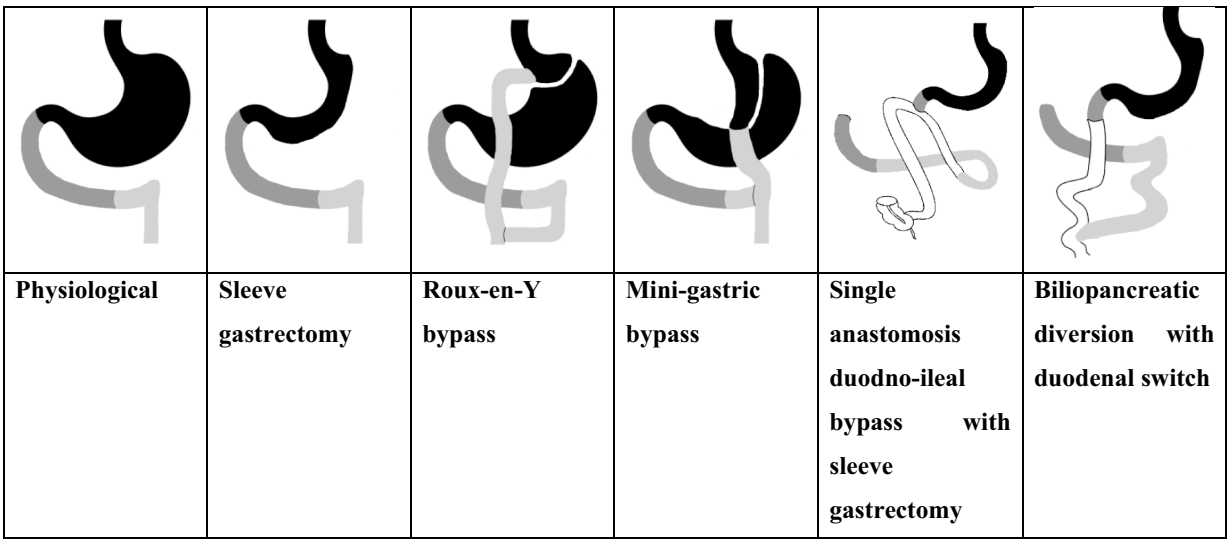

Fig. 1 Selected types of bariatric procedures. Black—stomach; dark grey—duodenum; light grey—jejunum; white—ileum

or less frequently also increase [5], and in addition to the type of BS, drug absorption is influenced also by the properties of the drug and characteristics of the patient (see Table 1).

In this review article, we focus on the absorption of drugs after the most common bariatric procedures, sleeve gastrectomy (SG), Roux-en-Y gastric bypass (RYGB), mini-gastric bypass (OAGB), and single anastomosis duodeno-ileal bypass with sleeve gastrectomy (SADI). Especially for the latter-mentioned procedure, very little data is available; therefore, we include also information from studies with today sparsely indicated but similar procedure, biliopancreatic diversion. After a brief introduction of basic principles in the "Introduction" section, we focus on the general suitability of various pharmaceutical dosage forms for patients after bariatric surgery (BS) in the "Characteristics of the Pharmaceutical Preparation" section. In the "Changes in GIT Physiology After Bariatric Procedures" section, we discuss physiological alterations that play a role in drug absorption from GIT after BS. The "Pharmacokinetic Alterations After Bariatric Surgery in Particular Drug Classes" section summarizes knowledge about the absorption of particular drugs and drug classes after BS, and the "Risk-Carrying Medication with Regard to Bariatric Surgery" section describes harmful medication that may cause complications after BS. The "Conclusion" section as well as Table 3 provides a brief summary of current knowledge and recommendations.

The absorption of drugs administered by a route other than parenteral is expressed usually by the percent of absorbed dose (BAV, bioavailability). The area under the drug plasma concentration plot over time after dosage is called the area under the curve (AUC). It provides the information about general exposure of the organism to the drug, and it is influenced by absorption as well as elimination [6]. By comparison of IV and PO, AUC of the absolute BAV can be determined. By comparison of the AUC of the drug administered before and after BS or after administration of two different dosage forms (e.g., liquid solution and tablet), relative changes in BAV can be determined. In this article, exposure refers to AUC, and alterations in exposure refer to changes in AUC.

Table 1 Factors influencing drug absorption after bariatric surgery

Characteristics of the procedure	Extent of restriction/malabsorption, residual absorption area time from surgery (adaptation in time)
Characteristics of pharmaceutical preparation	Dosage form (site of release, dissolution, and disintegration time), extent and rate of absorption (BAV, T_{max}, BCS classification), drug transporters involved, first-pass effect, physical and chemical characteristics (lipophilicity, pKa, molecular weight), stability in GIT, affinity to intestinal wall enzymes and efflux transporters
Characteristics of the patient	Gastric and intestinal pH (may be affected by interfering medication); production of bile salts; GIT motility (gastroparesis, intestinal transit time); blood flow, size, and integrity of absorption area; concurrent medication and nutritional intake (e.g., related drug-drug and drug-food interactions); GIT comorbidities (other surgeries, inflammation, etc.)

BAV bioavailability, *BCS* biopharmaceutics classification system, *GIT* gastrointestinal tract, *pKa* dissociation constant, T_{max} time to peak concentration

Characteristics of the Pharmaceutical Preparation

Characteristics of the pharmaceutical preparation are determined by its dosage form and properties of the active molecule. As for the formulations, liquid preparations do not need any disintegration and dissolution (= liberation) and therefore are more suitable for use after BS. On the other hand, using hyperosmolar liquids (e.g., syrups with non-absorbable sugars) carries a risk of dumping syndrome [7, 8••]. An added benefit of liquid formulations is a lower risk of mechanical irritation of the newly formed GIT anastomoses [9]. In the case of modified-release solid formulations, liberation of a drug can be significantly altered after BS: solid formulations with enteric coating might dissolve prematurely because of increased gastric pH [2], while formulations with extended release might not release the full amount of a drug [10•, 11]. Therefore immediate-release (IR) solid oral dosage forms should be preferred after BS. Characteristics of particular oral dosage forms should be sought in individual drug documentation, e.g., a summary of product characteristics. Some examples of modified-release oral drug dosage forms and their influence on absorption after BS are listed below in the "Pharmacokinetic Alterations After Bariatric Surgery in Particular Drug Classes" section (venlafaxine, metoprolol).

