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1 **Effects of medicines used to treat gastrointestinal diseases on the pharmacokinetics of co-administered**
2 **drugs: A PEARRL Review**

3

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12 Running Title: Pharmacokinetic interactions with GI drugs

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19

20 **ABSTRACT**

21 *Background*

22 Drugs used to treat gastrointestinal diseases (GI drugs) are widely used either as prescription or over-the-
23 counter (OTC) medications and belong to both the ten most prescribed and ten most sold OTC medications
24 worldwide. Current clinical practice shows that in many cases, these drugs are administered concomitantly
25 with other drug products. Due to their metabolic properties and mechanisms of action, the drugs used to
26 treat gastrointestinal diseases can change the pharmacokinetics of some co-administered drugs. In certain
27 cases, these interactions can lead to failure of treatment or to the occurrence of serious adverse events.
28 The mechanism of interaction depends highly on drug properties and differs among therapeutic
29 categories. Understanding these interactions is essential to providing recommendations for optimal drug
30 therapy.

31

32 *Objective*

33 To discuss the most frequent interactions between GI and other drugs, including identification of the
34 mechanisms behind these interactions, where possible.

35

36 *Conclusion*

37 Interactions with GI drugs are numerous and can be highly significant clinically. Whilst alterations in
38 bioavailability due to changes in solubility, dissolution rate and metabolic interactions can be (for the most
39 part) easily identified, interactions that are mediated through other mechanisms, such as permeability or
40 microbiota, are less well understood. Future work should focus on characterizing these aspects.

41

42 **KEYWORDS**

43 Drug-Drug Interactions, gastrointestinal drugs, Pharmacokinetic Interactions, GI pH, GI solubility,
44 permeability, dissolution rate, motility, microbiota

45

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71 **1. Introduction**

72 It is estimated that 60-70 million US-Americans suffer annually from various types of gastrointestinal (GI)
73 diseases, with GI diseases being the underlying cause of approximately 10% of all deaths in the U.S.^[1,2] In
74 fact, statistical data on global sales of prescription medication from 2014 indicate that sales of drug
75 products for the treatment of GI diseases rank 12th with regard to sales of prescription medication
76 worldwide.^[3]

77 The term gastrointestinal diseases covers a wide range of disorders, which can be either acute or chronic.
78 Non ulcer or functional dyspepsia, for example, is usually an acute condition that affects the upper GI tract
79 and is expressed by symptoms such as nausea, vomiting, heartburn, bloating and stomach discomfort. The
80 treatment of functional dyspepsia can involve various drug classes depending on the symptoms as well as
81 the possible causative factors.^[4-6] Crohn's disease, by contrast, is a chronic inflammatory disorder that can
82 affect any part of the GI tract from the mouth to the anus. Although as of yet there is no cure for Crohn's
83 disease, there are several treatment options which can relieve the symptoms and prevent relapse.^[7] As
84 illustrated by these two examples, it is evident that a diversity of drugs with different mechanisms of action
85 are required to address the various targets across the spectrum of GI diseases.

86 Frequently, patients are prescribed several drugs concomitantly. Drug-Drug Interactions (DDIs) are a
87 common problem during drug treatment and can sometimes lead to failure of treatment, or can cause
88 serious or even fatal adverse events.^[8]

89 Medications used for the treatment of GI diseases can alter the GI physiology and thus interact with the
90 absorption of concomitant medications, but they can also alter the metabolism and/or elimination of co-
91 administered drugs, potentially resulting, on the one hand, in a lack of efficacy of the co-administered drug
92 or, on the other hand, in adverse drug reactions. From a regulatory perspective, studies of potential drug-
93 drug interactions which lead to changes in absorption are required for the marketing authorization of
94 medicinal products in the European Union and United States.^[8,9] In particular, these studies are designed

95 to evaluate the effect of increased GI pH, the possibility of complexation and alterations in GI transit
96 time.^[8] Understanding the effect of GI drugs on the physiology of the GI tract and achieving a mechanistic
97 understanding of the interaction(s) involved are key to successfully managing concomitant drug therapy.
98 In clinical trials drug performance is determined under controlled conditions (e.g. with strict
99 inclusion/exclusion criteria, under absence of, or controlled co-medication and with monitoring of
100 compliance). But, in clinical practice, where a much wider variety of patient characteristics, disease states
101 and multimorbidity is usual, the potential for DDIs is much greater. In fact, statistics show that one in a
102 hundred hospital admissions occurs as a result of a drug-drug interaction.^[10] The number of unreported/
103 less severe interactions is probably far greater.

104 In addition to potential interactions with prescription drugs, one must also consider the possibility of
105 interactions with over-the-counter medication (OTC). FDA publishes information leaflets for consumers
106 about the most typical drug interactions that occur with specific OTC medications. It is interesting to note
107 that four out of the twelve drugs discussed by FDA in these leaflets involve drugs used to treat
108 gastrointestinal diseases.^[11] European statistics indicate that there may be similar issues with concomitant
109 use of OTC medication in the European Union, since 20-70% of those surveyed reported using OTC
110 medicines.^[12]

111 Keeping in mind these statistics, as well as the fact that medications used to treat GI diseases count among
112 the 10 most prescribed medicines - and also fall within the top 10 in terms of sales of OTC medications -
113 worldwide,^[3,13] it is evident that there is a high potential for DDIs with these medications.

114 The objective of this review is first, to present and discuss the effects of drugs used to treat GI diseases,
115 both prescription and OTC, on the pharmacokinetics and bioavailability of co-administered drugs and
116 second, to identify the mechanisms behind these interactions insofar as possible. The review is organized
117 according to the therapeutic indication of the drug (see Figure 1 for an overview) and covers drugs used
118 to prevent/treat all major GI diseases. Although several reviews concerning DDIs of specific GI drug classes,

119 e.g. PPIs, are available in the literature, to the best of these authors' knowledge this is the first to provide
120 an overview of interactions that are likely to occur across the range of drugs used to treat GI diseases.

121 **2. Medicines used to treat gastrointestinal diseases and their effect on co-administered drugs**

122 **2.1 Agents affecting gastrointestinal motility**

123 Various neurotransmitters have an effect on GI motility and its coordination. Dopamine, for example, is
124 present in significant amounts in the GI wall and has an inhibitory effect on motility.^[14,15] Dopamine
125 receptor antagonists are currently being used for motor disorders of the upper GI tract, gastroesophageal
126 reflux disease, chronic dyspepsia and gastroparesis and have also been investigated for therapy of motility
127 disorders of the lower GI tract.^[16,17] Acetylcholine, by contrast, stimulates GI motility through increased
128 contractile activity by the smooth muscle.^[18,19] Serotonin, which is mainly present in the enterochromaffin
129 cells in the enteric epithelium and colon, has a wide range of effects on the GI tract. The diversity of effects
130 can be explained by the presence of multiple subtypes of 5-HT receptors, located on different types of
131 cells. Both agonists and antagonists of 5-HT receptors are used for the treatment of GI diseases.^[20,21]

132 **2.1.1 Prokinetic agents**

133 Prokinetic agents promote gut wall contractions and increase their coordination, thus enhancing GI
134 motility. However, they do not disrupt the normal physiological pattern of motility.^[16,17]

135 **2.1.1.1 Metoclopramide**

136 Metoclopramide is a first generation prokinetic agent with antidopaminergic properties (D1 and D2
137 receptor antagonist). In addition, metoclopramide is a 5-HT₃ receptor antagonist and a 5-HT₄ receptor
138 agonist. Metoclopramide promotes the response to acetylcholine in the upper GI tract and therefore
139 accelerates gastric emptying and increases the tone of the lower esophageal sphincter.^[22] The effect is
140 observed in both healthy volunteers and those with GI diseases.^[23-25] For example, Fink et al.
141 demonstrated that metoclopramide accelerates gastric emptying in patients with gastroesophageal reflux
142 disease independent of their gastric emptying status (Figures 2a and 2b).^[25] Metoclopramide is used for
143 the symptomatic treatment of postoperative or chemotherapy-induced nausea and vomiting, gastro-
144 esophageal reflux disease and gastroparesis.^[23] A summary of the effects of concomitant use of

145 metoclopramide on the absorption of several APIs is presented in Table 1 and mechanistic explanations
146 for the observed effects are presented in the following text.

147 It is known that migraine attacks are often accompanied by delayed gastric emptying.^[26] Tokola et al.,
148 1984, investigated the effect of metoclopramide on the absorption of tolfenamic acid in patients
149 diagnosed with migraine. According to the protocol, the volunteers took part in the absorption studies
150 twice in the absence of migraine and twice as soon as possible after the beginning of a migraine attack.
151 After rectal administration of metoclopramide, the absorption of the tolfenamic acid was accelerated
152 compared to control (rectal administration of placebo) in all subjects. However, the total bioavailability of
153 tolfenamic acid did not change significantly.^[27] A similar study had been conducted in 1975 by Volans, in
154 which the effect of metoclopramide on the absorption of aspirin during migraine attacks was
155 investigated.^[28] In that study, the delayed gastric emptying during a migraine attack was confirmed. In
156 addition, it was shown that the plasma levels of salicylate achieved during a migraine attack, after
157 intramuscular administration of metoclopramide, were higher in comparison to those achieved without
158 metoclopramide pre-treatment.

159 Gothoni et al., 1972, reported an earlier time to achieve maximum plasma concentration (t_{max}) and
160 elevated serum tetracycline concentrations in six healthy volunteers after co-administration of
161 tetracycline with intramuscular metoclopramide. Nonetheless, the total area under the curve (AUC)
162 remained unaltered. In the same study, an increase in the rate of absorption of oral pivampicillin was
163 reported when administered along with metoclopramide.^[29]

164 Concomitant administration of metoclopramide has also been shown to increase the absorption rate of
165 acetaminophen, mexiletine, lithium, droxicam and morphine. Nimmo et al., 1973, studied the absorption
166 of acetaminophen with and without co-administration of metoclopramide in five healthy volunteers. The
167 mean t_{max} was reduced from 120 min to 48 min while the mean maximum plasma concentration (C_{max})
168 increased from 125 µg/mL to 205 µg/mL. The urinary excretion of acetaminophen was not influenced.

169 Given the fact that t_{max} is a function of both absorption and elimination rates, the shortened t_{max} after

170 pre-treatment with metoclopramide indicates an enhanced absorption rate.^[30] Similar results were
171 obtained in the study of Wing et al., 1980, in which the authors demonstrated an increased absorption
172 rate of mexiletine after co-administration of metoclopramide. Here too, it was observed that the
173 bioavailability of mexiletine was unaltered, indicating that during chronic dosing of mexiletine, the
174 antiarrhythmic effect is unlikely to change after concomitant use of metoclopramide.^[31] In a further study
175 by Crammer et al., 1974, it was shown that metoclopramide reduced the t_{max} of co-administered lithium
176 by two hours.^[32] Sánchez et al., 1989, investigated the effect of intravenous metoclopramide on the
177 absorption of droxicam (a piroxicam prodrug) and Manana et al., 1988, investigated the effect of oral
178 metoclopramide after concomitant administration of an oral controlled release formulation of morphine.
179 In both cases, a significant reduction of t_{max} was observed, but other pharmacokinetic parameters were
180 not significantly different.^[33,34] Thus, in most studies it has been demonstrated that although concomitant
181 administration of metoclopramide increases absorption rate, there is little or no effect on AUC, or clinical
182 efficacy.

183 In a study by Morris et al., 1976, it was likewise observed that the co-administration of metoclopramide
184 resulted in an increased rate of absorption of levodopa and higher peak plasma concentrations, consistent
185 with the earlier t_{max}.^[35] In this case, though, the authors emphasized the fact that higher peak
186 concentrations of levodopa may result in dyskinesic movements and therefore, this should be taken into
187 consideration when metoclopramide is co-administered with levodopa.

188 Considering the properties of metoclopramide and the fact that besides promoting gastric emptying, it
189 also increases the upper small intestinal motility, administration of metoclopramide could also decrease
190 the time available for absorption in the small intestine and thus lead to a reduction of total bioavailability.
191 Gugler et al., 1981, explored this hypothesis by studying the absorption of cimetidine when given
192 concomitantly with antacids or metoclopramide. The study was conducted in eight healthy volunteers and
193 showed that there was a tendency to a shorter time to reach maximum plasma concentrations when
194 metoclopramide was co-administered. Additionally, a decrease in AUC of approximately 22% was

195 observed, although in neither case did the difference reach statistical significance.^[36] On the other hand,
196 Mahony et al., 1984, conducted a clinical study with children with leukemia and reported that concomitant
197 administration of methotrexate tablets with oral metoclopramide led to significantly lower AUC.
198 Consistent with these findings, Pearson et al., 1985, demonstrated that a very fast or slow small intestinal
199 transit in children with leukemia reduces the C_{max} of methotrexate.^[37,38]

200 In the studies conducted by Manninen et al., co-administration of metoclopramide with digoxin in eight
201 healthy adults or in eleven patients on digoxin therapy resulted in reduced serum digoxin
202 concentrations.^[39,40] The lower bioavailability of digoxin was attributed to its dissolution rate-limited
203 absorption, since the changes were only observed when digoxin was given as a tablet and not when it was
204 given as a solution. For this reason, authors suggested that fast dissolving tablets of digoxin would be less
205 affected by co-administration of drugs which alter the GI motility. Supporting this hypothesis, Johnson et
206 al., 1984, demonstrated that digoxin was absorbed completely and more quickly when it was given as soft-
207 gelatin capsules rather as a tablet. Oral metoclopramide reduced the t_{max} for both formulations, but only
208 reduced the AUC of the tablet formulation.^[41] From these two studies it is apparent that co-administration
209 of metoclopramide may result in impaired drug absorption and decreased bioavailability in cases when a
210 poorly soluble API exhibits dissolution-rate limited absorption.

211 In contrast to the results discussed above, Wadhwa et al., 1986, conducted a clinical study in fourteen
212 kidney transplant patients with the aim of increasing the bioavailability of cyclosporine. Cyclosporine is
213 incompletely absorbed in the small intestine with a dose-dependent rate and extent of absorption. The
214 authors reasoned the concomitant administration of cyclosporine with metoclopramide would increase
215 the absorption rate and possibly the bioavailability of this immunosuppressive. Due to accelerated gastric
216 emptying, there was a very significant increase in the C_{max} of cyclosporine, as well as a decrease in t_{max}.
217 Furthermore, an average increase of 29% in the AUC was observed (p=0.003). However, the authors
218 concluded that further studies would be required to determine whether metoclopramide can reproducibly
219 increase the absorption of cyclosporine on a long term basis.^[42]

220 Overall, it appears that co-administration of metoclopramide, leads to a decreased t_{max} of the co-
221 administered drugs, indicating a faster rate of absorption. However, the effect of concomitant use of
222 metoclopramide on the AUC of the co-administered drug is variable. Although the reported examples are
223 limited, it appears that after co-administration of metoclopramide small intestinal transit may be too fast
224 for poorly permeable (e.g. cimetidine) or poorly dissolving (e.g. digoxin) drugs to be adequately absorbed.
225 Thus, in this case, BCS classification may be helpful in identifying potential problems in bioavailability when
226 metoclopramide is co-administered.

227 *2.1.2 Anticholinergic agents*

228 Propantheline is an anticholinergic agent which reduces gastrointestinal motility and prolongs gastric
229 emptying rate. It is usually used in combination with other medicines to treat stomach ulcers. As for
230 metoclopramide, propantheline has been investigated with respect to its potential effect on the
231 absorption of concomitant medications. As one would anticipate, propantheline decreased the absorption
232 rate of acetaminophen and lithium when given concurrently.^[30,32] Co-administration of propantheline with
233 a rapidly and a slowly dissolving tablet of digoxin resulted in increased serum digoxin concentrations only
234 for the slowly dissolving formulation.^[39,40]

235 *2.1.3 Laxatives*

236 Laxatives promote defecation and are often used OTC for the treatment of constipation. They can be
237 grouped in osmotic, stimulant and bulk laxatives (Table 2).^[43] An overview of the effects of laxatives and
238 antidiarrheal agents on gastrointestinal physiology is given in Table 3. Osmotic laxatives (indigestible
239 disaccharides, sugar alcohols, synthetic macromolecules, saline laxatives) attract and retain water in the
240 intestinal lumen by increasing the luminal osmotic pressure. Stimulant laxatives (such as bisacodyl, senna
241 and sodium picosulfate) act locally by increasing colonic motility and decreasing water absorption in the
242 large intestine.^[44] Bulk laxatives such as bran, isphagula and sterculia adsorb and retain luminal fluids and
243 increase the fecal mass. For constipation linked with specific diseases additional treatment options are

244 available: Linaclotide, an agonist of guanylate cyclase-C, stimulates fluid secretion, accelerates intestinal
245 transit and is used for constipation-predominant irritable bowel syndrome.^[45]

246 In general, laxatives shorten GI transit time, but depending on the type of laxative, the extent of the effect
247 on transit time through specific GI compartments may vary (Figure 3). Studies have been conducted with
248 a variety of methods including radiopaque markers method,^[46–48] following transit of a single metal sphere
249 (diameter 6 m, density 1.4 g/ml) using a metal detector^[49], [¹³C]-octanoate and lactose-^{[13}C] ureide breath
250 tests^[50] and scintigraphy.^[45,51–54]

251 For healthy subjects the following observations have been reported: The total GI transit time was reduced
252 in thirteen subjects after treatment for nine days with either the bulk laxative wheat bran (39.0 h vs. 69.0
253 h) or the stimulant laxative senna (41.0 h vs. 69.0 h) compared to the baseline value.^[46] Small intestinal
254 transit time was reduced by bisacodyl (dose 10 mg) from approximately 2.5 h to 1.5 h in ten subjects,^[49]
255 while the osmotic laxatives polyethylene glycol and lactulose, had a minimum effect (if any) on the small
256 intestinal transit time after being administered at a dose of 10 g twice daily for five days.^[51] Administration
257 of an isosmotic solution containing 40 g polyethylene glycol 3350 resulted in a significant decrease in oro-
258 caecal transit time from 423.8±28.1 min to 313.8±17.2 min in twelve subjects.^[50] In another study,
259 administration of 5 mg bisacodyl in twenty-five subjects significantly accelerated the transit through the
260 ascending colon (median 6.5 h vs. 11.0 h).^[54] Similarly, 10-20 mL of lactulose (Duphalac; Duphar
261 Laboratories Ltd., England) three times daily for five days resulted in a significant decrease of the mean
262 proximal colon transit time from 12.9±3.7 h to 7.0±2.5 h in eleven subjects.^[53] The total colonic transit
263 time was reduced to a greater extent after administration of 10 mg bisacodyl (from 31±14 h to 7±8 h) than
264 by treatment with 30 g lactulose (from 34±12 h to 30±19 h) in ten subjects.^[49]

265 In patient populations the following observations have been reported: In twelve subjects with
266 constipation-predominant irritable bowel syndrome, treatment with linalotide (dose 100 µg or 1000 µg)
267 did not affect the gastric or small intestinal transit time.^[45] However, the ascending colon transit time was
268 decreased by 54% at a high dose of 1000 µg of linaclotide. At a lower dose of 100 µg there was a decrease

269 of 33%, although this was not statistically significant. In line with these observations, the total colonic
270 transit time was only significantly accelerated by the higher dose.^[45] In nine subjects with chronic
271 nonorganic constipation, treatment with an isosmotic electrolyte solution containing polyethylene glycol
272 4000 (14.6 g) for eight weeks did not significantly alter the transit time through the proximal colon, while
273 the transit through the left colon and rectum was significantly accelerated (46±29 h vs. 62±20 h and 37±42
274 vs. 78±21 h, respectively).^[48] The results in eight patients with slow transit constipation were similar after
275 administration of 60 g polyethylene glycol 4000 daily for six weeks; the right colon transit time was not
276 significantly different compared to placebo, while the transit time through the left colon was significantly
277 accelerated (13 h vs. 45 h) resulting in a reduction of total colonic transit time from 91 h to 43 h.^[47] In
278 summary, laxatives decrease transit times in healthy subjects throughout the GI tract, while in constipated
279 patients the effects are mainly limited to the colon.

280 Changes in GI transit times induced by laxatives can lead to changes in bioavailability. For example, co-
281 administration of senna (20 mL of Liquidepur, Fa. Nattermann, Cologne, Germany) with a sustained-
282 release quinidine formulation (0.5 g every 12 hours) reduced quinidine plasma levels by 25% in nine
283 patients with cardiac arrhythmia on long-term treatment, resulting in reoccurrence of supraventricular
284 extrasystoles.^[55] Similarly, polyethylene glycol 4000 reduced the absorption of digoxin by 30% when co-
285 administered with digoxin tablets (dose 0.5 mg) in eighteen healthy subjects.^[56] However, it is not clear
286 whether the same effect would be observed in cardiac patients or what the clinical ramifications would
287 be. Further, a trend (although not statistically significant) to decreased AUC of estradiol glucuronide (dose
288 1.5 mg) was observed when co-administered for ten days with the maximum tolerated dose of wheat bran
289 (-13%) and senna (-10%) in twenty healthy postmenopausal women.^[57]

290 Many laxatives have been shown to alter the production of short chain fatty acids (SCFA). SCFA are usually
291 associated with a decrease in luminal pH. After treatment with senna or wheat bran, fecal SCFA
292 concentrations were increased in healthy subjects (n=13) by 82% and 19%, respectively.^[46] After
293 administration of senna, the pH in the middle and distal colon was decreased (6.39 vs. 6.85, 6.66 vs.