After a complex bariatric procedure, absorption of drugs with low and variable BAV or enterohepatic circulation is most affected [8••]. These are often highly lipophilic drugs, and their absorption may be affected by the availability of bile acids that increase their solubility. Bypass of the proximal part of the small intestine limits the contact of drugs with bile acids up to the section of the common post-anastomotic loop of the distal part of the small intestine, and "delayed mixing" therefore occurs in the more distant parts of GIT (Fig. 2), which may decrease drug absorption especially in more extensive procedures. Decreased absorption of cyclosporine, levothyroxine, phenytoin, rifampin or norethisterone, and levonorgestrel has been described in case reports and small case series [12].

Drug solubility and permeability across the cell membranes are two crucial factors influencing drug absorption. Biopharmaceutical classification system (BCS) divides the drug molecules according to their solubility and permeability into 4 classes (Table 2) [13]. Darwich et al. evaluated the changes in drug BAV in a BS patient population (mostly after jejuno-ileal bypass and RYGB) according to BCS. Exposure following BS was reduced for drugs with low solubility (BCS class II and IV), whereas BAV of highly soluble drugs (BCS class I and III) becomes variable. Nevertheless, differences in exposure were not statistically significant, and

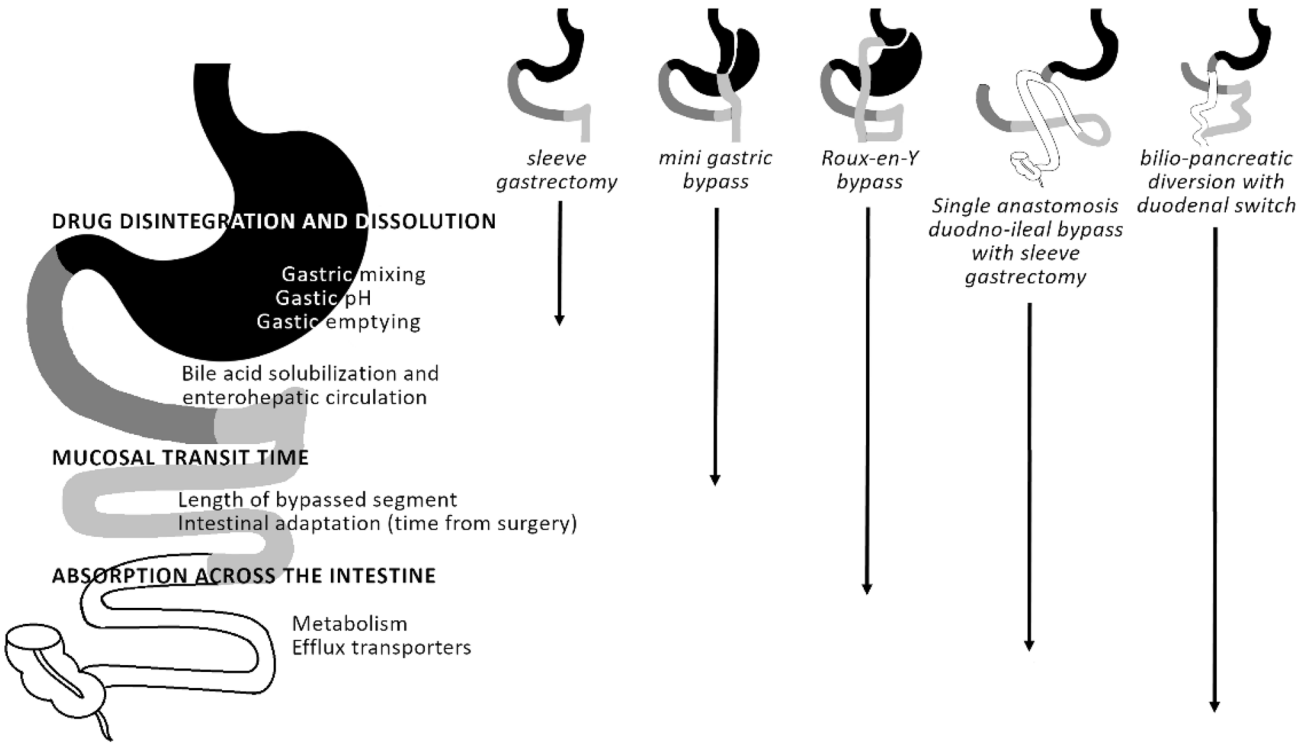

Fig. 2 Theoretical effect on drug absorption due to the different bariatric procedures. The arrows summarize the affected aspects of absorption, according to [12] with addition of SADI

most of the studies included only a small number of patients, so no firm conclusion can yet be drawn regarding the usefulness of BCS classification for predicting the effect of BS on drug absorption in agents from different classes.

Changes in GIT Physiology After Bariatric Procedures

To assess the effect of the surgery on drug absorption, the extent of the procedure has to be taken into account. Generally, SG influences drug absorption less than gastric bypasses [8••]. Figure 2 gives a theoretical summary of bariatric procedure effects on drug absorption [12].

Changes in Gastric pH

According to very sparse data from clinical studies in this field, gastric pH may rise (e.g., is less acidic) after BS. Additionally, prophylaxis with proton pump inhibitors (PPIs) [14] should be considered after RYGB and may be considered after SG for at least 30 days after surgery. This may affect the BAV of certain drugs. Porat et al. compared gastric pH preoperatively, after OAGB, and after SG. On day 1 after the procedure, pH was elevated by 3–4 units. This difference was more pronounced after OAGB, and in some cases, the absolute pH values exceeded 6. The overall indicative value of this study is largely limited by the fact that pH was assessed only 1 day after the procedure; therefore, it is not clear whether these results can be extrapolated to a longer postoperative and follow-up period [15•].

Alterations in GIT Passage

Fifty-two patients after SG were prospectively studied by Sista et al. Three months after SG, gastric emptying of liquids and solid food ($n = 26$ for both groups) was significantly accelerated (15.2 ± 13 and 33.5 ± 18 min) in comparison to preoperative measurements (26.7 ± 23 and 68.7 ± 25 min, $p < 0.05$) [16]. This is in line with the review of 9 available studies by Sioka et al., who describe accelerated gastric emptying, rapid gastroduodenal transit time, and reduced small bowel transit time after SG [17].

Regarding RYGB, shortly after the surgery period, self-limited gastroparesis may occur due to postoperative edema. After this period, gastric emptying is accelerated similarly as after SG [7]. Nevertheless, in contrast to SG, studies with patients after RYGB describe prolonged intestinal transit time. In a study by Pellegrini et al., passage time of solid, meat-containing food through the small intestine was measured in patients 3–30 months after total gastrectomy and RY esophagojejunostomy. In comparison to control subjects, total mouth-to-colon transit time was increased from 223 ± 18 to 298 ± 37 min. The passage of initial and final portions of food was increased from 187 ± 19 to 293 ± 37 min ($p < 0.02$) and from 175 ± 26 to 396 ± 28 min ($p < 0.001$), respectively [18]. This is in line with the study by Dirksen et al. that included 17 patients 14–26 months after RYGB in comparison with 9 controls, who all consumed radiolabelled food; the gastric emptying was faster, but small intestinal transit was slower in RYGB patients in comparison to control subjects [19].

Enterohepatic Circulation

An example of a drug with repeated peaks of plasmatic levels due to enterohepatic recirculation is mycophenolic acid (MPA). In non-bariatric populations, the first peak occurs 1–3 h after administration and the second peak, due to the recirculation, 6–8 h later. Rogers et al. observed a decrease in MPA AUC_{0-24} and peak concentration (C_{max}) and delayed time to reach maximal concentration (T_{max}) in patients after RYGB with blunting of the second peak in some of them. The lower AUC_{0-24}-to-dose ratio indicates that this population requires higher doses to achieve comparable exposure to the non-RYGB population. The authors hypothesize that lower exposure may be partly explained by the effect of the surgical procedure on the disruption of enterohepatic recirculation. A lower C_{max} was also attributed to reduced gastric surface area as MPA is partially absorbed already in the stomach [20].

Alterations of Metabolizing Enzymes and Efflux Transporters Along the Intestine

Absorption of drugs can be a passive procedure by diffusion or an active process through uptake carriers, such as peptide transporters 1 and 2 (ampicillin, captopril, valacyclovir), OATP1A2 (fexofenadine), OATP 2B1 (atorvastatin), and others [21]. Many drugs are also subject to efflux transporters, especially P-glycoprotein (digoxin, verapamil, cyclosporine, dexamethasone, colchicine, fexofenadine, etc.) and/or metabolism by intestinal enzymes which strongly

Table 2 BCS classification according to solubility and permeability

	High solubility	Low solubility
High permeability	Class I (e.g., metoprolol, acetaminophen)	Class II (e.g., ezetimibe, naproxen)
Low permeability	Class III (e.g., atenolol, ranitidine)	Class IV (e.g., furosemide, hydrochlorothiazide)

contributes to the decreased absorption of some drugs [21–23]. The expression of transporters and metabolizing enzymes is not uniform along GIT [24]. For example, the expression of CYP3A4 is high in the proximal part of the small intestine [8••, 25], and metabolism of its substrates (e.g., statins, benzodiazepines, calcineurin inhibitors, fentanyl) might be decreased after bypassing upper GIT parts; thus, lower doses might be necessary for desired therapeutic effect. The protective effect of the proximal intestine against exogenous substances is probably abrogated especially in patients a short time after BS before the postsurgical adaptation of GIT as was proven by Skottheim et al. in the case of atorvastatin in patients after biliopancreatic diversion [26]. The same authors described not so pronounced and rather variable effect of RYGB on atorvastatin absorption [27].

On the other hand, the efflux transporter P-glycoprotein (P-gp) which limits the absorption of many drugs (e.g., digoxin, calcineurin inhibitors, direct oral anticoagulants) has a lower occurrence in the duodenum and higher in distal parts of GIT [23, 25], which may theoretically lead to decreased absorption of drugs that are P-gp substrates. Depending on the affinity of a certain drug to these and many other enzymes and carriers, a variety of changes in BAV may occur; however, currently, there is not enough precise information at the moment to adapt drug dosing according to these alterations.

Post-bariatric GIT Physiology Adaptation Over Time

Initially, BS changes the anatomy and physiology of GIT very dramatically, but subsequent adaptation gradually occurs, and distal parts of GIT usually take over some functions of bypassed proximal parts [12]. After 6 months, GIT function stabilizes, and the resulting changes in drug absorption are not as pronounced as in the early postoperative period [3••, 10•, 28, 29]. Therefore, it is advisable to perform repeated therapeutic drug monitoring (TDM) and clinical evaluation of the effect of all orally administered drugs with a narrow therapeutic index (e.g., digoxin, tacrolimus, MPA, anticonvulsants, …) with subsequent adequate dose adjustments.

Pharmacokinetic Alterations After Bariatric Surgery in Particular Drug Classes

In the following text, we describe some changes in commonly used drugs from several therapeutic classes.