294 7.14).^[46] Lactulose significantly acidified the contents in the lower small intestine as well as in the right
295 colon.^[58-60] Sodium sulphate also decreased the pH, with the greatest effect in the left colon.^[58] By
296 contrast, wheat bran reduced the pH in the distal colon of thirteen healthy subjects only slightly (6.88 vs.
297 7.08).^[46] But mechanisms other than via SCFA can also be at play. For example, the increase in the pH in
298 the lower small intestine, colon and rectum observed after administration of magnesium sulphate is
299 postulated to be the result of gastric conversion to magnesium chloride and subsequent reconversion to
300 insoluble magnesium carbonate in the colon prompted by increased colonic bicarbonate secretion.^[58] The
301 possible pH changes observed with laxatives are not clearly associated with changes in drug product
302 performance. For example, mesalazine release from a delayed-release, pH-dependent formulation of
303 mesalazine (Asacol[®], SmithKline Beecham, UK) was not affected by the co-administration of ispaghula husk
304 or lactulose despite their known pH-lowering effect in the colon.^[61,62] Nonetheless, the UK manufacturers
305 of delayed-release mesalazine formulations (Asacol[®], Allergan Ltd, Bucks, UK and Salofalk[®] granules, Dr.
306 Falk Pharma UK Ltd, Bourne End, UK) suggest that drug release might be impaired by preparations with
307 pH-lowering effect.^[63,64]

308 With respect to the gut microbiota, the fecal microbiota of patients with chronic idiopathic constipation
309 (n=65) treated with lactulose over twenty-eight days was increased in Anaerobes by 3% and Bifidobacteria
310 by 8%, while treatment with polyethylene glycol 4000 resulted in a reduced fecal amount of Bifidobacteria
311 (-14%).^[65] Lactulose administration in patients taking coumarins (acenocoumarol, phenprocoumon)
312 increased their risk of over-anticoagulation, as assessed in a population-based cohort study, because of
313 changes in the vitamin K production of the colonic bacterial flora. By contrast, concomitant intake of
314 ispaghula with coumarins did not alter the risk of over-anticoagulation.^[66]

315 The importance of the gut microbiota on oral pharmacotherapy is discussed in section 2.6 “Antibiotics”.

316 *2.1.4 Antidiarrheal agents*

317 Antidiarrheal agents provide symptomatic relief of diarrhea by decreasing fluid loss, by slowing down the
318 passage of the gastrointestinal contents through the digestive tract, by increasing fluid absorption and/or
319 by reducing intestinal secretions.^[67] They can be classified according to their mechanism of action (Table
320 2). Opioids (such as loperamide, diphenoxylate and codeine phosphate) inhibit intestinal transit by
321 activating μ -opioid receptors. Adsorbents and bulking agents (kaolin, isphagula, methylcellulose) adsorb
322 water and increase the fecal mass, while the antisecretory action of racecadotril, an enkephalinase
323 inhibitor, is linked to reducing chloride and fluid flux into the GI lumen.

324 Differences in the GI transit time have been observed after oral loperamide administration (Figure 4). The
325 total GI transit time was increased after loperamide administration in healthy subjects (74.0 h vs. 50.3 h,
326 n=11), as measured by radiopaque marker pellets, presumably due to reduced, irregular motor activity
327 and therefore, prolonged transit time in the jejunum.^[46,68,69] Gastric emptying time was not significantly
328 different in twenty-four healthy subjects treated with 4 mg loperamide compared to placebo as measured
329 with a radio-labeled meal.^[70] However, gastric residence time measured with a radiotelemetry capsule
330 was increased two-fold in five healthy subjects treated with 8 mg loperamide (4 doses, every 6 hours).^[71]
331 Small intestinal transit time, as measured with the hydrogen breath test, was increased by 80-130% in
332 healthy subjects receiving 4 to 8 mg of loperamide.^[70-72]

333 With respect to the composition of GI fluids, loperamide has been shown to decrease prostaglandin-E2
334 induced water and electrolyte secretion in the jejunum of healthy volunteers and reduce postprandial
335 secretion of trypsin and bilirubin by more than 50% in patients with short bowel syndrome.^[69,73,74]

336 Similarly, basal and amino acid stimulated gallbladder motility was decreased by loperamide (dose 8 mg)
337 in eight healthy subjects as measured by ultrasonography and bilirubin output in the duodenum.^[75] After
338 loperamide administration fecal SCFA concentrations were decreased in healthy subjects (82.0 $\mu\text{mol/g}$ wet
339 weight vs. 152.0 $\mu\text{mol/g}$ wet weight; n=13).^[46]

340 In terms of DDIs, administration of 4 mg loperamide 24 h, 12 h and 1 h before desmopressin administration
341 increased the bioavailability of desmopressin in eighteen healthy subjects (AUC 3.1-fold, C_{max} 2.3-fold)
342 and prolonged the time to reach the maximum plasma concentration (2 h vs. 1.3 h) without affecting the
343 elimination half-life.^[76] These effects could be explained by the decrease in GI motility. Desmopressin is
344 highly soluble but poorly permeable (bioavailability approx. 0.1%), so longer transit times are expected to
345 lead to a longer contact time of the drug with the absorptive mucosa.^[77] Co-administration of loperamide
346 at the maximum tolerated dose over 10-12 days also increased the AUC of estradiol glucuronide (dose 1.5
347 mg) by 15% in twenty healthy postmenopausal women, although the difference did not reach statistical
348 significance.^[57]

349 On the other hand, a single dose of loperamide (16 mg) decreased the bioavailability of the poorly soluble
350 drug saquinavir (dose 600 mg) by 54% in twelve healthy subjects when administered concomitantly. This
351 could be explained by the decreased motility and/or a reduction of electrolyte and fluid secretion which
352 could hinder dissolution.^[78] Additionally, it is possible that a decreased secretion of bile salts secondary to
353 reduced gallbladder motility^[75] impeded the solubilisation of saquinavir.

354 On the other hand, loperamide co-administration (8 mg every 6 hours) in twelve healthy male subjects
355 decreased the absorption rate of theophylline from a sustained-release 600 mg formulation (C_{max} 3.2
356 mg/L vs. 4.6 mg/L, t_{max} 20 h vs. 11 h), which could be explained by impeded release from the formulation
357 due to a decrease in hydrodynamics (decreased motility) or perhaps a prolonged gastric residence time of
358 the formulation/released drug. However, the AUC was not affected.^[79]

359 Last but not least, the surface of bulk laxatives and bulking agents offers a site for drug adsorption.
360 Concomitant administration of kaolin-pectin decreased the absorption of tetracycline (20%), aspirin (5-
361 10%), procainamide (30%), quinidine (58%), trimethoprim (12-20%), lincomycin (90%), chloroquine (29%)
362 and digoxin (15-62%), which is most likely the result of adsorption of the drugs onto kaolin.^[80-88] Drug

363 adsorption is also observed onto dietary fibers and therefore, similar DDIs to those observed with dietary
364 fibers are further considered in section 2.2.

365 An overview of the effects of antidiarrheal agents on gastrointestinal physiology is given in Table 3.

366 **2.2 Dietary fibers**

367 The use of dietary fibers in the treatment of various diseases, such as diabetes, hypercholesterolemia,
368 obesity, chronic constipation and gastrointestinal motility disorders, has increased over the last years.
369 However, there are few studies that have investigated the impact of concomitant use of dietary fibers with
370 other drugs. From the studies available it seems that the effect of the concomitant use of dietary fibers
371 depends on the type of fiber used.

372 The interaction of levothyroxine with dietary fibers is well established. Concomitant use of dietary fibers,
373 such as oat bran, soy fiber and ispaghula husk, result in decreased bioavailability of levothyroxine, due to
374 adsorption of the drug to the fibers in the GI tract.^[89] The authors commented that the adsorption of
375 levothyroxine to soluble fibers and the consequent reduction in bioavailability might be greater than its
376 adsorption to insoluble fibers. The interaction with levothyroxine is also noted by FDA in a consumers'
377 information leaflet regarding drug interactions with food.^[90]

378 In a case study reported by Perlman, the blood levels of lithium were decreased by 48%, when a patient
379 was treated simultaneously with lithium and ispaghula husk .^[91] There is also some evidence that fibers
380 interact with some tricyclic antidepressants. The clinical effectiveness of tricyclic antidepressants appears
381 usually after an administration period of 2-6 weeks. During this period, due to anticholinergic effects of
382 the drugs, constipation is a common side effect. Therefore, patients receiving antidepressant medication
383 often ingest dietary fibers. Already in 1992, Stewart observed a decrease in plasma concentrations of three
384 tricyclic antidepressants (amitriptyline, doxepin and imipramine) in three patients, who concurrently
385 ingested a diet rich in fibers.^[92]

386 There are conflicting inputs in the literature about the interaction of dietary fibers and digoxin. Brown et
387 al., 1977, reported a significant decrease in the bioavailability of digoxin when given to twelve healthy
388 volunteers with regular or high fiber diet concomitantly, as opposed to administering digoxin alone in the
389 fasted state.^[93] Albert et al., 1978, reported that when kaolin-pectin suspension was given simultaneously
390 with digoxin, the total amount of digoxin absorbed was decreased by 62%. However, no significant
391 interactions were observed when digoxin was given 2 h before the administration of the fiber
392 suspension.^[85] However, studies by Lembcke et al., 1982, and Kasper et al., 1979, found no effect on the
393 bioavailability of digoxin when it was administered together with guar gum or other fibers.^[94,95] In a later
394 study Huupponen et al., 1984, investigated the effect of guar gum on the absorption of digoxin in ten
395 healthy volunteers. It was demonstrated that co-administration of guar gum with digoxin resulted in
396 reduced plasma concentrations of digoxin and a decrease of 15% of the AUC for the first six hours ($p <$
397 0.05).^[96]

398 Holt et al., 1979, investigated the effect of co-administration of the soluble fibers guar gum and pectin on
399 the absorption of acetaminophen. Concomitant administration with these fibers resulted in delayed
400 absorption and decreased C_{max} . However, the total absorption of acetaminophen was not significantly
401 reduced. The authors attributed their results to delayed gastric emptying. Moreover, they argued that
402 because guar gum, when hydrated, forms a viscous colloidal suspension, the high viscosity of this
403 suspension could be a possible reason for the observed delay in gastric emptying.^[97] The results from this
404 study correlate well with the study conducted by Reppas et al., 1998, in mongrel dogs, in which the effect
405 of elevated luminal viscosity on the absorption of acetaminophen, hydrochlorothiazide, cimetidine and
406 mefenamic acid was investigated.^[98] Elevated luminal viscosity was achieved by administering saline
407 solutions of the water-soluble guar gum. When given concurrently with the guar gum solutions, the C_{max}
408 and AUC of the highly soluble acetaminophen and hydrochlorothiazide were significantly decreased,
409 suggesting that the decreased rate of dissolution, due to the higher luminal viscosity, led to lower
410 concentrations at the absorption sites. In the case of cimetidine, concurrent administration of the guar

411 gum solution led only to a decrease in C_{max} and not AUC. For the poorly soluble but highly permeable
412 mefenamic acid, neither the C_{max} nor the AUC were significantly affected by the concomitant
413 administration of the guar gum in dogs.^[98] Huupponen et al., 1984, reported a decrease in C_{max} and AUC
414 of penicillin when given together with guar gum.^[96] Finally, Astarloa et al., 1992, investigated the effect of
415 a diet rich in insoluble fiber on the pharmacokinetics of levodopa. Consumption of two months of the
416 dietary supplement with the usual dose of levodopa led to elevated plasma levels of levodopa especially
417 at 30 and 60 minutes after oral administration.^[99,100]

418 It is evident from these studies that it is currently not possible to make any generalizations about DDIs
419 with dietary fibers although it seems that there is a tendency for decreased maximum plasma
420 concentrations of the co-administered drug. These events are likely attributable to slower gastric
421 emptying, higher viscosity and, perhaps in some cases, adsorption phenomena.^[101] It also seems that the
422 type of interaction, if any, is highly dependent on the type of dietary fiber used. It remains to be
423 investigated whether these interactions, such as they exist, lead to clinically significant differences.

424 **2.3 Antiemetics**

425 Antiemetics are classified according to their mechanism of action. There are five receptors that play a key
426 role in the vomiting reflex; muscarinic, dopaminergic, histaminic, serotonergic and substance
427 P/neurokinin receptors.

428 Aprepitant is a very potent neurokinin-1 receptor antagonist used for the prevention of acute and delayed
429 chemotherapy-induced nausea and vomiting.^[102,103] Aprepitant is metabolized primarily by CYP3A4 and
430 secondarily by CYP1A2 and CYP2C19. It also acts as a moderate inhibitor of CYP1A2, CYP2C9, CYP2C19,
431 CYP2E1 and as a weak inducer of CYP2C.^[102,103] Caution is therefore necessary, especially when
432 administered concomitantly with chemotherapy agents that are metabolized primarily by CYP3A4, as
433 inhibition by aprepitant may lead to higher plasma levels and toxic side effects. According to the Public
434 Assessment Report, EMEND® capsules (which contain aprepitant as API), should not be concomitantly

435 administered with ergot alkaloid derivatives, pimozide, terfenadine, astemizole, or cisapride, as the
436 competitive inhibition of the CYP3A4 by aprepitant results in elevated plasma concentrations, leading to
437 adverse effects.^[103] Further pharmacokinetic interactions that have been reported for aprepitant in the
438 literature are those with midazolam, warfarin, dexamethasone and methylprednisolone.^[22,104]

439 Majumdar et al., 2003, investigated the effect of aprepitant on the pharmacokinetics of single dose
440 midazolam on day 1 and on day 5 during daily administration of aprepitant for five days. In this study, two
441 dose regimens of aprepitant were used; 125/80 mg and 40/25 mg. It was concluded that co-administration
442 of midazolam with the 125/80 mg regimen (125 mg on day 1 and 80 mg on days 2-5) resulted in a 2.3-fold
443 increase in midazolam AUC on day 1 and a 3.3-fold increase on day 5. The plasma concentrations achieved
444 1 h after dosing (C_{1h}) and the half-life ($t_{1/2}$) were also increased due to the inhibition of first pass and
445 systemic metabolism and subsequent reduction in clearance. Although co-administration of midazolam
446 with the 40/25 mg dose regimen did not result in any significant change in the pharmacokinetics of
447 midazolam, this lower dose is not used in clinical practice.^[105] Majumdar et al., 2007, later investigated the
448 effect of aprepitant on intravenously administered midazolam and the findings were consistent with the
449 first study, but with an increase in AUC of 1.47-fold. The authors suggested that the lower increase in AUC
450 observed after intravenous administration of midazolam, might be due to lack of inhibition of presystemic
451 metabolism when midazolam is given intravenously.^[106]

452 In an analogous study by McCrea et al., 2003, the effect of a 5-day administration of 125/80 mg aprepitant
453 regimen on the pharmacokinetics of orally administered methylprednisolone and dexamethasone was
454 evaluated. Due to the inhibition of CYP3A4 by aprepitant, the C_{max} of methylprednisolone was increased
455 1.5-fold while the AUC increased 2.5-fold. An increase of 2.2-fold in AUC was observed for
456 dexamethasone.^[107] Clinically, unnecessary high exposure to corticosteroids should be avoided due to the
457 potential risk of adverse effects such as hyperglycemia and increased susceptibility to infections. For these
458 reasons, it is suggested that the oral doses of dexamethasone and methylprednisolone should be reduced
459 by half when used for the management of chemotherapy-induced nausea and vomiting concurrently with

460 aprepitant.^[107] The interaction of aprepitant with warfarin is less clear.^[108] In a study by Takaki et al., 2016,
461 a decrease in warfarin plasma levels was observed, but no significant interaction between warfarin and
462 aprepitant was established. One possible reason for the lack of interaction could be the fact that the
463 volunteers who took part in this clinical study were also receiving several other chemotherapeutic agents.
464 In any case, careful monitoring of patients on chronic warfarin therapy is required.^[104,109]

465 Serotonin plays an important role in various body functions. Most serotonin is synthesized in the GI tract
466 and it affects various aspects of intestinal physiology. Multiple subtypes of 5-HT receptors exist on various
467 types of cells, such as smooth muscle and enterocytes, and agonists or antagonists of 5-HT receptors are
468 used in the treatment of different gastrointestinal disorders.^[21] 5-HT₃ receptor antagonists, for example
469 ondansetron and granisetron, have been successfully used in the treatment of chemotherapy-induced
470 nausea and vomiting. Recommendations, published by the American Society of Clinical Oncology (ASCO)
471 for the use of the 5-HT₃ receptor antagonists, do not distinguish among them with regard to their safety
472 and efficacy. Nonetheless, these compounds differ significantly in their pharmacokinetic properties and
473 especially with respect to their potential to interact with CYP enzymes.^[110,111] Granisetron, for example,
474 does not inhibit any of the CYP enzymes which are commonly involved in drug metabolism, whereas
475 ondansetron inhibits both CYP1A2 and CYP2D6 and can thus interact with various concurrently used drugs.
476 However, the interactions reported in literature are not solely attributed to their enzyme inhibitory
477 properties. Concomitant use of ondansetron with cyclophosphamide resulted in reduced systemic
478 exposure, probably due to increased systemic clearance.^[112,113] In any case, there is a need for more studies
479 to increase knowledge about drug interactions of chemotherapeutic agents with commonly used
480 antiemetics, as even a slight change in the pharmacokinetic parameters or pharmacodynamics of the anti-
481 cancer medication could jeopardize the effectiveness of chemotherapy.^[112]

482 **2.4 Gastric acid reducing agents and Antacids**

483 Proton-pump inhibitors (PPIs), H₂-receptor antagonists (H₂RAs) and antacids are widely used in the
484 treatment of various gastric acid related disorders, such as peptic ulcers and gastroesophageal reflux
485 disease. In fact, PPIs and H₂RAs are classified among the three most prescribed drug classes for the years
486 2011-2014 and the situation is similar today.^[114] Indeed, esomeprazole, a proton-pump inhibitor, ranks
487 among the top five most prescribed medications worldwide.^[115] Of particular concern for these drugs is
488 their increasing OTC use. Despite the fact that gastric antisecretory agents or antacids are tolerated well,
489 with a low overall frequency of adverse reactions,^[116] their concurrent use with other medications can
490 have a great effect on drug absorption. If prescribed, identification of potential interactions by the
491 prescribing physician and/or dispensing pharmacist is possible, but this control mechanism is largely lost
492 if the drugs are obtained OTC or via e-pharmacies.

493 *2.4.1 Proton Pump Inhibitors*

494 Proton-pump inhibitors are a group of substituted benzimidazole sulfoxide drugs with strong inhibitory
495 effects on gastric acid secretion from the parietal cells in the stomach. At present, six PPIs
496 (dexlansoprazole, esomeprazole, lansoprazole, omeprazole, pantoprazole, rabeprazole) are available on
497 the market.^[117] PPIs are used in the treatment of acid-related disorders and for the prevention of
498 gastrointestinal bleeding in patients receiving dual antiplatelet therapy of clopidogrel and aspirin.
499 Furthermore, they are used as a component of combination therapy for the eradication of *H. pylori*,
500 because their properties enhance the anti-*H. pylori* activities of the co-administered antibacterials
501 (clarithromycin and amoxicillin).^[118] PPIs can affect the absorption of the co-administered drugs to a great
502 extent, mainly due to the increase in gastric pH. In a recent study, the effect of 40 mg of pantoprazole
503 administered orally once per day for four days and 20 mg of the H₂RA famotidine administered orally twice
504 within 12 hours, on the GI physiology of eight healthy male volunteers was investigated.^[119] In both cases,
505 the gastric pH differed significantly in comparison to the control group (Figure 5). However, PPIs can also

506 affect the pharmacokinetics of co-administered drugs through other mechanisms,^[120] and several excellent
507 reviews have been written regarding the drug-drug interactions of PPIs.^[121–123]

508 As already mentioned, gastric pH is an important parameter that can affect absorption of drugs, especially
509 these which are poorly soluble weak bases. For example, Jaruratanasirikul et al., 1998, investigated the
510 effect of 40 mg oral omeprazole on the pharmacokinetics of a single 200 mg capsule of itraconazole in
511 eleven healthy volunteers. Concomitant use of omeprazole resulted in reduction of the mean AUC and
512 Cmax of itraconazole by 64% and 66% respectively. No interaction due to omeprazole's inhibition of
513 CYP3A4 was reported.^[124] On the other hand, Johnson et al., 2003, investigated the effect of concomitant
514 use of 40 mg oral omeprazole with a 40 mg dose oral solution of itraconazole in twenty volunteers. It was
515 reported that there was no statistically significant difference on the AUC, tmax and Cmax with the co-
516 administration of omeprazole.^[125] The results of these two clinical studies (one with a solid dosage form,
517 one with itraconazole in solution) suggest that co-administration of omeprazole and elevation of gastric
518 pH, affects the dissolution of itraconazole capsules rather than the permeability of itraconazole. The
519 results regarding ketoconazole are similar. In 1995, Chin et al., conducted a clinical study with nine healthy
520 volunteers, in which the effects of 60 mg oral omeprazole or an acidic beverage on the pharmacokinetics
521 of orally administered 200 mg ketoconazole were investigated. Pre-treatment with omeprazole resulted
522 in significantly lower AUC and Cmax and a prolongation of tmax.^[126] Ketoconazole and itraconazole are
523 both practically insoluble at pH>4. Co-administration of PPIs with poorly soluble imidazole antifungal
524 agents when given as capsules or tablets is, therefore, not recommended.^[127] Interestingly, the elevated
525 gastric pH does not affect the bioavailability of fluconazole tablets.^[128] This lack of interaction is
526 underscored by the high solubility of fluconazole over the whole pH range of the GI tract. Thus, stomach
527 acidity does not limit the dissolution rate of fluconazole or its absorption.^[129,130]

528 The increase in the gastric pH caused by PPIs can also greatly affect the bioavailability and effectiveness of
529 anti-retroviral agents, depending on their pH/solubility profiles. Tappouni et al., 2008, conducted a clinical
530 study with sixteen patients, in which the effect of omeprazole on indinavir was evaluated. With pre-

531 treatment and co-administration of 20 mg oral omeprazole, the C_{max} of indinavir decreased by 29% and
532 the AUC by 34%, whereas at a higher dose of 40 mg omeprazole, the C_{max} and AUC of indinavir decreased
533 by 41% and 47% respectively.^[131] Co-administration of omeprazole resulted in reduction to the systemic
534 exposure to both nelfinavir and its metabolite. In particular, the AUC of nelfinavir was decreased by
535 36%.^[132] Tomilo et al., 2006, reported a 94% and 91% decrease in AUC and C_{max}, respectively, of 400 mg
536 oral atazanavir, when co-administered with 60 mg lansoprazole in ten healthy volunteers.^[133] The results
537 were similar when omeprazole was co-administered.^[134] However, the clinical impact of this drug-drug
538 interaction on the clinical effect of atazanavir is not clear.^[135,136] It seems that co-administration of PPIs
539 with an atazanavir/ritonavir regimen does not affect the ability of atazanavir to achieve the minimum
540 plasma concentration necessary for the virologic response, i.e. the concomitant use of atazanavir/ritonavir
541 regimen and PPIs was not associated with higher virologic failure rate.^[135] Nonetheless, further studies, in
542 which both the pharmacokinetic parameters and the clinical response rates are simultaneously
543 investigated, are needed to understand the interaction and its consequences more fully.