Oral Anticoagulants

Apixaban (BCS class III, T_{max} 3–4 h) is absorbed along the entire length of the intestine, independently of pH or food intake, and therefore, it is the preferred direct oral anticoagulant after bariatric procedures [30]. Steele et al. evaluated C_{max}, T_{max}, $T_{1/2}$, and $AUC_{0–72}$ of apixaban in a single dose study preoperatively and 1, 6, and 12 months after SG or RYGB. Pharmacodynamic parameters were assessed by anti-Xa activity. Twenty-eight patients (14 SG, 14 RYGB) were included, and the majority of them were women (89%) with a mean age of 43.8 years and a BMI of 48.7 kg/m^2. In comparison to baseline pre-surgical value, $AUC_{0–72}$ increased at 1 month (1232.9 versus 1009.1 ng/mL*h, $p = 0.002$), was comparable at the 6th month (1000.9 ng/mL*h, $p = 0.88$), and decreased at the 12th month (841.8 ng/mL*h, $p = 0.001$) after the procedures. The differences between SG and RYGB were not statistically significant. Percentage of patients achieving effective factor X inhibition (decrease to < 40% 3 h after intake) was higher post-procedure than preoperatively. Based on these findings, it was concluded that the pharmacokinetic and pharmacodynamic changes are of no clinical significance [31••].

Administration of a single dose of 10 mg of rivaroxaban (BCS class II, T_{max} 2–4 h) to 12 patients 3 days after bariatric surgery (6 × SG, 6 × RYGB) resulted in pharmacokinetic parameters comparable to those measured 1 day before surgery [32]. However, rivaroxaban is absorbed already in the stomach, absorption of higher doses (15 or 20 mg) is reliable only in the presence of food and a 29% decrease of $AUC_{0–24}$, and a 56% decrease of C_{max} was observed after administration directly into the proximal part of the small intestine [33]. Based on these findings, full-dose rivaroxaban should not be used after bariatric procedures associated with gastric area reduction [25]. This may be especially important when pylorus is bypassed, even though the experience is equivocal so far. For example, a case report of a patient successfully maintaining the expected plasma concentration of rivaroxaban approximately a month after gastric bypass without gastrectomy and Y-gastro-jejunostomy has been described [34]. On the other hand, a study of patients requiring long-term anticoagulation after bariatric surgery demonstrated subtherapeutic levels in 5 of 7 patients after SG or adjustable gastric banding (AGB) [35].

No data are available on the administration of edoxaban (BCS class IV, T_{max} 1–2 h) to patients after BS, but it is a highly acid-soluble drug absorbed almost exclusively in the proximal jejunum. Due to its very low dependence on CYP 3A4 metabolism and maintained sensitivity to P-gp, transport of the drug to the more distal parts of the GIT will only lead to a decrease in BAV [25]. This has been demonstrated by a decrease in both C_{max} and AUC of edoxaban when delivered to distal parts of the intestine in healthy volunteers, and edoxaban is therefore likely to be a less suitable alternative for patients after BS [36].

Dabigatran (BCS class II, T_{max} 0.5–2 h) is administered as a prodrug dabigatran etexilate. Capsules disintegrate in

the stomach, and the active drug is absorbed in the duodenum independently of food intake [37]. Absorption of dabigatran may be slightly reduced by increased gastric pH. Dabigatran capsules contain tartaric acid to eliminate the effect of acid suppressant therapy on the BAV of dabigatran, and the co-administration with pantoprazole decreased the exposure by 22% [38]. This is regarded as clinically non-significant, and therefore, under normal circumstances, the influence of gastric pH changes on dabigatran BAV is not considered to be clinically relevant [39]. Two post-SG patients taking dabigatran 5.1 and 3.7 years after surgery have been described; levels were within the expected range [35]. Nevertheless, several cases of patients with significantly reduced levels or therapeutic failure have been described after RYGB, probably due to the loss of the absorption area and faster drug transport to the distal jejunum and ileum with high P-gp expression [40, 41••]. For these reasons, dabigatran should not be administered to patients after bariatric procedures [42].

Due to the complex changes in pharmacokinetics, repeated measurements of plasma DOAC concentrations (peak and trough) are advisable in patients after bariatric surgery, given the gradual adaptation of the GIT over time since surgery [39].

Patients taking warfarin (BCS class I, T_{max} 4 h) should have more frequent INR controls after BS, due to its fluctuation; lower efficacious doses are expected during the first 3 months [3••]. This phenomenon was described by Steffen et al. [43] who investigated the relationship between warfarin dose and pharmacodynamic effect (i.e., INR) preoperatively and 6 months after RYGB. The mean weekly dose of warfarin decreased significantly in comparison to preoperative dose (28.08 ± 3.27 mg versus 37.08 ± 3.31 mg; $p < 0.001$), while INR increased significantly (2.94 ± 0.14 versus 2.36 ± 0.15; $p < 0.001$). The warfarin dose-to-INR ratio was also significantly reduced (17.64 ± 1.67 versus 10.94 ± 1.64; $p < 0.001$), i.e., a lower dose was required to achieve the target INR after the surgery. These changes, similarly described also by other authors [44–46], can be most likely caused by dietary changes after BS and a related decrease in vitamin K intake [47].

Levothyroxine

Levothyroxine belongs to drugs with low and variable BAV (BCS class III, T_{max} 2–4 h). Tablets have to be dissolved in acidic gastric pH, and the active substance is then absorbed predominantly in the upper part of the small intestine. A decrease in levothyroxine BAV due to the formation of complexes with iron and calcium has been reported as well as a decreased absorption when co-administered with PPI. As intake of these minerals and PPI is common after BS, it can further negatively affect the drug's BAV. Levothyroxine undergoes enterohepatic recirculation, which can be affected by bariatric procedures, as mentioned above. On the other hand, weight loss is associated with lower thyroid hormone supplementation requirements. According to a meta-analysis performed by Azran et al., there was a statistically significant decrease in TSH levels as well as a statistically significant decrease or discontinuation of levothyroxine after RYGB, OAGB, and SG, whereas often a dramatic increase of the levothyroxine dose was needed after jejuno-ileal bypass [48••]. For these reasons, a careful regular monitoring after BS and dose adjustment according to laboratory parameters is required [49]. Liquid formulations or soft gel capsules might help to overcome poor BAV even though no clear data are available so far.

Antidepressants

Citalopram (BCS class III, T_{max} 1–6 h) is absorbed independently on food intake with BAV around 80% [8••]. The only factor affecting citalopram absorption is dissolution. In a study by Hamad et al., AUC_{0-24} of citalopram was measured in 2 patients before RYGB and at the 1st, 6th, and 12th month after the procedure. While in the first patient, no change in time was observed, AUC_{0-24} in the second patient decreased after a month, whereas in the 6th and 12th month, it increased in comparison to the preoperative results [50]. Therefore, therapy should be re-evaluated in time and dosing adjusted according to plasmatic levels to avoid therapeutic failure.

Sertraline (BCS class II, T_{max} 4–8 h) is also absorbed independently of food intake. Hamad et al. described a decrease in sertraline AUC_{0-24} 1 month after RYGB in 1 patient. This decrease persisted unchanged during the following evaluations; in the second patient, no significant changes after surgery were noted [50].

Vortioxetine (BCS class II, T_{max} 7–11 h) is well absorbed. A case report by Vandenberghe et al. described changes in vortioxetine absorption in a 24-year-old woman after RYGB. C_{min} was measured before surgery and on days 91, 224, and 308 after the procedure. During the postoperative period, concentration-to-dose ratio (C/D) decreased by approx. 50%, therefore the dose was increased from 10 to 20 mg/day which effectively prevented possible therapeutic failure [51].

Dosing with extended-release venlafaxine (Venlafaxine XR, Aurobindo Pharma LTD) in 10 patients 3–4 months after RYGB was not associated with any clinically significant difference in peak concentration (C_{max}), time to C_{max} (T_{max}), and AUC_{0-24} neither for the parent drug nor for its active metabolite, desvenlafaxine, in comparison to pre-surgery values. AUC_{0-48} was comparable for venlafaxine but higher for desvenlafaxine. The reason for this is unclear, and it is probably of no clinical importance [52].

It is difficult to assess whether environmental and psychological factors and/or malabsorption are involved in mood changes during the first year after BS. Therefore, to avoid disease relapse, therapeutic drug monitoring of antidepressants is advisable, and in case of suspected malabsorption, a general approach, such as increasing the dose, switching to a liquid formulation, or crushing tablets (if possible), may improve BAV.

Antiplatelet Agents

Currently, not enough data are available to routinely perform dosing adjustments of antiplatelet agents after BS. However, their effect seems to be adequate [3••]. Obesity is associated with increased platelet reactivity [53], which may improve with body weight reduction after surgery. Mitrov-Winkelmolen et al. published a study with 34 patients undergoing RYGB using 80 mg of acetylsalicylic acid (ASA, BCS class I, T_{max} 1 h, without enteric coating) with 20 mg of omeprazole twice daily. T_{max} of salicylic acid (as a surrogate for rapidly hydrolyzed ASA) measured at least 6 weeks after the procedure was significantly shorter in comparison to preoperative measurement (0.7 versus 1 h ($p < 0.001$)) [54]. This could be explained by the shorter passage through the stomach after RYGB. C_{max} and $AUC_{0–24}$ of salicylic acid were significantly higher, but this was not regarded as clinically relevant as the values were comparable with a 100 mg dose in the non-bariatric population. This study demonstrates no decrease in salicylic acid BAV but does not clearly describe the BAV of ASA in the portal vein which is the place of action as hydrolysis of ASA to salicylic acid in the intestine before absorption cannot be ruled out. No information about the pharmacokinetics of clopidogrel (BCS class II, T_{max} 1 h), prasugrel (BCS class II, T_{max} 30 min), or ticagrelor (BCS class IV, T_{max} 2 h) after BS is currently available.

Analgesics

Goday Arno et al. studied pharmacokinetic parameters of acetaminophen (BCS class I, T_{max} 1 h) in patients before surgery and 4 weeks and 6 months after SG ($n = 10$) or RYGB ($n = 14$). They also compared its baseline pharmacokinetics in patients with obesity with a non-obese or overweight population. Obesity leads to increased volume of distribution (Vd) and clearance (CL) with a corresponding decrease in C_{max} and AUC in comparison to healthy non-bariatric volunteers. After BS, Vd, and CL values decreased together with BMI which decreased from over 40 kg/m^2 to around 30 kg/m^2 and AUC and C_{max} values increased, indicating a normalization of acetaminophen pharmacokinetics and suitability of standard dosing. The influence of changes in body composition cannot be distinguished from alteration in bioavailability after BS [55].

Patients living with obesity are more sensitive to the sedative effects of opioids and respiratory depression [56]. Opioid-induced nausea can also negatively affect postoperative recovery. In a study by Lloret-Linares et al., 30 patients with an initial mean BMI of 44.6 kg/m^2 were given an oral solution of morphine sulfate before RYGB, 7–15 days and 6 months after surgery, when the mean BMI decreased to 33.6 kg/m^2. Consequently, for visits 2 and 3, shorter median T_{max} (twofold and 7.5-fold, respectively), higher median C_{max} (1.7- and 3.3-fold, respectively), and a significant increase in $AUC_{0–12}$ (1.55-fold between visits 1 and 3) were observed [57]. Thus, RYGB patients might experience more adverse effects, and those with chronic opioid use might need dose reduction to avoid overdose and addiction. Fast onset of action is possibly influenced also by liquid dosage form which should be preferred after BS [58]. Recent recommendations support limited opioid use after BS [14].