544 In contrast to the results mentioned so far, in the study of Winston et al., 2006, co-administration of 40
545 mg oral omeprazole with 1000 mg saquinavir (given orally as 1000 mg saquinavir/100 mg ritonavir
546 combination) resulted in an 82% increase in the mean AUC of saquinavir in eighteen healthy volunteers.
547 The increase did not result in an increase in adverse effects. The authors commented that further work is
548 necessary in order to understand the mechanism of this DDI and to address whether the effects of
549 omeprazole on saquinavir's pharmacokinetics would be the same even in the absence of ritonavir. The
550 authors also discussed the possibility of whether the increase could be the result of inhibition of
551 transmembrane-transporters, such as P-gp or MRP by omeprazole.^[137]

552 As for most of the antifungal and antiviral drugs, the absorption of mycophenolate mofetil is impaired by
553 concomitant administration of PPIs. Kofler et al., 2009, measured the levels of mycophenolic acid (active
554 metabolite) in thirty-three patients concurrently receiving 40 mg oral pantoprazole. C_{max} and AUC of
555 mycophenolic acid were significantly lower when patients were pretreated with pantoprazole.^[138] As

556 anticipated, co-administration of pantoprazole with an enteric coated formulation of mycophenolic acid
557 had no significant effect on its pharmacokinetics.^[139]

558 Apart from affecting the solubility of APIs in the stomach, an increase in the gastric pH can jeopardize the
559 bioavailability of formulations with pH-dependent release. The effect of concomitant administration of
560 esomeprazole on the bioavailability of risedronate sodium DR was evaluated in a clinical study involving
561 eighty-seven postmenopausal women. The results showed that esomeprazole administration one hour
562 before dinner or one hour before breakfast resulted in 32% and 48% reduction in the bioavailability of
563 risedronate sodium DR, respectively. In the report, it was suggested that an increase in the gastric pH may
564 compromise the enteric coating of risedronate delayed release formulation, thus resulting in release of
565 risedronate sodium in the stomach, where it could convert to the less soluble free acid.^[140] However, as it
566 has been shown that PPIs (pantoprazole) decrease buffer capacity as well as increase gastric pH,^[119] a
567 premature release due to enteric coating failure appears unlikely.

568 A review of all the available clinical data from literature describing the effect of the administration of
569 various gastric acid reducing agents on the absorption and bioavailability of co-administered weakly basic
570 anticancer drugs was published by Budha et al.^[141] The authors attempted to correlate the physicochemical
571 properties and pH-solubility profiles of the different anticancer drugs with the observed effect on the
572 absorption caused by the elevation of the gastric pH after the administration of the acid reducing agents
573 (PPIs, H₂RAs and antacids). It was concluded that the impact of the elevation of gastric pH is more
574 prominent for the anticancer drugs which exhibit an exponentially decreasing solubility in the pH range 1-
575 4 and for which the maximum dose strength is not soluble in 250 mL of water. Elevation of gastric pH is
576 expected to substantially decrease the dissolution rate of these drug products, thus leading to incomplete
577 dissolution of the dose and impaired absorption.

578 In 2013, Mitra and Kesisoglou described strategies to minimize or avoid reduced absorption of weakly
579 basic drugs resulting from elevated gastric pH.^[142]

580 The observed DDIs with PPIs occur not only because of their elevation of gastric pH, but can also arise from
581 other properties. It has been shown that concurrent administration of 10 mg of nifedipine with 20 mg of
582 omeprazole for eight days (short-term treatment) resulted in an AUC increase of 26%, whereas no increase
583 was observed after co-administration of a single 20 mg dose of omeprazole.^[143] The authors hypothesize
584 that the higher levels might be due to inhibition of CYP3A4, but they note that this increase is not likely to
585 have major clinical relevance, especially when taking into account the intra- and inter-individual variability
586 observed for nifedipine.^[143] In contrast, in the study by Bliesath et al., 1996, co-administration of 20 mg of
587 nifedipine with 40 mg of pantoprazole for ten days, had no effect on the pharmacokinetics of
588 nifedipine.^[144] This apparent discrepancy in DDI tendency might be due to the different CYP-isoenzymes
589 inhibitory properties of the two PPIs. It is believed that among all PPIs, omeprazole is the one which has
590 the greatest potential for drug interactions, since it has a high affinity for CYP2C19 and CYP3A4.^[145–148]
591 Another example of a non-pH related DDI with PPIs is the delayed elimination of plasma methotrexate,
592 independent of renal function.^[149]
593 Last, but not least, there has been an increasing interest in investigating the mechanism of drug
594 interactions of PPIs with clopidogrel. Clopidogrel is a prodrug that requires activation via cytochrome P450
595 isozymes (CYP2C19, CYP3A4, CYP3A5) in order to transform to its pharmacologically active form.
596 Therefore, inhibition of the cytochrome isoenzymes, which are involved in the metabolic pathway of
597 clopidogrel, may reduce its antiplatelet activity and potentially increase the risk of thrombosis. In fact, in
598 2009 FDA published a warning note on the drug label of Plavix® (clopidogrel, Sanofi Clir SNC, France) and
599 continues to warn the public against concomitant use of clopidogrel and omeprazole. It should be noted
600 that, although studies have demonstrated that concomitant use of clopidogrel and PPIs, especially
601 omeprazole, reduces the antiplatelet effect of clopidogrel, the mechanism behind this interaction and the
602 clinical importance (cardiovascular risk) has not yet been clearly established.^[150–155]

603 2.4.2 H₂ receptor antagonists

604 The H₂RAs are another drug class used to treat gastric acid related disorders. These compounds bind to
605 histamine H₂ receptors on parietal cells and antagonize the action of histamine, which is the major
606 transmitter for stimulation of acid secretion.^[156] As with the PPIs, there are DDIs with different classes of
607 drugs and these are mainly attributed to the elevation of the gastric pH (see Figure 5). For example,
608 ketoconazole and itraconazole demonstrate impaired drug absorption when they are concomitantly used
609 with H₂RAs as well as with PPIs. Piscitelli et al., 1991, investigated the effect of 150 mg orally administered
610 ranitidine on 400 mg oral ketoconazole in six healthy volunteers. The decreased C_{max} and AUC and
611 bioavailability of ketoconazole in this study was attributed to the elevated gastric pH, which resulted in a
612 decreased and incomplete ketoconazole dissolution.^[157] The results were similar when the effect of
613 cimetidine on the absorption and pharmacokinetics of ketoconazole was investigated.^[122] Lim et al., 2007,
614 investigated the effect of famotidine on the absorption of fluconazole and itraconazole. Twenty healthy
615 volunteers received orally 40 mg famotidine with 200 mg itraconazole or 100 mg fluconazole. Co-
616 administration of famotidine resulted in a 52.9% decrease in C_{max} and a 51.1% decrease in the AUC of
617 itraconazole, but no difference was observed in the pharmacokinetics of fluconazole.^[158] This different
618 behavior of fluconazole had previously been observed by Blum et al., 1991 and can be explained by its
619 much higher solubility (see 2.4.1).^[159]

620 The situation is similar with anti-retroviral medications.^[160] Analogous to the PPIs/saquinavir interaction,
621 co-administration of cimetidine resulted in increased exposure to saquinavir. ^[137,161]

622 Russell et al., investigated the effect of a single dose of 40 mg of famotidine on the pharmacokinetics of
623 the weak base dipyridamole in eleven elderly adults with normal gastric acid secretion. After co-
624 administration of famotidine, the C_{max} and absorption constant (k_a) of dipyridamole decreased
625 significantly. The total AUC decreased by 37%, but this decrease was not found to be statistically
626 significant. The authors attributed the observed differences to slower dissolution rate of dipyridamole
627 tablets at elevated gastric pH.^[162] In other studies, co-administration of ranitidine with two weak bases,

628 enoxacin and cefpodoxime, resulted in decreased bioavailability, which was again attributed to decreased
629 solubility in the gastric environment at elevated pH.^[163,164]

630 As with the PPIs, DDIs with H₂RAs can occur not only because of their elevation of gastric pH, but can also
631 arise from their other properties. In particular, it has been shown that, among the various H₂RAs,
632 cimetidine is the most potent inhibitor of the CYP450 enzymes. The inhibition is attributable to the
633 imidazole ring in its structure, and results in changes in the metabolism of various co-administered
634 drugs.^[165] In cases where a clinical significant interaction is suspected, other H₂RAs (e.g. ranitidine,
635 famotidine) are preferred over cimetidine.^[166,167] Among the various metabolic interactions that have been
636 reported after co-administration of cimetidine,^[165] the metabolic interactions observed with warfarin and
637 propranolol have been most intensively studied and the clinical significance of these interactions has also
638 been evaluated. Toon et al., investigated the effect of a nine-day short treatment of cimetidine and
639 ranitidine (800 mg oral dose daily and 300 mg oral dose daily respectively) on the pharmacokinetics of 25
640 mg of racemic warfarin, administered orally starting on the fourth day of cimetidine treatment and
641 continuing for the next five days, in nine healthy volunteers.^[168] The prothrombin time and Factor VII
642 clotting time were also evaluated. Whilst ranitidine had no effect on the pharmacokinetics of either of the
643 two enantiomers of warfarin, cimetidine significantly increased the elimination half-life and decreased the
644 clearance of the (R)-enantiomer of warfarin. In contrast, the pharmacokinetics of the (S)-enantiomer of
645 warfarin were not affected by co-administration of cimetidine. Nonetheless, co-administration of either
646 ranitidine or cimetidine did not result in a clinically significant difference in terms of the anti-coagulation
647 effect of warfarin.^[168] These results were further confirmed by a later study from Niopas et al.^[169] It should
648 be noted however, that both studies were conducted in healthy volunteers and therefore, the clinical
649 effects on patient populations could differ.

650 The effect of a daily oral dose of 1000 mg cimetidine on the steady state plasma levels of propranolol,
651 administered as a 160 mg sustained-release formulation daily, was evaluated in seven healthy volunteers
652 during a thirteen-day treatment (administration of cimetidine started on the eighth day).^[170] It was

653 concluded that co-administration of cimetidine resulted in decreased clearance of propranolol and thus
654 increased propranolol plasma levels at steady state. In a similar study, Reimann et al. investigated the
655 effect of cimetidine (1000 mg daily, one day oral pretreatment) and ranitidine (300 mg daily oral dose, one
656 and six days pretreatment) on the steady state propranolol plasma levels (160 mg sustained-release
657 capsule, once daily) of five healthy volunteers.^[171] It was shown that one-day pretreatment with cimetidine
658 resulted in elevated propranolol plasma levels at steady state, while ranitidine pretreatment for one or six
659 days did not affect significantly the propranolol plasma levels at steady state. However, the authors stated
660 that the elevated plasma levels of propranolol observed after pretreatment with cimetidine did not lead
661 to a clinically significant effect.^[171] Again, the study was conducted in healthy volunteers and the clinical
662 effects on patient populations could differ. Nonetheless, it should be noted that the companies are
663 required by the regulatory authorities to inform the patients that there is a potentially clinically significant
664 DDI of cimetidine and propranolol in the patient information leaflets.^[172]

665 It is obvious that there are many interactions of PPIs and H₂RAs with other concomitantly used drugs,
666 especially poorly soluble weak bases, and that their use should be monitored, particularly in cases where
667 the DDI is well established. Besides the elevation of gastric pH and the interactions with metabolic
668 pathways, it should be noted that PPIs and H₂RAs can also affect other aspects of the physiology in the
669 gastrointestinal tract. Recent data in literature suggest that administration of PPIs or H₂RAs can be
670 accompanied by reduced buffer capacity, chloride ion concentration, osmolality and surface tension in
671 stomach and an increase in the pH of the upper small intestine of up to 0.7 units, an increase that would
672 be especially relevant for compounds (basic or acidic) with pK_as between 6 and 7.^[119] Carefully designed
673 DDI studies, in terms of dosing and duration of treatment, are needed in order to accurately determine
674 the effect of H₂RAs or PPIs on the pharmacokinetics of co-administered drugs and investigate the clinical
675 consequences of these interactions.

676 2.4.3 Antacids

677 The term “antacids” describe a category of salts, formulated as the combination of polyvalent cations such
678 as calcium, aluminium, or magnesium with a base, such as hydroxide, trisilicate or carbonate. Aluminium
679 hydroxide alone, or in combination with magnesium hydroxide, is the main ingredient of many antacid
680 products. Since the appearance of the PPIs and H₂RAs, which are more potent drugs and can be used for
681 a wide variety of gastrointestinal disorders, antacids have been mainly marketed as OTC medications.
682 However, the concomitant use of antacids with other drugs can significantly affect their absorption or
683 even their therapeutic effect. Considering the fact that the use of OTC antacids is widespread, there is a
684 particular need for appropriate information for patients, doctors and pharmacists. Besides interactions
685 associated with increased pH, the major DDIs with antacids involve chelation reactions. Various categories
686 of drugs, such as quercetin, catechol derivatives and tetracyclines, are known to form drug/metal
687 chelates.^[173–175] Fluoroquinolones also interact with multivalent cations and this interaction can lead to
688 reduced antimicrobial activity.^[176]

689 Deppermann et al., 1989, and Garty et al., 1980, investigated the effect of H₂RAs or antacids (mixture of
690 aluminium hydroxide and magnesium hydroxide) on the oral absorption of various tetracycline antibiotics.
691 The antacids resulted in reduction of the oral bioavailability of tetracyclines by 80% or more, whereas co-
692 administration of the H₂RAs did not affect the pharmacokinetic parameters of tetracyclines.^[177,178] For this
693 reason, it was concluded that chelation rather than elevation of gastric pH is the probable mechanism of
694 this DDI. The complexes that are formed by chelation are insoluble and therefore they precipitate,
695 preventing absorption. The results are similar with co-administration of antacids and fluoroquinolones.
696 Aluminium ions form a stable and insoluble complex with quinolones, thus preventing their intestinal
697 absorption and reducing their bioavailability.^[179,180] By contrast, concomitant administration of an H₂RA
698 did not have a significant effect on the AUC of ciprofloxacin.^[177] Since the formation of the chelate complex
699 is the limiting factor to absorption of quinolone antibiotics, many studies have been conducted in order to

700 establish an optimal interval of antacid dosing before or after the administration of the antimicrobial
701 agents. With regard to fluoroquinolones, it has been concluded that administration of antacids four hours
702 earlier or two hours later than the administration of the antibiotic, would circumvent the interaction.^{[181-}

703 ^{185]}

704 As with the PPIs and H₂RAs, the elevation of gastric pH that is observed after administration of antacids
705 could also impact the dissolution of oral solid formulations and change their pharmacokinetics. Indeed,
706 co-administration of itraconazole with antacids resulted in decreased AUC.^[186] However, in a pilot study
707 by Brass et al. (n=4) the absorption of ketoconazole was not significantly decreased.^[187]

708 The interaction of antacids and NSAIDs is also an interesting case. NSAIDs are among the most popular
709 OTC and frequently prescribed medications for acute or short-term pain and chronic inflammatory
710 diseases. Since NSAIDs cause dyspepsia and damage in the upper gastrointestinal mucosa they are often
711 given with antacids. Interactions of antacids with NSAIDs are not clearly established and no general
712 recommendations can be made for this drug category. However, there are studies indicating that co-
713 administration with antacids containing magnesium hydroxide or sodium bicarbonate could enhance the
714 rate and possibly the extent of absorption of some NSAIDs, i.e. ibuprofen, tolfenamic and mefenamic acid,
715 diflunisal and naproxen.^[188-191] This has been attributed to the fact that magnesium hydroxide, in addition
716 to increasing gastric pH, also accelerates gastric emptying. Such effects have not been observed for
717 aluminium hydroxide, which in contrast to magnesium hydroxide prolongs gastric emptying^[192]

718 There have been many further studies investigating the interactions of antacids with APIs from various
719 drug classes, including corticosteroids, cardiovascular agents and antidiabetic agents. However, it has not
720 been possible to make any generalizations about the observed interactions. Furthermore, in some cases
721 there is no evidence that differences in pharmacokinetic parameters translate into clinically significant
722 differences.^[192]

723 **2.5 Probiotics**

724 It is well known that the intestinal microflora plays a key role in physiological, metabolic, immunological
725 and nutritional processes in the human body. For this reason, there is currently great interest in influencing
726 the composition of the microflora and its activity using probiotics for both the prevention and treatment
727 of various diseases.^[193] According to WHO, probiotics are “live microorganisms which, when administered
728 in adequate amounts, confer a health benefit on the host”.^[194] There are several clinical studies that have
729 illustrated their beneficial effects on gastrointestinal disorders such as diarrhea and irritable bowel
730 syndrome. The gram-negative bacterium *Escherichia coli* Nissle 1917, for example, has been used since
731 1920 for the treatment or prevention of irritable bowel syndrome, chronic constipation, non-ulcer
732 dyspepsia and other gastrointestinal disorders.^[195] The mechanism of action of the probiotics is not yet
733 fully understood. It seems that they may modulate the intestinal epithelial barrier and transport across it,
734 noting that in inflammatory bowel diseases, e.g. ulcerative colitis and Crohn’s disease, the barrier
735 properties of the epithelium are compromised due to secreted cytokines and/or medication.^[196]

736 Despite the wealth of evidence regarding their advantageous and well-tolerated use, the literature on
737 interactions between concomitantly administered probiotics and drugs with respect to drug
738 pharmacokinetics is mainly limited to animal experiments. In the study of Mikov et al., 2006, the effect of
739 co-administration of probiotics (oral 2 g dose of freeze dried powder of a mixture of the strains
740 *Lactobacillus acidophilus* L10, *Bifidobacterium lactis* B94 and *Streptococcus salivarius* K12 every 12 h for
741 three days) on sulfasalazine metabolism (sulfasalazine administered as an oral dose of 100 mg/kg dissolved
742 in saline via gavage 6 h after completing the three day treatment with probiotics) in the rat gut lumen was
743 investigated. The authors showed that administration of probiotics significantly increased the conversion
744 of sulfasalazine to sulfapyridine and 5-aminosalicylic acid by increasing azoreductase activity. This could
745 possibly enhance sulfasalazine therapy, which would be important in patients with reduced gut microflora,
746 subsequent to antibiotic therapy, or in severe diarrhea.^[197] Lee et al., 2012, confirmed an increase of

747 azoreductase activity in *ex vivo* colon rat fluids. However, no differences were found in the
748 pharmacokinetic parameters of sulfasalazine and sulfapyridine.^[198] Kunes et al., 2011, investigated the
749 effect of *E. coli* Nissle 1917 probiotic medication on the absorption kinetics of 5-aminosalicylic acid in rats.
750 The results showed that there was no difference in the pharmacokinetics of 5-aminosalicylic acid and that
751 *E. coli* Nissle 1917 medication did not affect the absorption of 5-aminosalicylic acid.^[199] Al Salami et al.,
752 2008, investigated the effect of a mixture of three probiotics in diabetic rats on gliclazide
753 pharmacokinetics. They observed that gliclazide's absorption and bioavailability were reduced in healthy
754 rats. The authors attributed this change to several possible causes, most of which had to do with intestinal
755 efflux drug transporters.^[200] Saksena et al., 2011, reported that *Lactobacilli* or their soluble factors
756 significantly enhanced P-gp expression and function under normal and inflammatory conditions in
757 mice.^[201] Finally, Matuskova et al., 2014, investigated the effect of administration of *E. coli* Nissle 1917 on
758 amiodarone absorption in rats. This resulted in 43% increase in the AUC of amiodarone. Interestingly, this
759 effect was not observed when *E. coli* Nissle 1917 was replaced by a reference non-probiotic *E. coli* strain
760 suggesting that the increase in AUC of amiodarone was due to the administration of the probiotic.^[202]
761 Clearly, studies in humans are needed in order to investigate whether these results can be extrapolated
762 well to patients with altered intestinal microflora.

763 **2.6 Antibiotics used for gastrointestinal infections**

764 Antibiotics aim to attack targets specific to bacterial organisms such as bacterial cell walls, bacterial cell
765 membranes, bacterial metabolism or replication, in order to avoid damage to human cells. However,
766 antibiotics are not 100% selective for bacteria that are pathogenic for the host organism. As a result, the
767 GI microbiota is frequently disturbed after treatment with antibiotics.^[203,204] In fact depending on the
768 antibiotic, 5-25% of patients treated experience diarrhoea.^[205,206]

769 Sullivan et al. reviewed the effect of various antibiotics on the abundance of bacterial types and
770 species.^[204] Differences in the composition of the microbiota could alter the composition of colonic fluids
771 and permeability of the gut wall as well as the abundance of bacterial enzymes.

772 Colonic bacteria are involved in the cleavage of dietary fibres to oligosaccharides and monosaccharides
773 and their further fermentation to short chain fatty acids (SCFAs) such as acetate, propionate and
774 butyrate.^[207] Patients treated with antibiotics showed a decreased colonic carbohydrate fermentation and
775 consequently lower fecal concentrations of SCFAs.^[208–212] In other studies it was shown that SCFAs
776 stimulate ileal and colonic motility.^[213–215] The inhibition of gastric emptying by nutrients that reach the
777 ileo-colonic junction, the so-called “ileocolonic brake”, is also associated with SCFAs.^[216] But GI transit
778 times can also be affected by certain antibiotics through other mechanisms: for example, erythromycin
779 accelerates gastric emptying (-25% to -77%) by acting as a motilin agonist, while prolonging small intestinal
780 transit time (+20% to +45%) for liquids and solids in healthy volunteers and patients.^[217–222] For example,
781 when erythromycin was co-administered with a controlled-release formulation of pregabalin, designed to
782 remain for a prolonged time in the stomach, in eighteen healthy subjects there was a reduction of AUC
783 and C_{max} by 17% and 13% respectively, due to erythromycin’s prokinetic action.^[223] Since the pregabalin
784 exposure was still in the range calculated for patients receiving an immediate release formulation of
785 pregabalin, the interaction was deemed not to be clinically relevant.