Statins

Skottheim et al. investigated the effect of RYGB on the pharmacokinetics of atorvastatin (BCS class II, T_{max} 1–2 h) preoperatively and approximately 5 weeks (range 3–6) after surgery in 12 patients treated with 20–80 mg/day who did not take any medication interacting with atorvastatin pharmacokinetics. A variable effect of RYGB on systemic exposure to atorvastatin was observed, with $AUC_{0–8}$ ranging from a threefold decrease to a twofold increase (median ratio 1.1, $p = 0.99$). The exposure neither correlated with the dose of atorvastatin nor with the genetic profile of the metabolizing enzymes. The $AUC_{0–8}$ in 3 patients with the highest preoperative systemic exposure markedly decreased after surgery (median ratio 0.4, range 0.3–0.5, $p < 0.01$), whereas similar or increased $AUC_{0–8}$ (median ratio 1.2, range 0.8–2.3, $p = 0.03$) occurred in 8 from the remaining 9 patients. This led to more uniform exposure after RYGB [27]. The same group of authors described a two-fold increase of atorvastatin exposure 4–8 weeks after biliopancreatic diversion, which is most probably due to bypassing the most metabolically active part of the intestine where a large amount of the drug is degraded before absorption [26]. Interestingly this increase of exposure normalized after 21–45 months postsurgery which clearly suggests adaptation of distal intestine to postsurgical changes [29]. Nevertheless, statin dose should be adjusted according to lipid profile, which may improve due to the weight loss after BS.

Antihypertensives

Little is known about the potential decrease in the absorption of antihypertensives after BS. On the other hand, a substantial weight loss after BS can lead to a decrease in blood pressure thereby reducing the need for antihypertensive

medication [59•]. Therefore, it is important to monitor blood pressure regularly and possibly adjust the doses according to response. Standard dosing should be used [3••], and immediate-release formulations should be preferred [8••]. In the early postoperative period, patients may be at increased risk of dehydration if taking diuretics.

Yska et al. investigated the effect of RYGB on BAV on the release of metoprolol from immediate-release (IR) vs. controlled-release tablets. AUC of metoprolol was assessed 1 month before and 6 months after the surgery at a steady state. The AUC_{0-10} was non-significantly increased after the IR tablet ingestion with the ratio of AUC_{0-10} after and before surgery 1.19 ± 0.43 (range 0.74–1.98, $n=7$, $p=0.24$). In the case of controlled-release tablets, the AUC_{0-10} ratio after and before surgery was 0.59 ± 0.13 (range 0.43–0.77, $n=5$, $p<0.01$) even though the patients decreased their body weight and the AUC values were not body weight-normalized. These data suggest the need for careful monitoring and eventually dose adjustment according to the patient's clinical response [10•].

Proton Pump Inhibitors (PPIs)

According to ERAS (enhanced recovery after surgery) procedures, PPI prophylaxis for at least 30 days for all patients after RYGB is strongly recommended. Also after SG, 30-day PPI prophylaxis is prudent due to a high number of patients with gastroesophageal reflux after this procedure [14]. Mitrov-Winkelmolen et al. studied the pharmacokinetics of omeprazole (BCS class II, T_{max} 0.5–3.5 h) tablets with enteric coating in 34 patients 2 weeks before and > 6 weeks after RYGB. T_{max} after surgery decreased to 0.9 h compared to 2.1 h before surgery. An increase in C_{max} (958.6 ± 300.8 µg/l versus 731.1 ± 339.0 µg/l) and a decrease in AUC_{0-12} (2834.1 ± 1560.4 versus 3737.4 ± 2193.2 µg*h/L) was observed, with wide inter-individual variation [54]. In another study of 18 patients 1 year after RYGB compared to controls, shortened T_{max} (0.75 h versus 4 h, respectively) but no other changes in pharmacokinetic parameters were observed [60]. Shorter T_{max} can be attributed to faster dissolution of enterosolvent coating due to increased gastric pH [15•].

Anticonvulsants

Anticonvulsants are drugs with a narrow therapeutic index and poorly defined therapeutic concentration range. Based on pharmacokinetic properties, levetiracetam (BCS class I, T_{max} 3–4.5 h) and topiramate (BCS class I, T_{max} 1.5–4 h for IR) seem to be preferable for their hydrophilicity, absence of intestinal metabolism, and enterohepatic circulation and poor affinity to P-glycoprotein. On the other hand, carbamazepine (BCS class II, T_{max} 4–5 h for IR), oxcarbazepine (BCS class II, T_{max} 3–13 h for IR), phenytoin (BCS class II, T_{max} 4–12 h), and valproic acid (BCS class II, T_{max} 1–3 h) are lipophilic, are metabolized by the intestinal cells, and undergo enterohepatic circulation, and apart from valproic acid, they are also P-glycoprotein substrates and CYP 3A4 and P-gp autoinducers which may lead large variability in absorption after BS [61]. Porat et al. described a decrease in carbamazepine levels in 4 out of 8 patients after SG, all using a controlled-release formulation. Two patients also experienced decompensation of their chronic condition [62].

Due to the complexity of possible pharmacokinetic changes and the narrow therapeutic window, patients with epilepsy are at an increased risk of seizures after BS [63]. As well as in other clinical situations, where pharmacokinetic alterations are expected, plasma concentrations of anticonvulsants should be measured before BS to find out drug levels that lead to stable disease in a particular patient and then repeatedly during the first 6 months thereafter, ideally weekly for the first month and monthly for the next 3 months. After this period the frequency of measurements should be adjusted according to the individual fluctuations in plasmatic levels. Extended-release formulations should be avoided during the first 6 months [61]. Therapeutic drug monitoring of anticonvulsants plays a key role in these patients.

Oral Contraceptives

Ethinylestradiol, norethisterone, and levonorgestrel (all BCS class II) are subjects to extensive first-pass metabolism and enterohepatic circulation, both being impaired in bariatric patients [64]. After biliopancreatic diversion, 2 of 9 patients using oral contraceptives became pregnant in the study by Gerrits et al. which shows an impaired effect of this contraceptive measure [65]. The American College of Obstetricians and Gynecologists recommends hormonal contraceptive patches or intrauterine devices (IUDs) as safe alternatives for the first 12–24 months after BS [66]. In the study with 15 women who reached BMI < 30 kg/m^2 after RYGB that was performed at least a year before inclusion, levonorgestrel pharmacokinetic was not significantly altered when compared with BMI-matched women without BS [67].

Oral Anti-infectives

Montanha et al. [68] investigated the effect of RYGB on BAV of amoxicillin (T_{max} 1–2 h) in 875 mg tablets and 800 mg/10 ml suspension. According to BCS classification, the drug has a dose-dependent behavior, with class I categorization up to 875 mg, class II for doses 875–1000 mg, and class

IV for higher doses. C_{max} was higher for suspension than for tablets (8.73 ± 3.26 versus 7.42 ± 2.99 mg/l) with shorter T_{max} (1.7 ± 0.86 versus 2.0 ± 0.76 h) and comparable AUC; these changes were not statistically significant although there was a slight difference in dosing of the two formulations. Although no clinical results were reported, 30–40% time above minimal inhibitory concentration (T > MIC) for pathogens with MIC < 4 mg/L was achieved for both formulations and therefore both should be effective. Thus, oral amoxicillin can be used in bariatric patients, but its dose needs to be adjusted according to the patient's weight [69]. The same principle applies to co-amoxicillin, where sufficient weight-adjusted dose can be achieved by adding mono-component amoxicillin or ampicillin to the combination to avoid an unnecessary increase in beta-lactamase inhibitor dose and achieving an aminopenicillin dose of 50–100 mg/kg [70].

Nitrofurantoin (BCS class II, T_{max} 2 h) is a poorly soluble compound rapidly absorbed in the upper part of the small intestine with BAV around 40 to 50%, increased when taken with food. Macrocrystallic formulation has a slower dissolution and absorption rate. A reduced efficacy in people after OAGB, RYGB, and biliopancreatic diversion is expected [70].

Rivas et al. evaluated the pharmacokinetic parameters of a single 500 mg dose of ciprofloxacin (BCS class IV, T_{max} 2 h) administered to 17 RYGB patients preoperatively and 1 and 6 months after surgery in comparison with controls. AUC_{0-inf} decreased 1 month after the surgery when compared to the baseline value (7581.4 ± 1511.1 vs. 9141.3 ± 1774.0) and increased again 6 months after the surgery (9067.6 ± 3880.2). This shows that ciprofloxacin absorption after RYGB is impaired, but the effective exposure improves 6 months after surgery [71].

Padwal et al. studied the pharmacokinetics of azithromycin IR (BCS class II, T_{max} 1–2 h) in 14 female patients after RYGB (mean postoperative period 24.6 months) compared to 14 sex- and BMI-matched controls. Although C_{max} and T_{max} were not significantly altered, AUC_{0-24} was 32% lower in RYGB patients [72]. Despite the unknown clinical significance of this finding and due to the observed reduction of C_{max} for erythromycin in another study, some authors [3••, 73] suggest avoiding the use of orally administered macrolides. On the other hand, based on the pharmacokinetic properties and safety of macrolides, the lower BAV can be overcome by increasing the dose or prolonging the therapy which in the case of azithromycin would lead to significant drug accumulation and compensation of the decreased BAV.

In general, clinical implications of pharmacokinetic alterations of antibiotics after BS are largely unknown. Patients should be closely monitored for therapy failure due to malabsorption; adequate dosing at the upper limit of the recommended dosing range seems reasonable.

Risk-Carrying Medication with Regard to Bariatric Surgery

Even without considering pharmacokinetic changes, some drugs represent a risk for the patient after BS due to their gastric and intestinal toxicity. Patients should be instructed on which medications to avoid after BS due to the risk of damaging newly formed anastomoses. These drugs include, for example, non-steroidal anti-inflammatory drugs (NSAIDs) which belong to class II according to the BCS classification, have a pKa of approximately 3–5, and therefore have low solubility in the acidic environment of the unaffected stomach. However, due to the increase in gastric pH, dissolution of NSAIDs occurs already in the stomach after BS, which can increase their local toxicity and induce ulceration of the surgical anastomoses, GIT perforation, and leakage, as well as bleeding, gastritis, gastropathy, or GIT stenosis [8••, 74]. These complications occur most often in the first year after the procedure. Therefore, NSAID administration should be prevented in the first 6 months after the procedure and is not recommended even afterward [3••]. However, Zeid et al. found out in a retrospective case-control study with bariatric patients without severe organ failure or coagulation disorders that a short course of i.v. ketoprofen (up to 48 h) did not increase postoperative complications after BS and had an opioid-sparing effect [75]. If NSAID use is unavoidable, it is prudent to add a PPI [76, 77]. The recommended avoidance of NSAIDs does not apply to the administration of small doses of ASA as a part of ischemic vascular disease prophylaxis. In pain management, acetaminophen is a more suitable alternative, because, unlike NSAIDs, it does not increase the risk of bleeding, GIT, and renal adverse effects [14, 78].

If therapy with bisphosphonates is indicated due to osteoporosis, they should be administered intravenously (zoledronic acid 5 mg once a year or ibandronate 3 mg every 3 months) due to the concerns about inadequate oral absorption and potential risk of anastomotic ulceration and direct gastric irritation with orally administered bisphosphonates (strength of evidence D, expert opinion). If bisphosphonates are poorly tolerated or ineffective, denosumab (60 mg s.c. every 6 months) can be considered. Considering calcium and vitamin D deficiency, their supplementation is advisable [74].