786 If bacterial enzymes are involved in the biotransformation of a drug, the intake of antibiotics can affect its
787 metabolism by changing the composition of the microbiota and thus altering the bacterial enzyme
788 activity.^[224,225] At least thirty commercially available drugs have been reported to be metabolised by
789 bacterial enzymes in the gastrointestinal tract.^[224] The serum concentrations of digoxin, which is partly
790 metabolised by gut microbiota, increased two-fold after administration of erythromycin or tetracycline for
791 five days in four healthy volunteers.^[226] In another report, toxic digoxin plasma levels were observed in a
792 patient after co-treatment with erythromycin, possibly due to the inhibition of *Eubacterium lentum* which
793 converts digoxin to its reduced derivatives.^[227] Incubation of flucytosine with fecal specimens of

794 neutropenic patients before and after treatment with antibiotics (ciprofloxacin, penicillin, co-trimoxazole)
795 and antimycotics (amphotericin B, fluconazole, nystatin) indicated that the transformation of flucytosine
796 to its active metabolite, fluorouracil, was reduced.^[228] Similarly, concomitant administration with
797 ampicillin (250 mg four times daily for five days) with sulfasalazine (single dose 2 g) led to a decrease in
798 the AUC of sulfapyridine by 35% in five healthy subjects suggesting a decrease in azoreductase activity and
799 prodrug activation.^[229]

800 An altered colonic microflora could also adversely affect the drug release from colon-targeting
801 formulations coated with water-insoluble polysaccharides.^[230] Since polysaccharides such as guar gum,
802 pectin and chitosan are degraded by bacterial enzymes in the colon, release of the drug relies on the
803 abundance and activity of the polysaccharide-specific bacterial enzymes. Samples (fecal slurries) from
804 volunteers treated with antibiotics within the last three months should be excluded from the evaluation
805 of such formulations in *in vitro* dissolution tests.^[230]

806 The microbiota is also involved in the modification of primary bile acids to secondary bile acids, such as
807 deoxycholic acid and lithocholic acid, via microbial 7 α -dehydroxylase and in the deconjugation of
808 conjugated bile acids.^[231] Unconjugated bile acids are less likely to be reabsorbed in the terminal ileum
809 and therefore, bacterial action promotes the excretion of bile acids.^[232] Thus, antibiotic treatment may
810 cause changes in the bile acid pool. Indeed, treatment with oral vancomycin decreased fecal levels of
811 secondary bile acids and increased fecal levels of primary bile acids in healthy volunteers (n=10). By
812 contrast, treatment with oral amoxicillin showed no such effect.^[233] It has also been hypothesized that
813 antibiotic-induced differences in the bile acid composition could affect the solubilisation of lipophilic
814 drugs. However, a recent study evaluating the differences in the solubilisation capacity of primary and
815 secondary bile acids for nine poorly water-soluble drugs revealed at most minor differences between
816 conjugated and unconjugated bile acids. Only dehydroxylation at C-7 improved drug solubilisation
817 significantly for the compounds investigated.^[234]

818 With regard to DDIs at the level of metabolism, the effect of antibiotics on metabolic enzymes is often
819 specific to the antibiotic agent. Macrolide antibiotics interact with substrates metabolized by CYP3A4 (i.e.
820 carbamazepine, terfenadine, cyclosporine) depending on the macrolide's specific affinity for CYP3A4. The
821 interaction potential can be high (troleandomycin, erythromycin), moderate (clarithromycin,
822 roxithromycin) or low (azithromycin).^[235] For example, concomitant administration of erythromycin (500
823 mg three times daily for seven days) with midazolam (single dose 15 mg) resulted in a 4-fold increase of
824 the AUC of midazolam in fifteen healthy subjects.^[236] Similarly, when administered with clarithromycin
825 (500 mg twice daily for 7 days), the bioavailability of midazolam (single dose 4 mg) was increased 2.4-fold
826 in sixteen healthy subjects.^[237] But, after pretreatment with azathioprine (500 mg daily for three days), no
827 significant effect on the pharmacokinetics of midazolam (single dose 15 mg) was observed in twelve
828 healthy subjects.^[238]

829 For the fluoroquinolones, depending on the fluoroquinolone's specific affinity for CYP1A2, interactions
830 with CYP1A2 substrates (i.e. clozapine, theophylline) have been observed.^[239] Concomitant oral
831 administration of enoxacin (400 mg twice daily for six days) with theophylline (250 mg twice daily for
832 eleven days) resulted in a reduction in total clearance of theophylline by 74% in six healthy subjects,^[240]
833 while ciprofloxacin (500 mg twice daily for two and a half days) reduced theophylline's total clearance by
834 19% after a single oral dose of theophylline syrup (3.4 mg/kg) in nine healthy subjects.^[241] In contrast,
835 concomitant administration of norfloxacin (400 mg twice daily for four days) with theophylline (200 mg
836 three times daily for four days) had no significant effect on theophylline's total clearance in ten healthy
837 subjects.^[242] For more detailed information, the reader is referred to several review articles.^[235,239,243]

838 **2.7 Anti-inflammatory drugs for IBD**

839 Anti-inflammatory agents, such as aminosalicylates and corticosteroids, are the most commonly used
840 drugs in inflammatory bowel disease (IBD). Treatment with aminosalicylates includes a range of prodrugs
841 (sulfasalazine, olsalazine, balsalazine) or modified release formulations to deliver aminosalicylates to their

842 target site in the intestine. If remission cannot be achieved with aminosalicylates, the next treatment
843 option consists of different corticosteroids ranging from locally acting drugs (budesonide) to systemic
844 acting ones (hydrocortisone, prednisolone, dexamethasone).

845 Aminosalicylates have shown to alter the GI physiology. In terms of GI transit time, olsalazine accelerated
846 transit, with a mean gastric emptying time of 45.3 ± 24.2 min vs. 67.3 ± 33.1 min, a mouth to caecum transit
847 time of 242 ± 41 min vs. 325 ± 33 min and whole gut transit time of 37.8 ± 17.8 h vs. 60.5 ± 26 h in six patients
848 with ulcerative colitis whereas intake of sulfasalazine had no effect in six healthy subjects (measured by
849 scintigraphy of a solid radio-labelled meal or hydrogen breath test).^[244–246] The authors commented that
850 this may be the result of a direct action of olsalazine on contractile activity in the small intestine, inducing
851 hypersecretion or decreasing fluid absorption.^[245]

852 With respect to luminal pH, treatment with sulfasalazine in patients with ulcerative colitis in remission
853 resulted in a decrease in colonic pH to 4.90 ± 1.3 compared to treatment with Asacol® (mesalazine) with a
854 colonic pH of 5.52 ± 1.13 or Dipentum® (olsalazine) with a pH of 5.51 ± 0.37 .^[247] Nugent et al. postulated
855 that reduced colonic pH may impair drug release from delayed-release formulations targeting the terminal
856 ileum/colon (trigger pH for release is $>6-7$) or alter bacterial enzyme activity.^[248]

857 Regarding permeability, jejunal perfusion studies showed a decreased absorption of water, sodium,
858 potassium and chloride in the presence of olsalazine or sulfasalazine.^[249] In ileal perfusion studies, reduced
859 absorption of water and glucose was observed, when olsalazine was present, which in turn could explain
860 the higher volume of ileostomy fluid observed after oral administration of this drug.^[249,250] By contrast, no
861 changes in absorption or volume of fluids was observed in ileal perfusion studies in the presence of
862 sulfasalazine.^[249] With regard to specific uptake mechanisms, sulfasalazine reduced the uptake of folic acid
863 and methotrexate by folate transporters in biopsy specimens taken from the duodenojejunal region while
864 olsalazine only decreased folic acid uptake.^[251] In an intervention study, sulfasalazine treatment was
865 discontinued in rheumatoid arthritis patients who had previously received a combination of sulfasalazine
866 and methotrexate. The intervention resulted in a more than 2-fold increase of methotrexate serum

867 concentrations, in line with the ability of sulfasalazine to compete with methotrexate for the folic acid
868 transporter.^[252]

869 After treatment with sulfasalazine the fecal microbiota of patients with rheumatoid arthritis was richer in
870 *Bacillus*, whereas decreased numbers of aerobic bacteria, *Escherichia coli*, *Clostridium perfringens* and
871 *Bacteroides* were observed.^[253-255] Treatment with mesalazine resulted in a decreased diversity of the
872 intestinal microbiota and also reduced the quantity of fecal bacteria in patients with diarrhea-predominant
873 irritable bowel syndrome.^[256,257] These changes in colonic bacteria may have ramifications for drugs like
874 digoxin, which are partly metabolised by bacterial enzymes (see section 2.6 “Antibiotics”).^[258-260]

875 With regard to DDIs, pre-treatment with sulfasalazine (500 mg for six days) in ten healthy subjects
876 decreased the AUC of digoxin by 25% after being administered as oral solution (dose 0.5 mg).^[261] The
877 mechanism of the interaction is not yet understood. Differences in bioavailability could possibly be
878 attributed to a direct action of sulfasalazine on the intestinal mucosa or induced differences in the gut
879 microbiota enhancing digoxin metabolism. For a patient on concomitant treatment with cyclosporin (480
880 mg daily) and sulfasalazine (1.5 g daily), increased plasma concentrations of cyclosporine were observed
881 five days after the treatment of sulfasalazine was stopped making it necessary to reduce the dose of
882 cyclosporine by 60%.^[262] While the interaction is not yet understood, an induction of metabolic enzymes
883 is plausible considering the time course of the observation. For 6-mercaptopurine (50-75 mg), a metabolic
884 interaction was observed with concomitantly administered olsalazine (1000-1750 mg) in a patient with
885 Crohn’s disease, resulting in bone marrow suppression and required dose reduction of 6-
886 mercaptopurine.^[263] This interaction may be caused by the inhibition of thiopurine methyltransferase,
887 which is responsible for 6-mercaptopurine metabolism; inhibition of this enzyme by aminosalicylates has
888 been demonstrated in *in vitro* enzyme kinetic studies.^[264]

889 After treatment with corticosteroids, the phospholipid mucus layer can be fluidized, resulting in a thinner
890 mucus barrier.^[265] Impairment of membrane integrity can cause side-effects such as gastrointestinal

891 bleeding and bowel perforation.^[266] The corticosteroids can also affect active transport mechanisms such
892 as bile salt reuptake and exo-transport. Treatment with budesonide results in upregulation of the apical
893 sodium-dependent bile acid transporter in the terminal ileum, which enhances bile acid absorption in both
894 healthy controls and patients with Crohn's disease.^[267,268] Consequently, lower luminal bile salt
895 concentrations may impede solubilisation and absorption of lipophilic poorly soluble compounds.^[269] In
896 terms of transporters, budesonide and prednisone are substrates of the efflux transporter P-
897 glycoprotein.^[270] However, it is unclear whether these alterations result in clinically significant DDIs.

898 The main elimination pathway of corticosteroids is the metabolism by intestinal and hepatic CYP3A4 which
899 is especially important for high-clearance corticosteroids such as budesonide and prednisone.^[271] Co-
900 administration of prednisone with metronidazole in six patients with Crohn's disease reduced the
901 bioavailability of metronidazole by 31%, most likely attributed to the induction of liver enzymes
902 responsible for metabolizing metronidazole.^[272] Likewise, co-treatment with prednisone resulted in
903 decreased serum concentrations of salicylates in a 11-year-old child with juvenile rheumatoid arthritis due
904 to the induction of salicylate clearance by prednisone.^[273] On the other hand, drugs inhibiting CYP3A4 in
905 the intestinal wall and liver such as ketoconazole, itraconazole, clarithromycin and HIV-protease inhibitors
906 reduce the metabolism of corticosteroids and increase their bioavailability.^[274–277]

907 **2.8 Immunosuppressive agents for IBD**

908 Immunosuppressive agents are frequently used in gastroenterology for the treatment of inflammatory
909 bowel disease, autoimmune hepatitis, autoimmune pancreatitis, sclerosing cholangitis and in the post-
910 transplantation setting.^[278] Especially in IBD, therapy with immunosuppressive agents has gained in
911 importance over the last few years.^[279] Immunosuppressive agents can be classified in immunomodulators
912 (e.g., thiopurines (6-mercaptopurine, azathioprine), methotrexate, tacrolimus, sirolimus, everolimus,
913 cyclosporine A) and biologics (e.g., monoclonal antibodies: infliximab, adalimumab, vedolizumab,
914 golimumab).^[279] Depending on the specific immunosuppressive agent, gastrointestinal transit time, bile

915 flow and/or permeability can be altered, which could further affect drug product performance of co-
916 administered drugs.

917 Regarding transit time, gastric emptying time (as measured with magnetic markers after a standardized
918 meal using Alternating Current Biosusceptometry) was decreased in patients treated with tacrolimus after
919 kidney transplant (47 ± 34 min) compared to healthy subjects (176 ± 42 min) or patients treated with
920 cyclosporine A (195 ± 42 min).^[280]

921 In terms of drug absorption, immunosuppressants can result in increased permeability on the one hand,
922 but decreased surface area on the other hand. Intestinal permeability was increased (75% of median value;
923 indicated by an increased lactulose/L-rhamnose excretion ratio) in liver graft recipients treated with
924 tacrolimus (n=12) compared to healthy subjects (n=9) and by 48% compared to untreated liver transplant
925 patients (n=5).^[281] Only the permeability via the transcellular pathway seems to be increased by
926 tacrolimus, as indicated by an increased lactulose/L-rhamnose ratio (+160%) and unchanged excretion of
927 lactulose in treated orthotopic liver transplantation patients.^[281,282]

928 Another side-effect of immunosuppressive therapy, especially with methotrexate (including low-dose
929 therapy) is GI mucositis resulting in the loss of villi in the duodenum, crypts in the colon and
930 enterocytes.^[283–287] Oral mucositis is a side-effect of azathioprine therapy.^[288] In patients with oral
931 mucositis, bupivacaine absorption from lozenges was increased and a trend to higher fentanyl absorption
932 administered with a sublingual spray was observed but did not reach statistical significance.^[289,290] The
933 effect may be due to impairment of the barrier function of the mucosa.

934 In terms of transporter systems and metabolism, immunosuppressants (cyclosporine A, tacrolimus,
935 everolimus and sirolimus) are substrates of P-glycoprotein and CYP3A4.^[291–293] As a result, various drug
936 interactions with P-gp substrates such as aliskiren and anthracyclines have been reported for cyclosporine
937 A.^[294–296] Additionally, concomitant administration of inhibitors (e.g.azole antifungal drugs, macrolide
938 antibiotics) and inducers (e.g. anti-convulsants, rifampicin) of CYP3A4 can modify therapeutic response
939 and toxicity of the abovementioned immunosuppressants.^[297–299] Methotrexate intra muscular or

940 subcutaneous co-treatment in patients with Crohn's disease or oral co-treatment in patients with
941 rheumatoid arthritis resulted in increased infliximab concentrations, most likely due to a decrease in the
942 development of infliximab antibodies.^[300,301] Co-administration of azathioprine in patients treated with
943 warfarin resulted in higher warfarin doses needed to reach therapeutic anticoagulant effects but the
944 mechanism of the interaction is unclear.^[302-304]

945 **2.9 Bile acid sequestrants**

946 Bile acid sequestrants (BAS) such as cholestyramine, colestevlam and colestipol are used for the treatment
947 of primary hyperlipidaemia, as monotherapy or in combination with statins or ezetimibe, and in the
948 treatment of gastrointestinal diseases.^[305] Cholestyramine is indicated for diarrhea associated with
949 Crohn's disease, ileal resection, vagotomy, diabetes, diabetic vagal neuropathy and radiation.^[306] Whilst
950 colestevlam is not licensed for the treatment of bile acid malabsorption, several clinical trials have
951 demonstrated positive outcomes which has provoked its off-label use in this indication.^[307-309]

952 Bile acid sequestrants are positively charged ion-exchange resins which bind bile acids in the intestine to
953 form insoluble complexes and as a consequence reduce the bile acid pool.^[306] As a result of decreased
954 luminal bile acid concentrations, BAS are expected to interfere with the bioavailability of lipophilic, low-
955 soluble compounds by impeding their solubilization. For several drugs, such as rifaximin^[310] and
956 troglitazone^[311] the presence of bile acids was shown to increase drug solubility and therefore, their
957 absorption may be impeded by co-therapy with BAS.

958 The positive charge of BAS leads to a high affinity for deprotonated acidic drugs in the intestine. Binding
959 of these anions increases the excretion and impedes the absorption of acidic co-administered drugs. Drugs
960 that are known to be affected by this mechanism are furosemide,^[312] warfarin,^[313] phenprocoumon,^[314,315]
961 sulindac,^[316] cerivastatin,^[317] levothyroxine,^[318] glipizide,^[319] mycophenolic acid,^[320] folic acid^[321] and
962 valproate^[322]. The binding affinity for co-administered drugs can vary among the different BAS e.g.,
963 cholestyramine, which has a high affinity for hydrophobic compounds,^[305,323] decreased ibuprofen and

964 diclofenac absorption to a higher extent than colestipol; and colesevelam has a favorable DDI-profile
965 compared to other BAS.^[324–326]

966 High-molecular lipophilic drugs are typical substrates for enterohepatic recirculation.^[327] By binding drugs
967 or drug metabolites that undergo enterohepatic recirculation, BAS can enhance drug elimination of the
968 victim drug even if the administration was not concomitant. Drugs affected by this mechanism include oral
969 anticoagulants,^[313–315] cardiac glycosides^[328] and mycophenolate mofetil^[320]. It is difficult to predict which
970 drugs that undergo enterohepatic recirculation will be affected by BAS, since various factors such as
971 polarity, ionization properties and metabolism by liver and microbiota all influence biliary excretion.^[329]

972 Prolonging the interval between administration of BAS and co-medication often reduces the potential for
973 drug interactions and must be adapted for extended-release formulations.

974 BAS can also affect gastrointestinal transit time: Cholestyramine prolonged the transit time in the
975 transverse colon by up to eight hours in thirteen patients with idiopathic bile acid diarrhea (as measured
976 with radiopaque markers), while total colonic transit was not altered.^[330] After concomitant administration
977 of a sustained-release formulation of verapamil (dose 240 mg) with colesevelam (dose 4.5 g), a reduction
978 in AUC of 11% and decreased plasma levels of verapamil were observed in thirty-one healthy subjects.^[331]

979 This interaction was deemed not to be clinically relevant.^[331]

980 An overview of DDIs of bile acid sequestrants and their mechanism is given in Table 4.

981 3. Conclusions and future perspectives

982 Gastrointestinal events and conditions play a key role in the bioavailability of an orally administered drug
983 and its therapeutic action. Concomitant use of various medications can affect the absorption and the
984 pharmacokinetics of the administered drugs and therefore, their performance. As presented in this review
985 article, various interactions between drugs used to treat gastrointestinal diseases and co-administered
986 drugs have been identified. These interactions are of particular concern, since GI drugs are commonly
987 prescribed and many of them are also available OTC. Prescribing physicians and pharmacists need to be
988 aware of and monitor these potential interactions. Furthermore, information involving interactions with
989 GI drugs should be made available not only to clinical practitioners, but also to patients, in order to prevent
990 the appearance of adverse effects, on the one hand, and failure of treatment on the other hand.

991 It should be noted, however, that despite the large number of DDI studies with GI drugs reported in
992 literature, most studies have only investigated the effects of short-term treatment and little is known
993 about the ramifications of long-term administration on DDIs. Furthermore, most DDI studies have been
994 conducted in healthy volunteers and may not necessarily reflect the degree of interaction in patients. As
995 most of the DDIs have been based on changes in pharmacokinetics, it is also not clear in all cases whether
996 the DDI has any ramifications for the therapeutic effect. Indeed, some studies have suggested that even
997 quite significant changes in pharmacokinetics do not always lead to a change in the clinical response. More
998 work on pharmacokinetics/pharmacodynamics (PK/PD) relationships and the influence of DDIs on them
999 will be necessary to tease out the clinical implications of DDIs.

1000 However, the number of studies that can be conducted to test for potentially clinically relevant DDIs is
1001 limited, due to both ethical and cost-related issues. So there is a need for innovative evaluation methods
1002 to address knowledge gaps and provide key information on safe and effective drug use.^[332] In the last ten
1003 years, there has been an increasing use of Physiologically Based Pharmacokinetic (PBPK) modelling and
1004 simulation at different stages of drug development.^[333] To date, PBPK modelling and simulation has been

1005 mostly used for predicting enzyme interactions which, as mentioned in this article, can also occur with
1006 concomitant administration of GI drugs.^[334–339] PBPK modelling is gaining acceptance at the various
1007 regulatory agencies as a tool to qualitatively and quantitatively predict DDIs and, in some cases, the
1008 simulation results may even be used to support labeling, depending on the clinical importance of the
1009 interaction.^[8]

1010 One of the advantages of PBPK modelling is that it is able to account for both formulation characteristics
1011 and physiological parameters. As such, it can be used to help define a “safe space” by identifying the range
1012 of dosing conditions under which the pharmacokinetic parameters will not be significantly affected by
1013 changes in the release properties of the dosage form. This approach, which is sometimes referred to as
1014 “virtual bioequivalence”, has already been used to explore whether bioequivalence decisions based on
1015 clinical trials in healthy adults can be extrapolated to special populations, such as the hypochlorhydric or
1016 achlorhydric population, in whom the gastrointestinal physiology differs from that of healthy adults.^{[340–}
1017 ^{342]}

1018 The same approach could be extended to predict pre-absorptive DDIs with GI drugs, since these are
1019 intended to modify gastrointestinal physiology. First attempts have already been made for acid reducing
1020 agents, with results from *in vitro* dissolution experiments , which are tailored to mimic the changes in the
1021 upper gastrointestinal tract after the administration of these drugs, combined with PBPK models for
1022 healthy adults.^[340,341,343] This approach should be broadened to encompass other classes of GI drugs.
1023 Possible future steps include tailoring dissolution tests and PBPK models to the physiological conditions
1024 observed in special populations, thus allowing for predictions of the *in vivo* performance of drug products
1025 in special populations (pediatrics, geriatrics, ethnic groups, the obese, hepatically impaired etc.) who
1026 concomitantly receive GI drugs. This approach will provide the way forward to predicting pharmacokinetic
1027 differences resulting from these combinations and, especially when coupled with PK/PD relationships,
1028 whether these are likely to be clinically significant, in a wide variety of populations and dosing conditions.

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1032 **References**

- 1033 1. Everhart JE, Ruhl CE. Burden of Digestive Diseases in the United States Part I: Overall and Upper
1034 Gastrointestinal Diseases. *Gastroenterology* 2009; 136(2): 376–386.
1035 doi:10.1053/J.GASTRO.2008.12.015.
- 1036 2. Peery A *et al.* Burden of gastrointestinal disease in the United States: 2012 update.
1037 *Gastroenterology* 2012; 143(5): 1179–1187. doi:10.1053/j.gastro.2012.08.002.Burden.
- 1038 3. Lindsley CW. 2014 Global Prescription Medication Statistics: Strong Growth and CNS Well
1039 Represented. *ACS Chem Neurosci* 2015; 6(4): 505–506. doi:10.1021/acschemneuro.5b00098.
- 1040 4. Quigley EMM. Prokinetics in the Management of Functional Gastrointestinal Disorders. *Curr*
1041 *Gastroenterol Rep* 2017; 19(10): 53. doi:10.1007/s11894-017-0593-6.
- 1042 5. Enck P *et al.* Functional dyspepsia. *Nat Rev Dis Prim* 2017; 3: 17081. doi:10.1038/nrdp.2017.81.
- 1043 6. Pinto-Sanchez MI *et al.* Proton pump inhibitors for functional dyspepsia. *Cochrane Database Syst*
1044 *Rev* 2017; 3: CD011194. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/28271513>. Accessed
1045 January 10, 2018.
- 1046 7. Ford AC *et al.* Efficacy of 5-Aminosalicylates in Crohn’s Disease: Systematic Review and Meta-
1047 Analysis. *Am J Gastroenterol* 2011; 106(4): 617–29. doi:10.1038/ajg.2011.71.
- 1048 8. EMA. Guideline on the investigation of drug interactions. *Guid Doc* 2012; 44(June): 59.
1049 doi:10.1093/deafed/ens058.
- 1050 9. Huang S-M. Clinical Drug Interaction Studies — Study Design, Data Analysis, and Clinical
1051 Implications Guidance for Industry. *FDA Guid* 2009. Available at:
1052 <http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/default.htm>.
1053 Accessed January 10, 2018.