Chronic use of corticosteroids may also cause harm to the GIT after BS. Kaplan et al. tested a hypothesis that chronic corticosteroid use (≥ 4 years) is associated with increased mortality and major complications within the first 30 days after bariatric procedures [79]. In this retrospective study, 430 patients after RYGB and 385 after SG were included. There was a 3.4 higher probability of death (95% CI 1.4–8.1, $p = 0.007$) and a twofold higher probability

Table 3 Overview of the most commonly used drugs in patients after bariatric procedures

Pharmacotherapeutic group	Approach to medication after bariatric surgery
Oral anticoagulants	
DOAC	Apixaban is a preferred DOAC, and measurement of plasma levels is recommended.
Warfarin	More frequent regular INR measurements are necessary.
Antiplatelets	Doses are not routinely adjusted after the procedure, although there is evidence that obese patients have increased platelet activation. Immediate-release dosage formulations of ASA are preferred.
Thyroidal hormones (levothyroxine)	Regular controls of TSH a fT4 are needed.
Antidepressants	There is an increased risk of therapeutic failure during the first 6 months due to malabsorption. Careful monitoring of the therapeutic effect and dose adjustment, if needed, is recommended.
Analgesics	Acetaminophen: standard dosing; NSAIDs: use is not recommended; opioids: opioid dosing should be minimized and regularly re-evaluated.
Hypolipidemic	Standard dosing with controls of plasmatic lipid profile is recommended.
Antihypertensives	Standard dosing with adjustments according to blood pressure is recommended.
Proton pump inhibitors	Standard dosing is recommended.
Anticonvulsants	Measurement of effective plasmatic levels before the surgery. Regular therapeutic drug monitoring after the surgery is recommended to keep the plasmatic levels in pre-surgery range.
Contraceptives	A safe alternative to oral contraceptives should be chosen for the first 12–24 months after surgery: transdermal patches or IUDs. Pregnancy should be planned no sooner than 12–18 months after the procedure.
Anti-infectives	Dosing should be adjusted to patient's body weight, preferably at the upper range for therapy (assuming normal elimination functions).

ASA acetylsalicylic acid, *DOAC* direct oral anticoagulants, *fT4* free thyroxine, *INR* international normalized ratio, *IUDs* intrauterine devices, *NSAIDs* non-steroidal anti-inflammatory drugs, *TSH* thyroid stimulating hormone

of serious complications (reoperation, postoperative myocardial infarction, need for cardiopulmonary resuscitation or cardiac arrest, septic shock, stroke, reintubation, or prolonged ventilation beyond 48 h; 95% CI 1.2–2.3, $p = 0.008$) in patients on chronic therapy with corticosteroids, regardless of procedure type. Therefore, if possible, BS as well as any other surgical procedure should be postponed to the time when larger corticosteroid doses are possibly tapered down or even discontinued. Not only prolonged healing and a higher risk of infection are expected, but also the pharmacokinetics of corticoids can be disturbed, especially after gastric bypass, because they are absorbed mainly in the proximal intestine, which is bypassed by this procedure. In addition, corticosteroids can increase the risk of marginal ulcers that should be prevented by minimizing therapy and/or by administering PPIs [80].

Conclusion

Oral drug absorption is influenced by a number of factors related to the drug itself, the type of bariatric procedure, and the patient. The fundamental factor for enteral drug absorption is the preserved length of the intestine, i.e., the size of the absorption surface and/or the preserved enterohepatic circulation, the length of common loop where food and drugs are mixed with digestive enzymes and bile acids, and production of gastric acid. Bypassing of metabolizing enzymes or efflux pumps and changes in intestinal motility can also play an important role. Drugs may be affected by all these factors to varying extents, and the final effect may be very different or even opposite for two different drugs (i.e., decrease of BAV in one drug and increase of BAV in the other).

Pharmacotherapy should also be periodically reassessed over time, both in terms of weight loss after surgery and in terms of gradual GIT adaptation and consequent improvement in absorption. Unnecessary drugs or drugs that may be harmful (i.e., oral NSAIDs, bisphosphonates) should be discontinued, dose adjustments should be made with respect to the patient's current body weight, and drugs with a narrow therapeutic index should be monitored regularly by measuring plasma levels, coagulation parameters, and other laboratory findings.

Attention should also be paid to oral drug formulations, especially in the early postoperative period, when immediate-release and liquid formulations are preferred. Patients using oral contraceptives should be switched to formulations with other routes of administration. Table 3 lists the most common groups of orally administered medications and how to approach these medications after bariatric surgery in the first 6 months. This list is not exhausting, and some of the drugs with narrow therapeutic windows (such as antineoplastics or immunosuppressants) are not covered but would require extreme caution and frequent and close monitoring.

Abbreviations AUC: Area under the curve; ASA: Acetylsalicylic acid; BMI: Body mass index; BAV: Bioavailability; BCS: Biopharmaceutical classification system; BS: Bariatric surgery; CL : Clearance; C_{max}: Peak concentration; DOAC: Direct oral anticoagulant; GIP: Gastric inhibitory polypeptide; GIT: Gastrointestinal tract; INR: International normalized ratio; IR: Immediate release; IUDs: Intrauterine devices; H_2: Histamine H_2 receptor; k_a : Absorption rate constant; NSAIDs: Non-steroidal anti-inflammatory drugs; OAGB: Mini-gastric bypass; PPI: Proton pump inhibitor; RYGB: Roux-en-Y gastric bypass; SG: Sleeve gastrectomy; $T_{1/2}$: Biological half-life; TDM: Therapeutic drug monitoring; T_{max}: Time to peak concentration; TSH: Thyroid-stimulating hormone; Vd: Volume of distribution

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Compliance with Ethical Standards

Conflict of Interest The authors declare that they do not have any conflict of interest regarding published work.

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- •• Of major importance

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