- 1054 10. Dechanont S *et al.* Hospital admissions/visits associated with drug-drug interactions: a systematic
1055 review and meta-analysis. *Pharmacoepidemiol Drug Saf* 2014; 23(5): 489–497.
1056 doi:10.1002/pds.3592.
- 1057 11. Center for Drug Evaluation and Research. Resources for You - Drug Interactions: What You Should
1058 Know. Available at: <https://www.fda.gov/drugs/resourcesforyou/ucm163354.htm>. Accessed
1059 October 25, 2017.
- 1060 12. eurostat. File:Self-reported use of non-prescribed medicines by sex, 2014 (%).png - Statistics
1061 Explained. Available at: [http://ec.europa.eu/eurostat/statistics-explained/index.php/File:Self-](http://ec.europa.eu/eurostat/statistics-explained/index.php/File:Self-reported_use_of_non-prescribed_medicines_by_sex,_2014_(%25).png)
1062 [reported_use_of_non-prescribed_medicines_by_sex,_2014_\(%25\).png](http://ec.europa.eu/eurostat/statistics-explained/index.php/File:Self-reported_use_of_non-prescribed_medicines_by_sex,_2014_(%25).png). Accessed October 25,
1063 2017.
- 1064 13. Sales of over-the-counter medicines in 2015 by clinical area and top 50 selling brands. *Pharm J*
1065 2016. doi:10.1211/PJ.2016.20200923.
- 1066 14. Holzbauer M, Sharman DF. The Distribution of Catecholamines in Vertebrates. In:
1067 *Catecholamines*. Berlin, Heidelberg: Springer Berlin Heidelberg, 1972: 110–185. doi:10.1007/978-
1068 3-642-65249-3_5.
- 1069 15. Orloff LA *et al.* Dopamine and norepinephrine in the alimentary tract changes after chemical
1070 sympathectomy and surgical vagotomy. *Life Sci* 1985; 36(17): 1625–31. Available at:
1071 <http://www.ncbi.nlm.nih.gov/pubmed/3921790>. Accessed August 22, 2017.
- 1072 16. Longo WE, Vernava AM. Prokinetic agents for lower gastrointestinal motility disorders. *Dis Colon*
1073 *Rectum* 1993; 36(7): 696–708. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/8348856>.
1074 Accessed August 22, 2017.
- 1075 17. Tonini M. Recent advances in the pharmacology of gastrointestinal prokinetics. *Pharmacol Res*

- 1076 1996; 33(4–5): 217–226. doi:10.1006/phrs.1996.0030.
- 1077 18. Ehrlein HJ, Schemann M. Gastrointestinal Motility. Available at:
1078 <http://humanbiology.wzw.tum.de/motvid01/tutorial.pdf>. Accessed January 15, 2018.
- 1079 19. Mandl P, Kiss JP. Role of presynaptic nicotinic acetylcholine receptors in the regulation of
1080 gastrointestinal motility. *Brain Res Bull* 2007; 72(4–6): 194–200.
1081 doi:10.1016/j.brainresbull.2007.02.005.
- 1082 20. Gershon MD. Review article: serotonin receptors and transporters - roles in normal and abnormal
1083 gastrointestinal motility. *Aliment Pharmacol Ther* 2004; 20(s7): 3–14. doi:10.1111/j.1365-
1084 2036.2004.02180.x.
- 1085 21. Halpert A, Drossman D. 5-HT modulators and other antidiarrheal agents and cathartics. In: *Pocket*
1086 *Guide to Gastrointestinal Drugs*. Chichester, UK: John Wiley & Sons, Ltd, 2014: 57–81.
1087 doi:10.1002/9781118481530.ch5.
- 1088 22. Kale H, Fass R. Prokinetic agents and antiemetics. In: *Pocket Guide to Gastrointestinal Drugs*.
1089 Chichester, UK: John Wiley & Sons, Ltd, 2014: 1–14. doi:10.1002/9781118481530.ch1.
- 1090 23. Lee A, Kuo B. Metoclopramide in the treatment of diabetic gastroparesis. *Expert Rev Endocrinol*
1091 *Metab* 2010; 5(5): 653–662. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/21278804>.
1092 Accessed May 16, 2018.
- 1093 24. McCallum RW *et al*. Effects of metoclopramide and bethanechol on delayed gastric emptying
1094 present in gastroesophageal reflux patients. *Gastroenterology* 1983; 84(6): 1573–7. Available at:
1095 <http://www.ncbi.nlm.nih.gov/pubmed/6132852>. Accessed May 16, 2018.
- 1096 25. Fink SM *et al*. Effect of metoclopramide on normal and delayed gastric emptying in
1097 gastroesophageal reflux patients. *Dig Dis Sci* 1983; 28(12): 1057–1061. doi:10.1007/BF01295802.

- 1098 26. Parkman HP. Migraine and Gastroparesis From a Gastroenterologist's Perspective. *Headache J*
1099 *Head Face Pain* 2013; 53(S1): 4–10. doi:10.1111/head.12112.
- 1100 27. Tokola R, Neuvonen P. Effects of migraine attack and metoclopramide on the absorption of
1101 tolfenamic acid. *Br J Clin Pharmacol* 1984; 17(1): 67–75. doi:10.1111/j.1365-2125.1984.tb05001.x.
- 1102 28. Volans GN. The effect of metoclopramide on the absorption of effervescent aspirin in migraine. *Br*
1103 *J Clin Pharmacol* 1975; 2(1): 57–63. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/791318>.
1104 Accessed August 30, 2017.
- 1105 29. Gothoni G *et al.* Absorption of antibiotics: influence of metoclopramide and atropine on serum
1106 levels of pivampicillin and tetracycline. *Ann Clin Res* 1972; 4(4): 228–32. Available at:
1107 <http://www.ncbi.nlm.nih.gov/pubmed/4629803>. Accessed August 24, 2017.
- 1108 30. Nimmo J *et al.* Pharmacological modification of gastric emptying: effects of propantheline and
1109 metoclopramide on paracetamol absorption. *Br Med J* 1973; 1(5853): 587–589.
1110 doi:10.1136/bmj.1.5853.587.
- 1111 31. Wing LM *et al.* The effect of metoclopramide and atropine on the absorption of orally
1112 administered mexiletine. *Br J Clin Pharmacol* 1980; 9(5): 505–9. Available at:
1113 <http://www.ncbi.nlm.nih.gov/pubmed/6994791>. Accessed August 30, 2017.
- 1114 32. Crammer JL *et al.* Blood levels and management of lithium treatment. *Br Med J* 1974; 3(5932):
1115 650–4. doi:10.1136/bmj.3.5932.650.
- 1116 33. Sánchez J *et al.* The influence of gastric emptying on droxicam pharmacokinetics. *J Clin Pharmacol*
1117 1989; 29(8): 739–45. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/2778095>. Accessed
1118 August 30, 2017.
- 1119 34. Manara AR *et al.* The effect of metoclopramide on the absorption of oral controlled release

- 1120 morphine. *Br J Clin Pharmacol* 1988; 25(4): 518–21. Available at:
1121 <http://www.ncbi.nlm.nih.gov/pubmed/3382595>. Accessed August 30, 2017.
- 1122 35. MORRIS JGL *et al.* Plasma Dopa Concentrations After Different Preparations of Levodopa in
1123 Normal Subjects. *Br J Clin Pharmacol* 1976; 3(6): 983–990. doi:10.1111/j.1365-
1124 2125.1976.tb00347.x.
- 1125 36. Gugler R *et al.* Impaired cimetidine absorption due to antacids and metoclopramide. *Eur J Clin*
1126 *Pharmacol* 1981; 20(3): 225–228. doi:10.1007/BF00544602.
- 1127 37. Mahony MJ *et al.* Modification of oral methotrexate absorption in children with leukemia. *Cancer*
1128 *Chemother Pharmacol* 1984; 12(2): 131–3. Available at:
1129 <http://www.ncbi.nlm.nih.gov/pubmed/6583027>. Accessed August 24, 2017.
- 1130 38. Pearson ADJ *et al.* Small intestinal transit time affects methotrexate absorption in children with
1131 acute lymphoblastic leukemia. *Cancer Chemother Pharmacol* 1985; 14(3): 211–215.
1132 doi:10.1007/BF00258118.
- 1133 39. Manninen V *et al.* Altered absorption of digoxin in patients given propantheline and
1134 metoclopramide. *Lancet (London, England)* 1973; 1(7800): 398–400. Available at:
1135 <http://www.ncbi.nlm.nih.gov/pubmed/4119707>. Accessed August 23, 2017.
- 1136 40. Manninen V *et al.* Effect of propantheline and metoclopramide on absorption of digoxin. *Lancet*
1137 *(London, England)* 1973; 1(7812): 1118–9. Available at:
1138 <http://www.ncbi.nlm.nih.gov/pubmed/4122033>. Accessed August 23, 2017.
- 1139 41. Johnson BF *et al.* Effect of metoclopramide on digoxin absorption from tablets and capsules. *Clin*
1140 *Pharmacol Ther* 1984; 36(6): 724–730.
- 1141 42. Wadhwa NK *et al.* The effect of oral metoclopramide on the absorption of cyclosporine.

- 1142 *Transplantation* 1987; 43(2): 211–213. Available at:
1143 <http://www.ncbi.nlm.nih.gov/pubmed/3544377>.
- 1144 43. Cash BD, Lacy BE. Systematic Review: FDA-Approved Prescription Medications for Adults With
1145 Constipation. *Gastroenterol Hepatol (N Y)* 2006; 2(10): 736–749. Available at:
1146 <http://www.ncbi.nlm.nih.gov/pubmed/28325992>. Accessed September 25, 2017.
- 1147 44. Tack J *et al.* Diagnosis and treatment of chronic constipation - a European perspective.
1148 *Neurogastroenterol Motil* 2011; 23(8): 697–710. doi:10.1111/j.1365-2982.2011.01709.x.
- 1149 45. Andresen V *et al.* Effect of 5 Days Linaclotide on Transit and Bowel Function in Females With
1150 Constipation-Predominant Irritable Bowel Syndrome. *Gastroenterology* 2007; 133(3): 761–768.
1151 doi:10.1053/j.gastro.2007.06.067.
- 1152 46. Lewis SJ, Heaton KW. Increasing butyrate concentration in the distal colon by accelerating
1153 intestinal transit. *Gut* 1997; 41(2): 245–51. Available at:
1154 <http://www.ncbi.nlm.nih.gov/pubmed/9301506>. Accessed September 25, 2017.
- 1155 47. Klauser AG *et al.* Polyethylene glycol 4000 for slow transit constipation. *Z Gastroenterol* 1995;
1156 33(1): 5–8. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/7886986>. Accessed June 8, 2018.
- 1157 48. Corazziari E *et al.* Small volume isosmotic polyethylene glycol electrolyte balanced solution (PMF-
1158 100) in treatment of chronic nonorganic constipation. *Dig Dis Sci* 1996; 41(8): 1636–42. Available
1159 at: <http://www.ncbi.nlm.nih.gov/pubmed/8769292>. Accessed June 8, 2018.
- 1160 49. Ewe K *et al.* Effect of lactose, lactulose and bisacodyl on gastrointestinal transit studied by metal
1161 detector. *Aliment Pharmacol Ther* 1995; 9(1): 69–73. Available at:
1162 <http://www.ncbi.nlm.nih.gov/pubmed/7766747>. Accessed September 25, 2017.
- 1163 50. Coremans G *et al.* Small doses of the unabsorbable substance polyethylene glycol 3350 accelerate

- 1164 oro-caecal transit, but slow gastric emptying in healthy subjects. *Dig Liver Dis* 2005; 37(2): 97–
1165 101. doi:10.1016/j.dld.2004.09.016.
- 1166 51. JOUËT P *et al.* Effects of therapeutic doses of lactulose vs. polyethylene glycol on isotopic colonic
1167 transit. *Aliment Pharmacol Ther* 2008; 27(10): 988–993. doi:10.1111/j.1365-2036.2008.03654.x.
- 1168 52. Fritz E *et al.* Effects of lactulose and polyethylene glycol on colonic transit. *Aliment Pharmacol*
1169 *Ther* 2005; 21(3): 259–268. doi:10.1111/j.1365-2036.2005.02244.x.
- 1170 53. Barrow L *et al.* Scintigraphic demonstration of lactulose-induced accelerated proximal colon
1171 transit. *Gastroenterology* 1992; 103(4): 1167–73. Available at:
1172 <http://www.ncbi.nlm.nih.gov/pubmed/1397874>. Accessed June 8, 2018.
- 1173 54. MANABE N *et al.* Effects of bisacodyl on ascending colon emptying and overall colonic transit in
1174 healthy volunteers. *Aliment Pharmacol Ther* 2009; 30(9): 930–936. doi:10.1111/j.1365-
1175 2036.2009.04118.x.
- 1176 55. Guckenbiehl W *et al.* [Effect of laxatives and metoclopramide on plasma quinidine concentration
1177 during prolonged administration in patients with heart rhythm disorders]. [in German]. *Med Welt*
1178 1976; 26: 1273–6. Available at: [http://mbbsdost.com/Guckenbiehl-W-et-al-1976-Jun/et-](http://mbbsdost.com/Guckenbiehl-W-et-al-1976-Jun/et-al/4620603)
1179 [al/4620603](http://mbbsdost.com/Guckenbiehl-W-et-al-1976-Jun/et-al/4620603).
- 1180 56. Ragueneau I *et al.* Pharmacokinetic and pharmacodynamic drug interactions between digoxin and
1181 macrogol 4000, a laxative polymer, in healthy volunteers. *Br J Clin Pharmacol* 1999; 48(3): 453–6.
1182 Available at: <http://www.ncbi.nlm.nih.gov/pubmed/10510161>. Accessed September 25, 2017.
- 1183 57. Lewis SJ *et al.* Intestinal absorption of oestrogen: the effect of altering transit-time. *Eur J*
1184 *Gastroenterol Hepatol* 1998; 10(1): 33–9. Available at:
1185 <http://www.ncbi.nlm.nih.gov/pubmed/9512951>. Accessed September 25, 2017.

- 1186 58. Bown RL *et al.* Effects of lactulose and other laxatives on ileal and colonic pH as measured by a
1187 radiotelemetry device. *Gut* 1974; 15(12): 999–1004. Available at:
1188 <http://www.ncbi.nlm.nih.gov/pubmed/4448417>. Accessed September 25, 2017.
- 1189 59. Agostini L *et al.* Faecal ammonia and pH during lactulose administration in man: comparison with
1190 other cathartics. *Gut* 1972; 13(11): 859–66. Available at:
1191 <http://www.ncbi.nlm.nih.gov/pubmed/4646289>. Accessed September 25, 2017.
- 1192 60. Mann NS *et al.* Effect of lactulose, neomycin and antacid on colonic pH recorded continuously
1193 with an implanted electrode. *Am J Gastroenterol* 1979; 72(2): 141–5. Available at:
1194 <http://www.ncbi.nlm.nih.gov/pubmed/38663>. Accessed September 25, 2017.
- 1195 61. Hussain FN *et al.* Mesalazine release from a pH dependent formulation: effects of omeprazole
1196 and lactulose co-administration. *Br J Clin Pharmacol* 1998; 46(2): 173–5. doi:10.1046/j.1365-
1197 2125.1998.00762.x.
- 1198 62. Riley SA *et al.* Mesalazine release from coated tablets: effect of dietary fibre. *Br J Clin Pharmacol*
1199 1991; 32(2): 248–50. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/1657094>. Accessed
1200 January 30, 2018.
- 1201 63. Medicines.org.uk. (2018). Asacol 400mg MR Tablets- Summary of Product Characteristics (SPC) -
1202 (eMC). Available at: <https://www.medicines.org.uk/emc/product/2217/smpc>. Accessed June 3,
1203 2018.
- 1204 64. Medicines.org.uk. (2018). Salofalk 1000mg gastro-resistant prolonged-release granules- Summary
1205 of Product Characteristics (SPC) - (eMC). Available at:
1206 <https://www.medicines.org.uk/emc/product/140/smpc>. Accessed June 3, 2018.
- 1207 65. Bouhnik Y *et al.* Prospective, randomized, parallel-group trial to evaluate the effects of lactulose

- 1208 and polyethylene glycol-4000 on colonic flora in chronic idiopathic constipation. *Aliment*
1209 *Pharmacol Ther* 2004; 19(8): 889–899. doi:10.1111/j.1365-2036.2004.01918.x.
- 1210 66. Visser LE *et al.* Overanticoagulation associated with combined use of lactulose and
1211 acenocoumarol or phenprocoumon. *Br J Clin Pharmacol* 2004; 57(4): 522–524.
1212 doi:10.1046/j.1365-2125.2003.02036.x.
- 1213 67. Ippoliti C. Antidiarrheal agents for the management of treatment-related diarrhea in cancer
1214 patients. *Am J Health Syst Pharm* 1998; 55(15): 1573–80. Available at:
1215 <http://www.ncbi.nlm.nih.gov/pubmed/9706182>. Accessed September 25, 2017.
- 1216 68. Kachel G *et al.* Human intestinal motor activity and transport: effects of a synthetic opiate.
1217 *Gastroenterology* 1986; 90(1): 85–93. Available at:
1218 <http://www.ncbi.nlm.nih.gov/pubmed/3940260>. Accessed September 25, 2017.
- 1219 69. Press AG *et al.* Effect of loperamide on jejunal electrolyte and water transport, prostaglandin E 2-
1220 induced secretion and intestinal transit time in man. *Eur J Clin Pharmacol* 1991; 41(3): 239–243.
1221 doi:10.1007/BF00315436.
- 1222 70. Sninsky CA *et al.* Effect of lidamidine hydrochloride and loperamide on gastric emptying and
1223 transit of the small intestine: A double-blind study. *Gastroenterology* 1986; 90(1): 68–73.
1224 doi:10.5555/URI:PII:0016508586900764.
- 1225 71. Kirby MG *et al.* Effect of metoclopramide, bethanechol, and loperamide on gastric residence time,
1226 gastric emptying, and mouth-to-cecum transit time. *Pharmacotherapy* 1989; 9(4): 226–31.
1227 Available at: <http://www.ncbi.nlm.nih.gov/pubmed/2771808>. Accessed May 28, 2018.
- 1228 72. Bryson JC *et al.* Effect of altering small bowel transit time on sustained release theophylline
1229 absorption. *J Clin Pharmacol* 1989; 29(8): 733–8. Available at:

- 1230 <http://www.ncbi.nlm.nih.gov/pubmed/2778094>. Accessed September 25, 2017.
- 1231 73. Hughes S *et al.* Loperamide has antisecretory activity in the human jejunum in vivo. *Gut* 1984;
1232 25(9): 931–5. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/6590431>. Accessed September
1233 25, 2017.
- 1234 74. Remington M *et al.* Inhibition of postprandial pancreatic and biliary secretion by loperamide in
1235 patients with short bowel syndrome*. *Gut* 1982; 23: 98–101. Available at:
1236 <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC1419546/pdf/gut00411-0020.pdf>. Accessed
1237 September 25, 2017.
- 1238 75. Thimister PWL *et al.* Inhibition of pancreaticobiliary secretion by loperamide in humans.
1239 *Hepatology* 1997; 26(2): 256–261. doi:10.1002/hep.510260201.
- 1240 76. Callréus T *et al.* Changes in gastrointestinal motility influence the absorption of desmopressin. *Eur*
1241 *J Clin Pharmacol* 1999; 55(4): 305–309. doi:10.1007/s002280050633.
- 1242 77. Fredholt K *et al.* alpha-Chymotrypsin-catalyzed degradation of desmopressin (dDAVP): influence
1243 of pH, concentration and various cyclodextrins. *Int J Pharm* 1999; 178(2): 223–9. Available at:
1244 <http://www.ncbi.nlm.nih.gov/pubmed/10205642>. Accessed January 30, 2018.
- 1245 78. Mikus G *et al.* Reduction of Saquinavir Exposure by Coadministration of Loperamide. *Clin*
1246 *Pharmacokinet* 2004; 43(14): 1015–1024. doi:10.2165/00003088-200443140-00004.
- 1247 79. Bryson JC *et al.* Effect of Altering Small Bowel Transit Time on Sustained Release Theophylline
1248 Absorption. *J Clin Pharmacol* 1989; 29(8): 733–738. doi:10.1002/j.1552-4604.1989.tb03408.x.
- 1249 80. Wafik Gouda M. Effect of an antidiarrhoeal mixture on the bioavailability of tetracycline. *Int J*
1250 *Pharm* 1993; 89(1): 75–77. doi:10.1016/0378-5173(93)90309-4.
- 1251 81. Juhl RP. Comparison of kaolin-pectin and activated charcoal for inhibition of aspirin absorption.

- 1252 *Am J Hosp Pharm* 1979; 36(8): 1097–8. Available at:
1253 <http://www.ncbi.nlm.nih.gov/pubmed/484570>. Accessed September 25, 2017.
- 1254 82. A1-Shora HI *et al.* Interactions of procainamide, verapamil, guanethidine and hydralazine with
1255 adsorbent antacids and antidiarrhoeal mixtures. *Int J Pharm* 1988; 47: 209–213. Available at:
1256 [https://ac.els-cdn.com/0378517388902335/1-s2.0-0378517388902335-main.pdf?_tid=0dd2e3f0-](https://ac.els-cdn.com/0378517388902335/1-s2.0-0378517388902335-main.pdf?_tid=0dd2e3f0-a1f2-11e7-87e0-00000aacb35e&acdnat=1506344844_7889d472baf071990619377602a157e4)
1257 [a1f2-11e7-87e0-00000aacb35e&acdnat=1506344844_7889d472baf071990619377602a157e4](https://ac.els-cdn.com/0378517388902335/1-s2.0-0378517388902335-main.pdf?_tid=0dd2e3f0-a1f2-11e7-87e0-00000aacb35e&acdnat=1506344844_7889d472baf071990619377602a157e4).
1258 Accessed September 25, 2017.
- 1259 83. Gupta KC *et al.* Effect of pectin and kaolin on bioavailability of co-trimoxazole suspension. *Int J*
1260 *Clin Pharmacol Ther Toxicol* 1987; 25(6): 320–1. Available at:
1261 <http://www.ncbi.nlm.nih.gov/pubmed/3497885>. Accessed September 25, 2017.
- 1262 84. Albert KS *et al.* Influence of kaolin--pectin suspension on digoxin bioavailability. *J Pharm Sci* 1978;
1263 67(11): 1582–6. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/712596>. Accessed
1264 September 6, 2017.
- 1265 85. Albert KS *et al.* Pharmacokinetic evaluation of a drug interaction between kaolin--pectin and
1266 clindamycin. *J Pharm Sci* 1978; 67(11): 1579–82. Available at:
1267 <http://www.ncbi.nlm.nih.gov/pubmed/712595>. Accessed September 25, 2017.
- 1268 86. Albert KS *et al.* Influence of kaolin-pectin suspension on steady-state plasma digoxin levels. *J Clin*
1269 *Pharmacol* 1981; 21(10): 449–55. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/7309906>.
1270 Accessed September 25, 2017.
- 1271 87. Brown DD *et al.* Decreased Bioavailability of Digoxin Due to Antacids and Kaolin-Pectin. *N Engl J*
1272 *Med* 1976; 295(19): 1034–1037. doi:10.1056/NEJM197611042951902.
- 1273 88. Moustafa MA *et al.* Decreased bioavailability of quinidine sulphate due to interactions with

- 1274 adsorbent antacids and antidiarrhoeal mixtures. *Int J Pharm* 1987; 34(3): 207–211.
1275 doi:10.1016/0378-5173(87)90181-5.
- 1276 89. Liel Y *et al.* Evidence for a clinically important adverse effect of fiber-enriched diet on the
1277 bioavailability of levothyroxine in adult hypothyroid patients. *J Clin Endocrinol Metab* 1996; 81(2):
1278 857–859. doi:10.1210/jcem.81.2.8636317.
- 1279 90. FDA. Avoid Food and Drug Interactions. Available at:
1280 [https://www.fda.gov/downloads/drugs/resourcesforyou/consumers/buyingusingmedicinesafely/](https://www.fda.gov/downloads/drugs/resourcesforyou/consumers/buyingusingmedicinesafely/ensuringsafeuseofmedicine/generaluseofmedicine/ucm229033.pdf)
1281 [ensuringsafeuseofmedicine/generaluseofmedicine/ucm229033.pdf](https://www.fda.gov/downloads/drugs/resourcesforyou/consumers/buyingusingmedicinesafely/ensuringsafeuseofmedicine/generaluseofmedicine/ucm229033.pdf). Accessed September 6, 2017.
- 1282 91. Perlman B. Interaction between lithium salts and ispaghula husk. *Lancet* 1990; 335(8686): 416.
1283 doi:10.1016/0140-6736(90)90256-5.
- 1284 92. Stewart DE. High-fiber diet and serum tricyclic antidepressant levels. *J Clin Psychopharmacol*
1285 1992; 12(6): 438–40. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/1335461>. Accessed
1286 September 6, 2017.
- 1287 93. Brown DD *et al.* Decreased bioavailability of digoxin due to hypocholesterolemic interventions.
1288 *Circulation* 1978; 58(1): 164–72. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/647881>.
1289 Accessed January 22, 2018.
- 1290 94. Lembcke B *et al.* Plasma digoxin concentrations during administration of dietary fibre (guar gum)
1291 in man. *Z Gastroenterol* 1982; 20(3): 164–7. Available at:
1292 <http://www.ncbi.nlm.nih.gov/pubmed/6282000>. Accessed September 6, 2017.
- 1293 95. Kasper H *et al.* The effect of dietary fiber on postprandial serum digoxin concentration in man.
1294 *Am J Clin Nutr* 1979; 32(12): 2436–8. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/506966>.
1295 Accessed September 6, 2017.

- 1296 96. Huupponen R *et al.* Effect of guar gum, a fibre preparation, on digoxin and penicillin absorption in
1297 man. *Eur J Clin Pharmacol* 1984; 26(2): 279–81. Available at:
1298 <http://www.ncbi.nlm.nih.gov/pubmed/6327318>. Accessed September 6, 2017.
- 1299 97. Holt S *et al.* Effect of gel fibre on gastric emptying and absorption of glucose and paracetamol.
1300 *Lancet (London, England)* 1979; 1(8117): 636–9. Available at:
1301 <http://www.ncbi.nlm.nih.gov/pubmed/85872>. Accessed September 6, 2017.
- 1302 98. Reppas C *et al.* Effect of elevated viscosity in the upper gastrointestinal tract on drug absorption
1303 in dogs. *Eur J Pharm Sci* 1998; 6(2): 131–139. doi:10.1016/S0928-0987(97)00077-8.
- 1304 99. Astarloa R *et al.* Clinical and pharmacokinetic effects of a diet rich in insoluble fiber on Parkinson
1305 disease. *Clin Neuropharmacol* 1992; 15(5): 375–80. Available at:
1306 <http://www.ncbi.nlm.nih.gov/pubmed/1330307>. Accessed September 6, 2017.
- 1307 100. González Canga A *et al.* Dietary fiber and its interaction with drugs. *Nutr Hosp* 25(4): 535–9.
1308 Available at: <http://www.ncbi.nlm.nih.gov/pubmed/20694287>. Accessed September 6, 2017.
- 1309 101. Reppas C *et al.* Effect of hydroxypropylmethylcellulose on gastrointestinal transit and luminal
1310 viscosity in dogs. *Gastroenterology* 1991; 100(5): 1217–1223. doi:10.1016/0016-5085(91)90772-
1311 D.
- 1312 102. FDA-Emend Capsules Pharmacology Review Part 1.pdf. Available at:
1313 https://www.accessdata.fda.gov/drugsatfda_docs/nda/2003/21-549_Emend.cfm.
- 1314 103. EMA. EMEND: SUMMARY OF PRODUCT CHARACTERISTICS. Available at:
1315 [http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-
1316 _Product_Information/human/000527/WC500026537.pdf](http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Product_Information/human/000527/WC500026537.pdf). Accessed October 25, 2017.
- 1317 104. Blower P *et al.* Drug-drug interactions in oncology: Why are they important and can they be

- 1318 minimized? *Crit Rev Oncol Hematol* 2005; 55(2): 117–142. doi:10.1016/j.critrevonc.2005.03.007.
- 1319 105. Majumdar AK *et al.* Effects of aprepitant on cytochrome P450 3A4 activity using midazolam as a
1320 probe. *Clin Pharmacol Ther* 2003; 74(2): 150–156. doi:10.1016/S0009-9236(03)00123-1.
- 1321 106. Majumdar AK *et al.* Effect of aprepitant on the pharmacokinetics of intravenous midazolam. *J Clin*
1322 *Pharmacol* 2007; 47(6): 744–750. doi:10.1177/0091270007300807.
- 1323 107. McCrea JB *et al.* Effects of the neurokinin1 receptor antagonist aprepitant on the
1324 pharmacokinetics of dexamethasone and methylprednisolone. *Clin Pharmacol Ther* 2003; 74(1):
1325 17–24. doi:10.1016/S0009-9236(03)00066-3.
- 1326 108. Takaki J *et al.* Assessment of Drug–Drug Interaction between Warfarin and Aprepitant and Its
1327 Effects on PT-INR of Patients Receiving Anticancer Chemotherapy. *Biol Pharm Bull* 2016; 39(5):
1328 863–868. doi:10.1248/bpb.b16-00014.
- 1329 109. EMEND® Clinical Pharmacology and Biopharmaceutics Review. Available at:
1330 https://www.accessdata.fda.gov/drugsatfda_docs/nda/2003/21-549_Emend_biopharmr.pdf.
1331 Accessed August 31, 2017.
- 1332 110. Blower PR. Granisetron: relating pharmacology to clinical efficacy. *Support Care Cancer* 2003;
1333 11(2): 93–100. doi:10.1007/s00520-002-0410-z.
- 1334 111. Gralla RJ *et al.* Recommendations for the Use of Antiemetics: Evidence-Based, Clinical Practice
1335 Guidelines. *J Clin Oncol* 1999; 17(9): 2971–2971. doi:10.1200/JCO.1999.17.9.2971.
- 1336 112. Cagnoni PJ *et al.* Modification of the pharmacokinetics of high-dose cyclophosphamide and
1337 cisplatin by antiemetics. *Bone Marrow Transpl* 1999; 24(February 1998): 1–4.
1338 doi:10.1038/sj.bmt.1701832.
- 1339 113. Gilbert CJ *et al.* Pharmacokinetic interaction between ondansetron and cyclophosphamide during

- 1340 high-dose chemotherapy for breast cancer. *Cancer Chemother Pharmacol* 1998; 42(6): 497–503.
1341 doi:10.1007/s002800050851.
- 1342 114. Speaks M. Health United States Report 2016. 2016. Available at:
1343 <https://www.cdc.gov/nchs/data/hus/hus16.pdf#080>. Accessed August 28, 2017.
- 1344 115. 100 Best-Selling, Most Prescribed Branded Drugs Through March. Available at:
1345 http://www.medscape.com/viewarticle/844317#vp_1. Accessed August 28, 2017.
- 1346 116. Arnold R. Safety of proton pump inhibitors--an overview. *Aliment Pharmacol Ther* 1994; 8 Suppl
1347 1: 65–70. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/8180297>. Accessed August 28,
1348 2017.
- 1349 117. Blanton WP, Wolfe MM. Proton pump inhibitors. In: *Pocket Guide to Gastrointestinal Drugs*.
1350 Chichester, UK: John Wiley & Sons, Ltd, 2014: 15–30. doi:10.1002/9781118481530.ch2.
- 1351 118. Sugimoto M *et al*. Treatment strategy to eradicate *Helicobacter pylori* infection: impact of
1352 pharmacogenomics-based acid inhibition regimen and alternative antibiotics. *Expert Opin*
1353 *Pharmacother* 2007; 8(16): 2701–2717. doi:10.1517/14656566.8.16.2701.
- 1354 119. Litou C *et al*. Characteristics of the Human Upper Gastrointestinal Contents in the Fasted State
1355 Under Hypo- and A-chlorhydric Gastric Conditions Under Conditions of Typical Drug – Drug
1356 Interaction Studies. *Pharm Res* 2016; 33(6): 1399–1412. doi:10.1007/s11095-016-1882-8.
- 1357 120. Meyer UA. Interaction of proton pump inhibitors with cytochromes P450: Consequences for drug
1358 interactions. *Yale J Biol Med* 1996; 69(3): 203–209.
- 1359 121. Ogawa R, Echizen H. Drug-drug interaction profiles of proton pump inhibitors. *Clin Pharmacokinet*
1360 2010; 49(8): 509–533. doi:10.2165/11531320-000000000-00000.
- 1361 122. Lahner E *et al*. Systematic review: Impaired drug absorption related to the co-administration of

- 1362 antisecretory therapy. *Aliment Pharmacol Ther* 2009; 29(12): 1219–1229. doi:10.1111/j.1365-
1363 2036.2009.03993.x.
- 1364 123. Wedemeyer R-S, Blume H. Pharmacokinetic Drug Interaction Profiles of Proton Pump Inhibitors:
1365 An Update. *Drug Saf* 2014; 37(4): 201–211. doi:10.1007/s40264-014-0144-0.
- 1366 124. Jaruratanasirikul S, Sriwiriyan S. Effect of omeprazole on the pharmacokinetics of itraconazole.
1367 *Eur J Clin Pharmacol* 1998; 54(2): 159–61. Available at:
1368 <http://www.ncbi.nlm.nih.gov/pubmed/9626921>. Accessed August 29, 2017.
- 1369 125. Johnson MD *et al.* A randomized comparative study to determine the effect of omeprazole on the
1370 peak serum concentration of itraconazole oral solution. *J Antimicrob Chemother* 2003; 51(2):
1371 453–7. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/12562722>. Accessed September 1,
1372 2017.
- 1373 126. Chin TW *et al.* Effects of an acidic beverage (Coca-Cola) on absorption of ketoconazole.
1374 *Antimicrob Agents Chemother* 1995; 39(8): 1671–5. Available at:
1375 <http://www.ncbi.nlm.nih.gov/pubmed/7486898>. Accessed August 29, 2017.
- 1376 127. Nexium® Clinical Pharmacology and Biopharmaceutics Review. Available at:
1377 https://www.accessdata.fda.gov/drugsatfda_docs/nda/2001/21154_Nexium_biopharmr_P1.pdf.
1378 Accessed August 29, 2017.
- 1379 128. DIFLUCAN® (Fluconazole Tablets) (Fluconazole for Oral Suspension). Available at:
1380 https://www.accessdata.fda.gov/drugsatfda_docs/label/2014/019949s060,020090s044lbl.pdf.
1381 Accessed August 29, 2017.
- 1382 129. Hörter D, Dressman J. Influence of physicochemical properties on dissolution of drugs in the
1383 gastrointestinal tract. *Adv Drug Deliv Rev* 2001; 46(1–3): 75–87. doi:10.1016/S0169-

1384 409X(00)00130-7.

1385 130. Thorpe JE *et al.* Effect of Oral Antacid Administration on the Pharmacokinetics of Oral
1386 Fluconazole. *Antimicrob Agents Chemother* 1990; 34(10): 2032–3. Available at:
1387 <http://www.ncbi.nlm.nih.gov/pubmed/2291673>. Accessed August 31, 2017.

1388 131. Tappouni HL *et al.* Effect of omeprazole on the plasma concentrations of indinavir when
1389 administered alone and in combination with ritonavir. *Am J Health Syst Pharm* 2008; 65(5): 422–
1390 8. doi:10.2146/ajhp070226.

1391 132. Fang AF *et al.* Significant Decrease in Nelfinavir Systemic Exposure After Omeprazole
1392 Coadministration in Healthy Subjects. *Pharmacotherapy* 2008; 28(1): 42–50.
1393 doi:10.1592/phco.28.1.42.

1394 133. Tomilo DL *et al.* Inhibition of atazanavir oral absorption by lansoprazole gastric acid suppression
1395 in healthy volunteers. *Pharmacotherapy* 2006; 26(3): 341–346. doi:10.1592/phco.26.3.341.

1396 134. Klein CE *et al.* Effects of Acid-Reducing Agents on the Pharmacokinetics of Lopinavir/Ritonavir and
1397 Ritonavir-Boosted Atazanavir. *J Clin Pharmacol* 2008; 48(5): 553–562.
1398 doi:10.1177/0091270007313392.

1399 135. Furtek KJ *et al.* Proton pump inhibitor therapy in atazanavir-treated patients: contraindicated? *J*
1400 *Acquir Immune Defic Syndr* 2006; 41(3): 394–6. doi:10.1097/01.qai.0000192002.23400.6e.

1401 136. Sahloff EG, Duggan JM. Clinical Outcomes Associated with Concomitant Use of Atazanavir and
1402 Proton Pump Inhibitors. *Ann Pharmacother* 2006; 40(10): 1731–1736. doi:10.1345/aph.1H217.

1403 137. Winston A *et al.* Effect of omeprazole on the pharmacokinetics of saquinavir-500 mg formulation
1404 with ritonavir in healthy male and female volunteers. *AIDS* 2006; 20(10): 1401–1406.
1405 doi:10.1097/01.aids.0000233573.41597.8a.

- 1406 138. Kofler S *et al.* Proton Pump Inhibitor Co-medication Reduces Mycophenolate Acid Drug Exposure
1407 in Heart Transplant Recipients. *J Hear Lung Transplant* 2009; 28(6): 605–611.
1408 doi:10.1016/j.healun.2009.03.006.
- 1409 139. Rupprecht K *et al.* Bioavailability of Mycophenolate Mofetil and Enteric-Coated Mycophenolate
1410 Sodium Is Differentially Affected by Pantoprazole in Healthy Volunteers. *J Clin Pharmacol* 2009;
1411 49(10): 1196–1201. doi:10.1177/0091270009344988.
- 1412 140. Actonel® Clinical Pharmacology and Biopharmaceutics Review. Available at:
1413 https://www.accessdata.fda.gov/drugsatfda_docs/nda/98/20835_Actonel_biopharmr.pdf.
1414 Accessed August 29, 2017.
- 1415 141. Budha NR *et al.* Drug Absorption Interactions Between Oral Targeted Anticancer Agents and PPIs:
1416 Is pH-Dependent Solubility the Achilles Heel of Targeted Therapy? *Clin Pharmacol Ther* 2012;
1417 92(2): 203–213. doi:10.1038/clpt.2012.73.
- 1418 142. Mitra A, Kesisoglou F. Impaired drug absorption due to high stomach pH: A review of strategies
1419 for mitigation of such effect to enable pharmaceutical product development. *Mol Pharm* 2013;
1420 10(11): 3970–3979. doi:10.1021/mp400256h.
- 1421 143. Soons PA *et al.* Influence of single- and multiple-dose omeprazole treatment on nifedipine
1422 pharmacokinetics and effects in healthy subjects. *Eur J Clin Pharmacol* 1992; 42(3): 319–24.
1423 Available at: <http://www.ncbi.nlm.nih.gov/pubmed/1577051>. Accessed August 29, 2017.
- 1424 144. Bliesath H *et al.* Pantoprazole does not interact with nifedipine in man under steady-state
1425 conditions. *Int J Clin Pharmacol Ther* 1996; 34(2): 51–5. Available at:
1426 <http://www.ncbi.nlm.nih.gov/pubmed/8929746>. Accessed August 29, 2017.
- 1427 145. Zvyaga T *et al.* Evaluation of Six Proton Pump Inhibitors As Inhibitors of Various Human

- 1428 Cytochromes P450: Focus on Cytochrome P450 2C19. *Drug Metab Dispos* 2012; 40(9): 1698–
1429 1711. doi:10.1124/dmd.112.045575.
- 1430 146. Li X-Q *et al.* Comparison of inhibitory effects of the proton pump-inhibiting drugs omeprazole,
1431 esomeprazole, lansoprazole, pantoprazole, and rabeprazole on human cytochrome P450
1432 activities. *Drug Metab Dispos* 2004; 32(8): 821–7. Available at:
1433 <http://www.ncbi.nlm.nih.gov/pubmed/15258107>. Accessed January 11, 2018.
- 1434 147. Ko JW *et al.* Evaluation of omeprazole and lansoprazole as inhibitors of cytochrome P450
1435 isoforms. *Drug Metab Dispos* 1997; 25(7): 853–62. doi:10.1124/dmd.32.8.821.
- 1436 148. Blume H *et al.* Pharmacokinetic drug interaction profiles of proton pump inhibitors. *Drug Saf*
1437 2006; 29(9): 769–84. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/16944963>. Accessed
1438 January 18, 2018.
- 1439 149. Suzuki K *et al.* Co-administration of proton pump inhibitors delays elimination of plasma
1440 methotrexate in high-dose methotrexate therapy. *Br J Clin Pharmacol* 2009; 67(1): 44–49.
1441 doi:10.1111/j.1365-2125.2008.03303.x.
- 1442 150. Drug Safety and Availability - FDA reminder to avoid concomitant use of Plavix (clopidogrel) and
1443 omeprazole. Available at: <https://www.fda.gov/Drugs/DrugSafety/ucm231161.htm>. Accessed
1444 August 29, 2017.
- 1445 151. Stockl KM *et al.* Risk of Rehospitalization for Patients Using Clopidogrel With a Proton Pump
1446 Inhibitor. *Arch Intern Med* 2010; 170(8): 704. doi:10.1001/archinternmed.2010.34.
- 1447 152. Evanchan J *et al.* Recurrence of Acute Myocardial Infarction in Patients Discharged on Clopidogrel
1448 and a Proton Pump Inhibitor After Stent Placement for Acute Myocardial Infarction. *Clin Cardiol*
1449 2010; 33(3): 168–171. doi:10.1002/clc.20721.

- 1450 153. Gaglia MA *et al.* Relation of Proton Pump Inhibitor Use After Percutaneous Coronary Intervention
1451 With Drug-Eluting Stents to Outcomes. *Am J Cardiol* 2010; 105(6): 833–838.
1452 doi:10.1016/j.amjcard.2009.10.063.
- 1453 154. Chua D *et al.* Clopidogrel and proton pump inhibitors: a new drug interaction? *Can J Hosp Pharm*
1454 2010; 63(1): 47–50. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/22478955>. Accessed
1455 January 11, 2018.
- 1456 155. Bundhun PK *et al.* Is the concomitant use of clopidogrel and Proton Pump Inhibitors still
1457 associated with increased adverse cardiovascular outcomes following coronary angioplasty?: a
1458 systematic review and meta-analysis of recently published studies (2012 - 2016). *BMC Cardiovasc*
1459 *Disord* 2017; 17(1): 3. doi:10.1186/s12872-016-0453-6.
- 1460 156. Sugano K. Histamine H₂-receptor antagonists. In: *Pocket Guide to Gastrointestinal Drugs*.
1461 Chichester, UK: John Wiley & Sons, Ltd, 2014: 31–43. doi:10.1002/9781118481530.ch3.
- 1462 157. Piscitelli SC *et al.* Effects of Ranitidine and Sucralfate on Ketoconazole Bioavailability. *Antimicrob*
1463 *Agents Chemother* 1991; 35(9): 1765–1771. Available at:
1464 <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC245265/pdf/aac00053-0099.pdf>. Accessed
1465 August 30, 2017.
- 1466 158. LIM SG *et al.* Short report: the absorption of fluconazole and itraconazole under conditions of low
1467 intragastric acidity. *Aliment Pharmacol Ther* 2007; 7(3): 317–321. doi:10.1111/j.1365-
1468 2036.1993.tb00103.x.
- 1469 159. Blum RA *et al.* Increased gastric pH and the bioavailability of fluconazole and ketoconazole. *Ann*
1470 *Intern Med* 1991; 114(9): 755–7. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/2012358>.
1471 Accessed August 30, 2017.

- 1472 160. Ford SL *et al.* Effect of Antacids and Ranitidine on the Single-Dose Pharmacokinetics of
1473 Fosamprenavir. *Antimicrob Agents Chemother* 2005; 49(1): 467–469. doi:10.1128/AAC.49.1.467–
1474 469.2005.
- 1475 161. Boffito M *et al.* Pharmacokinetics of saquinavir co-administered with cimetidine. *J Antimicrob*
1476 *Chemother* 2002; 50(6): 1081–4. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/12461038>.
1477 Accessed August 30, 2017.
- 1478 162. Russell TL *et al.* pH-Related Changes in the Absorption of Dipyridamole in the Elderly. *Pharm Res*
1479 1994; 11(1): 136–143. doi:10.1023/A:1018918316253.
- 1480 163. Grasela TH *et al.* Inhibition of enoxacin absorption by antacids or ranitidine. *Antimicrob Agents*
1481 *Chemother* 1989; 33(5): 615–7. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/2751276>.
1482 Accessed August 30, 2017.
- 1483 164. Hughes GS *et al.* The effects of gastric pH and food on the pharmacokinetics of a new oral
1484 cephalosporin, cefpodoxime proxetil. *Clin Pharmacol Ther* 1989; 46(6): 674–85. Available at:
1485 <http://www.ncbi.nlm.nih.gov/pubmed/2557183>. Accessed August 30, 2017.
- 1486 165. Gerber MC *et al.* Drug interactions with cimetidine: an update. *Pharmacol Ther* 1985; 27(3): 353–
1487 70. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/2864708>. Accessed May 23, 2018.
- 1488 166. Berardi RR *et al.* Comparison of famotidine with cimetidine and ranitidine. *Clin Pharm* 1988; 7(4):
1489 271–84. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/2896559>. Accessed May 23, 2018.
- 1490 167. O’Reilly RA. Comparative interaction of cimetidine and ranitidine with racemic warfarin in man.
1491 *Arch Intern Med* 1984; 144(5): 989–91. Available at:
1492 <http://www.ncbi.nlm.nih.gov/pubmed/6324710>. Accessed May 23, 2018.
- 1493 168. Toon S *et al.* Comparative effects of ranitidine and cimetidine on the pharmacokinetics and

- 1494 pharmacodynamics of warfarin in man. *Eur J Clin Pharmacol* 1987; 32(2): 165–72. Available at:
1495 <http://www.ncbi.nlm.nih.gov/pubmed/3582481>. Accessed May 23, 2018.
- 1496 169. Niopas I *et al.* The effect of cimetidine on the steady-state pharmacokinetics and
1497 pharmacodynamics of warfarin in humans. *Eur J Clin Pharmacol* 1999; 55(5): 399–404. Available
1498 at: <http://www.ncbi.nlm.nih.gov/pubmed/10456491>. Accessed May 23, 2018.
- 1499 170. Reimann IW *et al.* Cimetidine increases steady state plasma levels of propranolol. *Br J Clin*
1500 *Pharmacol* 1981; 12(6): 785–90. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/7340880>.
1501 Accessed May 23, 2018.
- 1502 171. Reimann IW *et al.* Effects of cimetidine and ranitidine on steady-state propranolol kinetics and
1503 dynamics. *Clin Pharmacol Ther* 1982; 32(6): 749–757. doi:10.1038/clpt.1982.232.
- 1504 172. Medicines.org.uk. (2018). Propranolol film-coated tablets- Patient Information Leaflet (PIL) -
1505 (eMC). Available at: <https://www.medicines.org.uk/emc/files/pil.2904.pdf>. Accessed June 3,
1506 2018.
- 1507 173. Cornard J., Merlin J. Spectroscopic and structural study of complexes of quercetin with Al(III). *J*
1508 *Inorg Biochem* 2002; 92(1): 19–27. doi:10.1016/S0162-0134(02)00469-5.
- 1509 174. Türkel N *et al.* Potentiometric and spectroscopic studies on aluminium(III) complexes of some
1510 catechol derivatives. *Chem Pharm Bull (Tokyo)* 2004; 52(8): 929–34. Available at:
1511 <http://www.ncbi.nlm.nih.gov/pubmed/15304983>. Accessed August 31, 2017.
- 1512 175. Khan MA *et al.* Differential binding of tetracyclines with serum albumin and induced structural
1513 alterations in drug-bound protein. *Int J Biol Macromol* 2002; 30(5): 243–9. Available at:
1514 <http://www.ncbi.nlm.nih.gov/pubmed/12297231>. Accessed August 31, 2017.
- 1515 176. Córdoba-Díaz M *et al.* Modification of fluorescent properties of norfloxacin in the presence of

- 1516 certain antacids. *J Pharm Biomed Anal* 1998; 18(4–5): 565–71. Available at:
1517 <http://www.ncbi.nlm.nih.gov/pubmed/9919956>. Accessed August 31, 2017.
- 1518 177. Deppermann KM *et al.* Influence of ranitidine, pirenzepine, and aluminum magnesium hydroxide
1519 on the bioavailability of various antibiotics, including amoxicillin, cephalexin, doxycycline, and
1520 amoxicillin-clavulanic acid. *Antimicrob Agents Chemother* 1989; 33(11): 1901–7. Available at:
1521 <http://www.ncbi.nlm.nih.gov/pubmed/2610502>. Accessed August 31, 2017.
- 1522 178. Garty M, Hurwitz A. Effect of cimetidine and antacids on gastrointestinal absorption of
1523 tetracycline. *Clin Pharmacol Ther* 1980; 28(2): 203–7. Available at:
1524 <http://www.ncbi.nlm.nih.gov/pubmed/7398187>. Accessed August 31, 2017.
- 1525 179. Timmers K, Sternglanz R. Ionization and divalent cation dissociation constants of nalidixic and
1526 oxolinic acids. *Bioinorg Chem* 1978; 9(2): 145–55. Available at:
1527 <http://www.ncbi.nlm.nih.gov/pubmed/698279>. Accessed August 31, 2017.
- 1528 180. Radandt JM *et al.* Interactions of fluoroquinolones with other drugs: mechanisms, variability,
1529 clinical significance, and management. *Clin Infect Dis* 1992; 14(1): 272–84. Available at:
1530 <http://www.ncbi.nlm.nih.gov/pubmed/1571442>. Accessed August 31, 2017.
- 1531 181. Nix DE *et al.* Effects of aluminum and magnesium antacids and ranitidine on the absorption of
1532 ciprofloxacin. *Clin Pharmacol Ther* 1989; 46(6): 700–5. Available at:
1533 <http://www.ncbi.nlm.nih.gov/pubmed/2598571>. Accessed August 31, 2017.
- 1534 182. Grasela TH *et al.* Inhibition of enoxacin absorption by antacids or ranitidine. *Antimicrob Agents*
1535 *Chemother* 1989; 33(5): 615–7. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/2751276>.
1536 Accessed August 31, 2017.
- 1537 183. Krishna G *et al.* Effect of an Aluminum- and Magnesium-Containing Antacid on the Bioavailability

1538 of Garenoxacin in Healthy Volunteers. *Pharmacotherapy* 2007; 27(7): 963–969.
1539 doi:10.1592/phco.27.7.963.

1540 184. Lober S *et al.* Pharmacokinetics of gatifloxacin and interaction with an antacid containing
1541 aluminum and magnesium. *Antimicrob Agents Chemother* 1999; 43(5): 1067–71. Available at:
1542 <http://www.ncbi.nlm.nih.gov/pubmed/10223915>. Accessed August 31, 2017.

1543 185. Allen A *et al.* Effect of Maalox on the bioavailability of oral gemifloxacin in healthy volunteers.
1544 *Chemotherapy* 1999; 45(6): 504–11. Available at:
1545 <http://www.ncbi.nlm.nih.gov/pubmed/10567782>. Accessed September 1, 2017.

1546 186. Lohitnavy M *et al.* Reduced oral itraconazole bioavailability by antacid suspension. *J Clin Pharm*
1547 *Ther* 2005; 30(3): 201–206. doi:10.1111/j.1365-2710.2005.00632.x.

1548 187. Brass C *et al.* Disposition of ketoconazole, an oral antifungal, in humans. *Antimicrob Agents*
1549 *Chemother* 1982; 21(1): 151–8. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/6282204>.
1550 Accessed August 31, 2017.

1551 188. Neuvonen PJ. The effect of magnesium hydroxide on the oral absorption of ibuprofen, ketoprofen
1552 and diclofenac. *Br J Clin Pharmacol* 1991; 31(3): 263–6. Available at:
1553 <http://www.ncbi.nlm.nih.gov/pubmed/2054265>. Accessed August 31, 2017.

1554 189. Tobert JA *et al.* Effect of antacids on the bioavailability of diflunisal in the fasting and postprandial
1555 states. *Clin Pharmacol Ther* 1981; 30(3): 385–9. Available at:
1556 <http://www.ncbi.nlm.nih.gov/pubmed/7023791>. Accessed August 31, 2017.

1557 190. Neuvonen PJ, Kivistö KT. Effect of magnesium hydroxide on the absorption of tolfenamic and
1558 mefenamic acids. *Eur J Clin Pharmacol* 1988; 35(5): 495–501. Available at:
1559 <http://www.ncbi.nlm.nih.gov/pubmed/3266151>. Accessed August 31, 2017.

- 1560 191. Segre EJ *et al.* Transport of Organic Acids across Cell Membrane. *N Engl J Med* 1974; 291(11):
1561 582–582. doi:10.1056/NEJM197409122911115.
- 1562 192. Ogawa R, Echizen H. Clinically significant drug interactions with antacids: An update. *Drugs* 2011;
1563 71(14): 1839–1864. doi:10.2165/11593990-000000000-00000.
- 1564 193. Gareau MG *et al.* Probiotics and the gut microbiota in intestinal health and disease. *Nat Rev*
1565 *Gastroenterol Hepatol* 2010; 7(9): 503–514. doi:10.1038/nrgastro.2010.117.
- 1566 194. Guidelines for the Evaluation of Probiotics in Food Report. Joint FAO/WHO Working Group Report
1567 on Drafting Guidelines for the Evaluation of Probiotics in Food. 2002. Available at:
1568 http://www.who.int/foodsafety/fs_management/en/probiotic_guidelines.pdf. Accessed
1569 September 5, 2017.
- 1570 195. Westendorf AM *et al.* Intestinal immunity of *Escherichia coli* NISSLE 1917: a safe carrier for
1571 therapeutic molecules. *FEMS Immunol Med Microbiol* 2005; 43(3): 373–384.
1572 doi:10.1016/j.femsim.2004.10.023.
- 1573 196. Resta-Lenert SC, Barrett KE. Modulation of intestinal barrier properties by probiotics: Role in
1574 reversing colitis. *Ann N Y Acad Sci* 2009; 1165: 175–182. doi:10.1111/j.1749-6632.2009.04042.x.
- 1575 197. Mikov M *et al.* The influence of probiotic treatment on sulfasalazine metabolism in rat gut
1576 contents. *Asian J Pharmacodyn Pharmacokinet Pap ID 1608*. Available at:
1577 [https://www.researchgate.net/profile/Momir_Mikov2/publication/237720727_The_influence_of](https://www.researchgate.net/profile/Momir_Mikov2/publication/237720727_The_influence_of_probiotic_treatment_on_sulfasalazine_metabolism_in_rat_gut_contents/links/0046352780e4b5d364000000.pdf)
1578 [_probiotic_treatment_on_sulfasalazine_metabolism_in_rat_gut_contents/links/0046352780e4b](https://www.researchgate.net/profile/Momir_Mikov2/publication/237720727_The_influence_of_probiotic_treatment_on_sulfasalazine_metabolism_in_rat_gut_contents/links/0046352780e4b5d364000000.pdf)
1579 [5d36400000.pdf](https://www.researchgate.net/profile/Momir_Mikov2/publication/237720727_The_influence_of_probiotic_treatment_on_sulfasalazine_metabolism_in_rat_gut_contents/links/0046352780e4b5d364000000.pdf). Accessed September 5, 2017.
- 1580 198. Lee HJ *et al.* The influence of probiotic treatment on sulfasalazine metabolism in rat. *Xenobiotica*
1581 2012; 42(8): 791–797. doi:10.3109/00498254.2012.660508.

- 1582 199. Kunes M *et al.* Absorption kinetics of 5-aminosalicylic acid in rat: influence of indomethacin-
1583 induced gastrointestinal lesions and Escherichia Coli Nissle 1917 medication. *Neuro Endocrinol*
1584 *Lett* 2011; 32 Suppl 1: 46–52. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/22167206>.
1585 Accessed September 5, 2017.
- 1586 200. Al-Salami H *et al.* Probiotic treatment reduces blood glucose levels and increases systemic
1587 absorption of gliclazide in diabetic rats. *Eur J Drug Metab Pharmacokinet* 2008; 33(2): 101–106.
1588 doi:10.1007/BF03191026.
- 1589 201. Saksena S *et al.* Upregulation of P-glycoprotein by probiotics in intestinal epithelial cells and in the
1590 dextran sulfate sodium model of colitis in mice. *AJP Gastrointest Liver Physiol* 2011; 300(6):
1591 G1115–G1123. doi:10.1152/ajpgi.00027.2011.
- 1592 202. Matuskova Z *et al.* Administration of a probiotic can change drug pharmacokinetics: Effect of E.
1593 coli Nissle 1917 on amidarone absorption in rats. *PLoS One* 2014; 9(2): 3–7.
1594 doi:10.1371/journal.pone.0087150.
- 1595 203. Fröhlich EE *et al.* Cognitive impairment by antibiotic-induced gut dysbiosis: Analysis of gut
1596 microbiota-brain communication. *Brain Behav Immun* 2016; 56: 140–55.
1597 doi:10.1016/j.bbi.2016.02.020.
- 1598 204. Sullivan Å *et al.* Effect of antimicrobial agents on the ecological balance of human microflora.
1599 *Lancet Infect Dis* 2001; 1(2): 101–114. doi:10.1016/S1473-3099(01)00066-4.
- 1600 205. Edlund C, Nord CE. Effect on the human normal microflora of oral antibiotics for treatment of
1601 urinary tract infections. *J Antimicrob Chemother* 2000; 46 Suppl 1: 41-8; discussion 63–5.
1602 Available at: <http://www.ncbi.nlm.nih.gov/pubmed/11051623>. Accessed September 28, 2017.
- 1603 206. Beaugerie L, Petit J-C. Antibiotic-associated diarrhoea. *Best Pract Res Clin Gastroenterol* 2004;

- 1604 18(2): 337–352. doi:10.1016/j.bpg.2003.10.002.
- 1605 207. Tremaroli V, Bäckhed F. Functional interactions between the gut microbiota and host metabolism.
1606 *Nature* 2012; 489(7415): 242–249. doi:10.1038/nature11552.
- 1607 208. Clausen MR *et al.* Colonic fermentation to short-chain fatty acids is decreased in antibiotic-
1608 associated diarrhea. *Gastroenterology* 1991; 101(6): 1497–504. Available at:
1609 <http://www.ncbi.nlm.nih.gov/pubmed/1955116>. Accessed September 25, 2017.
- 1610 209. Edwards CA *et al.* Effect of clindamycin on the ability of a continuous culture of colonic bacteria to
1611 ferment carbohydrate. *Gut* 1986; 27(4): 411–7. Available at:
1612 <http://www.ncbi.nlm.nih.gov/pubmed/3514388>. Accessed September 25, 2017.
- 1613 210. Gustafsson A *et al.* Faecal short-chain fatty acids in patients with antibiotic-associated diarrhoea,
1614 before and after faecal enema treatment. *Scand J Gastroenterol* 1998; 33(7): 721–7. Available at:
1615 <http://www.ncbi.nlm.nih.gov/pubmed/9712236>. Accessed September 25, 2017.
- 1616 211. Mellon AF *et al.* Effect of oral antibiotics on intestinal production of propionic acid. *Arch Dis Child*
1617 2000; 82(2): 169–72. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/10648377>. Accessed
1618 September 25, 2017.
- 1619 212. Høverstad T *et al.* Influence of oral intake of seven different antibiotics on faecal short-chain fatty
1620 acid excretion in healthy subjects. *Scand J Gastroenterol* 1986; 21(8): 997–1003. Available at:
1621 <http://www.ncbi.nlm.nih.gov/pubmed/3775265>. Accessed September 25, 2017.
- 1622 213. Kamath PS *et al.* Short-chain fatty acids stimulate ileal motility in humans. *Gastroenterology* 1988;
1623 95(6): 1496–502. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/3181675>. Accessed
1624 September 25, 2017.
- 1625 214. Fich A *et al.* Stimulation of ileal emptying by short-chain fatty acids. *Dig Dis Sci* 1989; 34(10):

- 1626 1516–20. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/2791802>. Accessed September 25,
1627 2017.
- 1628 215. Aguilera M *et al.* Antibiotic-induced dysbiosis alters host-bacterial interactions and leads to
1629 colonic sensory and motor changes in mice. *Gut Microbes* 2015; 6(1): 10–23.
1630 doi:10.4161/19490976.2014.990790.
- 1631 216. Cherbut C *et al.* Effects of Short-Chain Fatty Acids on Gastrointestinal Motility. *Scand J*
1632 *Gastroenterol* 1997; 32(sup222): 58–61. doi:10.1080/00365521.1997.11720720.
- 1633 217. Edelbroek MA *et al.* Effects of erythromycin on gastric emptying, alcohol absorption and small
1634 intestinal transit in normal subjects. *J Nucl Med* 1993; 34(4): 582–8. Available at:
1635 <http://www.ncbi.nlm.nih.gov/pubmed/8455074>. Accessed September 25, 2017.
- 1636 218. Mantides A *et al.* The effect of erythromycin in gastric emptying of solids and hypertonic liquids in
1637 healthy subjects. *Am J Gastroenterol* 1993; 88(2): 198–202. Available at:
1638 <http://www.ncbi.nlm.nih.gov/pubmed/8424420>. Accessed September 25, 2017.
- 1639 219. Landry C *et al.* Effects of erythromycin on gastric emptying, duodeno-caecal transit time, gastric
1640 and biliopancreatic secretion during continuous gastric infusion of a liquid diet in healthy
1641 volunteers. *Eur J Gastroenterol Hepatol* 1995; 7(8): 797–802. Available at:
1642 <http://www.ncbi.nlm.nih.gov/pubmed/7496872>. Accessed September 25, 2017.
- 1643 220. Caron F *et al.* Effects of two oral erythromycin ethylsuccinate formulations on the motility of the
1644 small intestine in human beings. *Antimicrob Agents Chemother* 1996; 40(8): 1796–800. Available
1645 at: <http://www.ncbi.nlm.nih.gov/pubmed/8843283>. Accessed September 25, 2017.
- 1646 221. Annese V *et al.* Erythromycin accelerates gastric emptying by inducing antral contractions and
1647 improved gastroduodenal coordination. *Gastroenterology* 1992; 102(3): 823–8. Available at:

- 1648 <http://www.ncbi.nlm.nih.gov/pubmed/1537520>. Accessed September 25, 2017.
- 1649 222. Leung WK *et al.* Effect of oral erythromycin on gastric and small bowel transit time of capsule
1650 endoscopy. *World J Gastroenterol* 2005; 11(31): 4865–8. Available at:
1651 <http://www.ncbi.nlm.nih.gov/pubmed/16097060>. Accessed September 25, 2017.
- 1652 223. Chew ML *et al.* Effect of the gastrointestinal prokinetic agent erythromycin on the
1653 pharmacokinetics of pregabalin controlled-release in healthy individuals: a phase I, randomized
1654 crossover trial. *Clin Drug Investig* 2015; 35(5): 299–305. doi:10.1007/s40261-015-0281-y.
- 1655 224. Sousa T *et al.* The gastrointestinal microbiota as a site for the biotransformation of drugs. *Int J*
1656 *Pharm* 2008; 363(1–2): 1–25. doi:10.1016/j.ijpharm.2008.07.009.
- 1657 225. Saad R *et al.* Gut Pharmacomicrobiomics: the tip of an iceberg of complex interactions between
1658 drugs and gut-associated microbes. *Gut Pathog* 2012; 4(1): 16. doi:10.1186/1757-4749-4-16.
- 1659 226. Lindenbaum J *et al.* Inactivation of Digoxin by the Gut Flora: Reversal by Antibiotic Therapy. *N*
1660 *Engl J Med* 1981; 305(14): 789–794. doi:10.1056/NEJM198110013051403.
- 1661 227. Morton MR, Cooper JW. Erythromycin-induced digoxin toxicity. *DICP* 1989; 23(9): 668–70.
1662 Available at: <http://www.ncbi.nlm.nih.gov/pubmed/2800579>. Accessed September 28, 2017.
- 1663 228. Vermes A *et al.* An in vitro study on the active conversion of flucytosine to fluorouracil by
1664 microorganisms in the human intestinal microflora. *Chemotherapy* 2003; 49(1–2): 17–23.
1665 doi:69784.
- 1666 229. Houston JB *et al.* Azo reduction of sulphasalazine in healthy volunteers. *Br J Clin Pharmacol* 1982;
1667 14(3): 395–8. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/6127096>. Accessed May 28,
1668 2018.
- 1669 230. Singh SK *et al.* A novel dissolution method for evaluation of polysaccharide based colon specific

- 1670 delivery systems: A suitable alternative to animal sacrifice. *Eur J Pharm Sci* 2015; 73: 72–80.
1671 doi:10.1016/J.EJPS.2015.03.012.
- 1672 231. Hofmann AF, Hagey LR. Bile Acids: Chemistry, Pathochemistry, Biology, Pathobiology, and
1673 Therapeutics. *Cell Mol Life Sci* 2008; 65(16): 2461–2483. doi:10.1007/s00018-008-7568-6.
- 1674 232. Brestoff JR, Artis D. Commensal bacteria at the interface of host metabolism and the immune
1675 system. *Nat Immunol* 2013; 14(7): 676–684. doi:10.1038/ni.2640.
- 1676 233. Vrieze A *et al.* Impact of oral vancomycin on gut microbiota, bile acid metabolism, and insulin
1677 sensitivity. *J Hepatol* 2014; 60(4): 824–831. doi:10.1016/j.jhep.2013.11.034.
- 1678 234. Söderlind E *et al.* Simulating Fasted Human Intestinal Fluids: Understanding the Roles of Lecithin
1679 and Bile Acids. *Mol Pharm* 2010; 7(5): 1498–1507. doi:10.1021/mp100144v.
- 1680 235. von Rosensteil NA, Adam D. Macrolide antibacterials. Drug interactions of clinical significance.
1681 *Drug Saf* 1995; 13(2): 105–22. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/7576262>.
1682 Accessed May 30, 2018.
- 1683 236. Olkkola KT *et al.* A potentially hazardous interaction between erythromycin and midazolam. *Clin*
1684 *Pharmacol Ther* 1993; 53(3): 298–305. Available at:
1685 <http://www.ncbi.nlm.nih.gov/pubmed/8453848>. Accessed May 30, 2018.
- 1686 237. Gorski JC *et al.* The contribution of intestinal and hepatic CYP3A to the interaction between
1687 midazolam and clarithromycin. *Clin Pharmacol Ther* 1998; 64(2): 133–143. doi:10.1016/S0009-
1688 9236(98)90146-1.
- 1689 238. Yeates RA *et al.* Interaction between midazolam and clarithromycin: comparison with
1690 azithromycin. *Int J Clin Pharmacol Ther* 1996; 34(9): 400–5. Available at:
1691 <http://www.ncbi.nlm.nih.gov/pubmed/8880291>. Accessed May 30, 2018.

- 1692 239. Douros A *et al.* Safety issues and drug–drug interactions with commonly used quinolones. *Expert*
1693 *Opin Drug Metab Toxicol* 2014; 11(1): 1–15. doi:10.1517/17425255.2014.970166.
- 1694 240. Beckmann J *et al.* Enoxacin--a potent inhibitor of theophylline metabolism. *Eur J Clin Pharmacol*
1695 1987; 33(3): 227–30. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/3480222>. Accessed May
1696 30, 2018.
- 1697 241. Batty KT *et al.* The effect of ciprofloxacin on theophylline pharmacokinetics in healthy subjects. *Br*
1698 *J Clin Pharmacol* 1995; 39(3): 305–11. Available at:
1699 <http://www.ncbi.nlm.nih.gov/pubmed/7619673>. Accessed May 30, 2018.
- 1700 242. Bowles SK *et al.* Effect of norfloxacin on theophylline pharmacokinetics at steady state.
1701 *Antimicrob Agents Chemother* 1988; 32(4): 510–2. Available at:
1702 <http://www.ncbi.nlm.nih.gov/pubmed/3377462>. Accessed May 30, 2018.
- 1703 243. Pai MP *et al.* Antibiotic Drug Interactions. *Med Clin North Am* 2006; 90(6): 1223–1255.
1704 doi:10.1016/j.mcna.2006.06.008.
- 1705 244. Rao SS *et al.* Influence of Olsalazine and Sulphasalazine on Gastrointestinal Transit Influence of
1706 Olsalazine and Sulphasalazine on Gastrointestinal Transit. *Scand J Gastroenterol* 1988; 23: 148–
1707 96. doi:10.3109/00365528809101560.
- 1708 245. Rao SS *et al.* Influence of olsalazine on gastrointestinal transit in ulcerative colitis. *Gut* 1987;
1709 28(11): 1474–7. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/3428673>. Accessed
1710 September 28, 2017.
- 1711 246. Staniforth DH. Comparison of oro-caecal transit times assessed by the lactulose/breath hydrogen
1712 and the sulphasalazine/sulphapyridine methods. *Gut* 1989; 30(7): 978–82. Available at:
1713 <http://www.ncbi.nlm.nih.gov/pubmed/2569435>. Accessed September 28, 2017.

- 1714 247. Raimundo A *et al.* Gastrointestinal pH profiles in ulcerative colitis. *Gastroenterology* 1992;
1715 4(A681).
- 1716 248. Nugent SG *et al.* Intestinal luminal pH in inflammatory bowel disease: possible determinants and
1717 implications for therapy with aminosalicylates and other drugs. *Gut* 2001; 48(4): 571–7. Available
1718 at: <http://www.ncbi.nlm.nih.gov/pubmed/11247905>. Accessed May 28, 2018.
- 1719 249. Raimundo AH *et al.* Effects of olsalazine and sulphasalazine on jejunal and ileal water and
1720 electrolyte absorption in normal human subjects. *Gut* 1991; 32(3): 270–4. Available at:
1721 <http://www.ncbi.nlm.nih.gov/pubmed/1672860>. Accessed September 28, 2017.
- 1722 250. Sandberg-Gertzén H *et al.* Azodisal sodium in the treatment of ulcerative colitis. A study of
1723 tolerance and relapse-prevention properties. *Gastroenterology* 1986; 90(4): 1024–30. Available
1724 at: <http://www.ncbi.nlm.nih.gov/pubmed/2868964>. Accessed September 28, 2017.
- 1725 251. Zimmerman J. Drug interactions in intestinal transport of folic acid and methotrexate. Further
1726 evidence for the heterogeneity of folate transport in the human small intestine. *Biochem*
1727 *Pharmacol* 1992; 44(9): 1839–42. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/1360212>.
1728 Accessed May 28, 2018.
- 1729 252. Okada M *et al.* Drug interaction between methotrexate and salazosulfapyridine in Japanese
1730 patients with rheumatoid arthritis. *J Pharm Heal care Sci* 2017; 3: 7. doi:10.1186/s40780-017-
1731 0073-z.
- 1732 253. Kanerud L *et al.* Effect of sulphasalazine on gastrointestinal microflora and on mucosal heat shock
1733 protein expression in patients with rheumatoid arthritis. *Br J Rheumatol* 1994; 33(11): 1039–48.
1734 Available at: <http://www.ncbi.nlm.nih.gov/pubmed/7981991>. Accessed September 28, 2017.
- 1735 254. Neumann VC *et al.* Effects of sulphasalazine on faecal flora in patients with rheumatoid arthritis: a

- 1736 comparison with penicillamine. *Br J Rheumatol* 1987; 26(5): 334–7. Available at:
1737 <http://www.ncbi.nlm.nih.gov/pubmed/2889501>. Accessed September 28, 2017.
- 1738 255. Bradley SM *et al.* Sequential study of bacterial antibody levels and faecal flora in rheumatoid
1739 arthritis patients taking sulphasalazine. *Br J Rheumatol* 1993; 32(8): 683–8. Available at:
1740 <http://www.ncbi.nlm.nih.gov/pubmed/8102304>. Accessed September 28, 2017.
- 1741 256. Xue L *et al.* The possible effects of mesalazine on the intestinal microbiota. *Aliment Pharmacol*
1742 *Ther* 2012; 36(8): 813–814. doi:10.1111/apt.12034.
- 1743 257. Andrews CN *et al.* Mesalazine (5-aminosalicylic acid) alters faecal bacterial profiles, but not
1744 mucosal proteolytic activity in diarrhoea-predominant irritable bowel syndrome. *Aliment*
1745 *Pharmacol Ther* 2011; 34(3): 374–383. doi:10.1111/j.1365-2036.2011.04732.x.
- 1746 258. Juhl RP *et al.* Effect of sulfasalazine on digoxin bioavailability. *Clin Pharmacol Ther* 1976; 20(4):
1747 387–394. doi:10.1002/cpt1976204387.
- 1748 259. Marcus FI. Pharmacokinetic interactions between digoxin and other drugs. *J Am Coll Cardiol* 1985;
1749 5(5 Suppl A): 82A–90A. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/2985676>. Accessed
1750 September 28, 2017.
- 1751 260. Haiser HJ *et al.* Mechanistic insight into digoxin inactivation by *Eggerthella lenta* augments our
1752 understanding of its pharmacokinetics. *Gut Microbes* 2014; 5(2): 233–238.
1753 doi:10.4161/gmic.27915.
- 1754 261. Juhl RP *et al.* Effect of sulfasalazine on digoxin bioavailability. *Clin Pharmacol Ther* 1976; 20(4):
1755 387–94. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/10123>. Accessed May 28, 2018.
- 1756 262. Du Cheyron D *et al.* Effect of sulfasalazine on cyclosporin blood concentration. *Eur J Clin*
1757 *Pharmacol* 1999; 55(3): 227–228. doi:10.1007/s002280050622.

- 1758 263. Lewis LD *et al.* Olsalazine and 6-mercaptopurine-related bone marrow suppression: A possible
1759 drug-drug interaction. *Clin Pharmacol Ther* 1997; 62(4): 464–475. doi:10.1016/S0009-
1760 9236(97)90125-9.
- 1761 264. Lowry PW *et al.* Balsalazide and azathioprine or 6-mercaptopurine: evidence for a potentially
1762 serious drug interaction. *Gastroenterology* 1999; 116(6): 1505–6. Available at:
1763 <http://www.ncbi.nlm.nih.gov/pubmed/10391741>. Accessed May 28, 2018.
- 1764 265. Bengmark S, Jeppsson B. Gastrointestinal Surface Protection and Mucosa Reconditioning. *J*
1765 *Parenter Enter Nutr* 1995; 19(5): 410–415. doi:10.1177/0148607195019005410.
- 1766 266. Narum S *et al.* Corticosteroids and risk of gastrointestinal bleeding: a systematic review and meta-
1767 analysis. *BMJ Open* 2014; 4(5): e004587. doi:10.1136/bmjopen-2013-004587.
- 1768 267. Jung D *et al.* Human ileal bile acid transporter gene ASBT (SLC10A2) is transactivated by the
1769 glucocorticoid receptor. *Gut* 2004; 53(1): 78–84. Available at:
1770 <http://www.ncbi.nlm.nih.gov/pubmed/14684580>. Accessed September 28, 2017.
- 1771 268. BAJOR A *et al.* Budesonide treatment is associated with increased bile acid absorption in
1772 collagenous colitis. *Aliment Pharmacol Ther* 2006; 24(11–12): 1643–1649. doi:10.1111/j.1365-
1773 2036.2006.03168.x.
- 1774 269. Fleisher D *et al.* Drug, Meal and Formulation Interactions Influencing Drug Absorption After Oral
1775 Administration. *Clin Pharmacokinet* 1999; 36(3): 233–254. doi:10.2165/00003088-199936030-
1776 00004.
- 1777 270. Dilger K *et al.* Identification of budesonide and prednisone as substrates of the intestinal drug
1778 efflux pump P-glycoprotein. *Inflamm Bowel Dis* 2004; 10(5): 578–83. Available at:
1779 <http://www.ncbi.nlm.nih.gov/pubmed/15472518>. Accessed September 28, 2017.

- 1780 271. Schwab M, Klotz U. Pharmacokinetic Considerations in the Treatment of Inflammatory Bowel
1781 Disease. *Clin Pharmacokinet* 2001; 40(10): 723–751. doi:10.2165/00003088-200140100-00003.
- 1782 272. Eradiri O *et al.* Interaction of metronidazole with phenobarbital, cimetidine, prednisone, and
1783 sulfasalazine in Crohn’s disease. *Biopharm Drug Dispos* 9(2): 219–27. Available at:
1784 <http://www.ncbi.nlm.nih.gov/pubmed/2897213>. Accessed June 18, 2018.
- 1785 273. Koren G *et al.* Corticosteroids-salicylate interaction in a case of juvenile rheumatoid arthritis. *Ther*
1786 *Drug Monit* 1987; 9(2): 177–9. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/3617157>.
1787 Accessed September 28, 2017.
- 1788 274. Seidegård J. Reduction of the inhibitory effect of ketoconazole on budesonide pharmacokinetics
1789 by separation of their time of administration. *Clin Pharmacol Ther* 2000; 68(1): 13–17.
1790 doi:10.1067/mcp.2000.106895.
- 1791 275. RAASKA K *et al.* Plasma concentrations of inhaled budesonide and its effects on plasma cortisol
1792 are increased by the cytochrome P4503A4 inhibitor itraconazole. *Clin Pharmacol Ther* 2002;
1793 72(4): 362–369. doi:10.1067/mcp.2002.127397.
- 1794 276. De Wachter E *et al.* Inhaled budesonide induced Cushing’s syndrome in cystic fibrosis patients,
1795 due to drug inhibition of cytochrome P450. *J Cyst Fibros* 2003; 2(2): 72–75. doi:10.1016/S1569-
1796 1993(03)00022-5.
- 1797 277. Gray D *et al.* Adrenal suppression and Cushing’s syndrome secondary to ritonavir and budesonide.
1798 *South African Med J* 2010; 100(5): 296. doi:10.7196/SAMJ.3848.
- 1799 278. Orlicka K *et al.* Prevention of infection caused by immunosuppressive drugs in gastroenterology.
1800 *Ther Adv Chronic Dis* 2013; 4(4): 167–85. doi:10.1177/2040622313485275.
- 1801 279. Zenlea T, Peppercorn MA. Immunosuppressive therapies for inflammatory bowel disease. *World J*

- 1802 *Gastroenterol* 2014; 20(12): 3146–52. doi:10.3748/wjg.v20.i12.3146.
- 1803 280. Teixeira M do CB *et al.* Influence of Post-Transplant Immunosuppressive Therapy on
1804 Gastrointestinal Transit Using Biomagnetic Method: A Pilot Study. *Dig Dis Sci* 2015; 60(1): 174–
1805 180. doi:10.1007/s10620-014-3335-8.
- 1806 281. Gabe SM *et al.* The effect of tacrolimus (FK506) on intestinal barrier function and cellular energy
1807 production in humans. *Gastroenterology* 1998; 115(1): 67–74. Available at:
1808 <http://www.ncbi.nlm.nih.gov/pubmed/9649460>. Accessed September 28, 2017.
- 1809 282. Parrilli G *et al.* Effect of chronic administration of tacrolimus and cyclosporine on human
1810 gastrointestinal permeability. *Liver Transplant* 2003; 9(5): 484–488. doi:10.1053/jlts.2003.50088.
- 1811 283. Helderma JH, Goral S. Gastrointestinal complications of transplant immunosuppression. *J Am*
1812 *Soc Nephrol* 2002; 13(1): 277–87. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/11752050>.
1813 Accessed September 28, 2017.
- 1814 284. Deeming GMJ *et al.* Methotrexate and oral ulceration. *Br Dent J* 2005; 198(2): 83–85.
1815 doi:10.1038/sj.bdj.4811972.
- 1816 285. Kalantzis A *et al.* Oral effects of low-dose methotrexate treatment. *Oral Surgery, Oral Med Oral*
1817 *Pathol Oral Radiol Endodontology* 2005; 100(1): 52–62. doi:10.1016/j.tripleo.2004.08.020.
- 1818 286. Troeltzsch M *et al.* Oral mucositis in patients receiving low-dose methotrexate therapy for
1819 rheumatoid arthritis: report of 2 cases and literature review. *Oral Surg Oral Med Oral Pathol Oral*
1820 *Radiol* 2013; 115(5): e28–e33. doi:10.1016/j.oooo.2012.12.008.
- 1821 287. Fijlstra M *et al.* Reduced absorption of long-chain fatty acids during methotrexate-induced
1822 gastrointestinal mucositis in the rat. *Clin Nutr* 2013; 32(3): 452–459.
1823 doi:10.1016/j.clnu.2012.10.002.

- 1824 288. Chun JY *et al.* Adverse Events Associated with Azathioprine Treatment in Korean Pediatric
1825 Inflammatory Bowel Disease Patients. *Pediatr Gastroenterol Hepatol Nutr* 2013; 16(3): 171.
1826 doi:10.5223/pghn.2013.16.3.171.
- 1827 289. Mogensen S *et al.* Absorption of Bupivacaine after Administration of a Lozenge as Topical
1828 Treatment for Pain from Oral Mucositis. *Basic Clin Pharmacol Toxicol* 2017; 120(1): 71–78.
1829 doi:10.1111/bcpt.12644.
- 1830 290. Parikh N *et al.* A single-dose pharmacokinetic study of fentanyl sublingual spray in cancer patients
1831 with and without oral mucositis. *J Pain* 2013; 14(4): S73. doi:10.1016/j.jpain.2013.01.631.
- 1832 291. Amundsen R *et al.* Cyclosporine A- and Tacrolimus-Mediated Inhibition of CYP3A4 and CYP3A5 In
1833 Vitro. *Drug Metab Dispos* 2012; 40(4): 655–661. doi:10.1124/dmd.111.043018.
- 1834 292. Moes DJAR *et al.* Sirolimus and everolimus in kidney transplantation. *Drug Discov Today* 2015;
1835 20(10): 1243–1249. doi:10.1016/j.drudis.2015.05.006.
- 1836 293. Finch A, Pillans P. P-glycoprotein and its role in drug-drug interactions. *Aust Prescr* 2014; 37(4):
1837 137–139. doi:10.18773/austprescr.2014.050.
- 1838 294. Rebello S *et al.* Effect of Cyclosporine on the Pharmacokinetics of Aliskiren in Healthy Subjects. *J*
1839 *Clin Pharmacol* 2011; 51(11): 1549–1560. doi:10.1177/0091270010385934.
- 1840 295. Rushing DA *et al.* The effects of cyclosporine on the pharmacokinetics of doxorubicin in patients
1841 with small cell lung cancer. *Cancer* 1994; 74(3): 834–41. Available at:
1842 <http://www.ncbi.nlm.nih.gov/pubmed/8039111>. Accessed September 28, 2017.
- 1843 296. Eising EG *et al.* Does the multidrug-resistance modulator cyclosporin A increase the cardiotoxicity
1844 of high-dose anthracycline chemotherapy? *Acta Oncol* 1997; 36(7): 735–40. Available at:
1845 <http://www.ncbi.nlm.nih.gov/pubmed/9490093>. Accessed September 28, 2017.

- 1846 297. Galetin A *et al.* Maximal inhibition of intestinal first-pass metabolism as a pragmatic indicator of
1847 intestinal contribution to the drug-drug interactions for CYP3A4 cleared drugs. *Curr Drug Metab*
1848 2007; 8(7): 685–93. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/17979656>. Accessed
1849 January 30, 2018.
- 1850 298. Yee GC, McGuire TR. Pharmacokinetic Drug Interactions with Cyclosporin (Part II). *Clin*
1851 *Pharmacokinet* 1990; 19(5): 400–415. doi:10.2165/00003088-199019050-00004.
- 1852 299. Yee GC, McGuire TR. Pharmacokinetic Drug Interactions with Cyclosporin (Part I)1. *Clin*
1853 *Pharmacokinet* 1990; 19(4): 319–332. doi:10.2165/00003088-199019040-00004.
- 1854 300. Vermeire S *et al.* Effectiveness of concomitant immunosuppressive therapy in suppressing the
1855 formation of antibodies to infliximab in Crohn’s disease. *Gut* 2007; 56(9): 1226–1231.
1856 doi:10.1136/gut.2006.099978.
- 1857 301. Maini RN *et al.* Therapeutic efficacy of multiple intravenous infusions of anti-tumor necrosis
1858 factor ? monoclonal antibody combined with low-dose weekly methotrexate in rheumatoid
1859 arthritis. *Arthritis Rheum* 1998; 41(9): 1552–1563. doi:10.1002/1529-
1860 0131(199809)41:9<1552::AID-ART5>3.0.CO;2-W.
- 1861 302. Havrda DE *et al.* A case report of warfarin resistance due to azathioprine and review of the
1862 literature. *Pharmacotherapy* 2001; 21(3): 355–7. Available at:
1863 <http://www.ncbi.nlm.nih.gov/pubmed/11253860>. Accessed September 28, 2017.
- 1864 303. Joo Ng H, Crowther MA. Azathioprine and inhibition of the anticoagulant effect of warfarin:
1865 Evidence from a case report and a literature review. *Am J Geriatr Pharmacother* 2006; 4(1): 75–
1866 77. doi:10.1016/j.amjopharm.2006.03.001.
- 1867 304. Vazquez SR *et al.* Azathioprine-induced warfarin resistance. *Ann Pharmacother* 2008; 42(7):

- 1868 1118–23. doi:10.1345/aph.1L077.
- 1869 305. Scaldaferrri F *et al.* Use and indications of cholestyramine and bile acid sequestrants. *Intern Emerg*
1870 *Med* 2013; 8(3): 205–210. doi:10.1007/s11739-011-0653-0.
- 1871 306. Joint Formulary Committee. Colestyramine. In: JOINT FORMULARY COMMITTEE. British National
1872 Formulary London: BMJ Group and Pharmaceutical Press [online] 2017. Available at:
1873 <https://bnf.nice.org.uk/drug/colestyramine.html>. Accessed June 26, 2017.
- 1874 307. Bile acid malabsorption: colesevelam | Guidance and guidelines | NICE. Available at:
1875 <https://www.nice.org.uk/advice/esuom22/chapter/Key-points-from-the-evidence>. Accessed
1876 September 28, 2017.
- 1877 308. Wedlake L *et al.* Effectiveness and tolerability of colesevelam hydrochloride for bile-acid
1878 malabsorption in patients with cancer: A retrospective chart review and patient questionnaire.
1879 *Clin Ther* 2009; 31(11): 2549–2558. doi:10.1016/j.clinthera.2009.11.027.
- 1880 309. Odunsi–Shiyanbade ST *et al.* Effects of Chenodeoxycholate and a Bile Acid Sequestrant,
1881 Colesevelam, on Intestinal Transit and Bowel Function. *Clin Gastroenterol Hepatol* 2010; 8(2):
1882 159–165.e5. doi:10.1016/j.cgh.2009.10.020.
- 1883 310. Darkoh C *et al.* Bile acids improve the antimicrobial effect of rifaximin. *Antimicrob Agents*
1884 *Chemother* 2010; 54(9): 3618–24. doi:10.1128/AAC.00161-10.
- 1885 311. Young MA *et al.* Concomitant administration of cholestyramine influences the absorption of
1886 troglitazone. *Br J Clin Pharmacol* 1998; 45(1): 37–40. Available at:
1887 <http://www.ncbi.nlm.nih.gov/pubmed/9489592>. Accessed September 29, 2017.
- 1888 312. Neuvonen PJ *et al.* Effects of resins and activated charcoal on the absorption of digoxin,
1889 carbamazepine and frusemide. *Br J Clin Pharmacol* 1988; 25(2): 229–33. Available at:

- 1890 <http://www.ncbi.nlm.nih.gov/pubmed/3358884>. Accessed September 29, 2017.
- 1891 313. Jähnchen E *et al.* Enhanced elimination of warfarin during treatment with cholestyramine. *Br J*
1892 *Clin Pharmacol* 1978; 5(5): 437–40. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/656283>.
1893 Accessed September 29, 2017.
- 1894 314. Meinertz T *et al.* Interruption of the enterohepatic circulation of phenprocoumon by
1895 cholestyramine. *Clin Pharmacol Ther* 1977; 21(6): 731–5. Available at:
1896 <http://www.ncbi.nlm.nih.gov/pubmed/862312>. Accessed September 29, 2017.
- 1897 315. Balmelli N *et al.* Fatal drug interaction between cholestyramine and phenprocoumon. *Eur J Intern*
1898 *Med* 2002; 13: 210–211. Available at: www.elsevier.com. Accessed September 29, 2017.
- 1899 316. Malloy MJ *et al.* Influence of cholestyramine resin administration on single dose sulindac
1900 pharmacokinetics. *Int J Clin Pharmacol Ther* 1994; 32(6): 286–9. Available at:
1901 <http://www.ncbi.nlm.nih.gov/pubmed/7921528>. Accessed September 29, 2017.
- 1902 317. Mück W *et al.* Influence of cholestyramine on the pharmacokinetics of cerivastatin. *Int J Clin*
1903 *Pharmacol Ther* 1997; 35(6): 250–4. Available at:
1904 <http://www.ncbi.nlm.nih.gov/pubmed/9208341>. Accessed September 29, 2017.
- 1905 318. Kaykhaei MA *et al.* Low doses of cholestyramine in the treatment of hyperthyroidism. *Endocrine*
1906 2008; 34(1–3): 52–55. doi:10.1007/s12020-008-9107-5.
- 1907 319. Kivistö KT, Neuvonen PJ. The effect of cholestyramine and activated charcoal on glipizide
1908 absorption. *Br J Clin Pharmacol* 1990; 30(5): 733–6. Available at:
1909 <http://www.ncbi.nlm.nih.gov/pubmed/2271372>. Accessed September 29, 2017.
- 1910 320. Bullingham RES *et al.* Clinical Pharmacokinetics of Mycophenolate Mofetil. *Clin Pharmacokinet*
1911 1998; 34(6): 429–455. doi:10.2165/00003088-199834060-00002.

- 1912 321. West RJ, Lloyd JK. The effect of cholestyramine on intestinal absorption. *Gut* 1975; 16(2): 93–8.
1913 Available at: <http://www.ncbi.nlm.nih.gov/pubmed/1168607>. Accessed September 29, 2017.
- 1914 322. Malloy MJ *et al.* Effect of cholestyramine resin on single dose valproate pharmacokinetics. *Int J*
1915 *Clin Pharmacol Ther* 1996; 34(5): 208–11. Available at:
1916 <http://www.ncbi.nlm.nih.gov/pubmed/8738857>. Accessed September 29, 2017.
- 1917 323. Zhu XX *et al.* Bile Salt Anion Sorption by Polymeric Resins: Comparison of a Functionalized
1918 Polyacrylamide Resin with Cholestyramine. *J Colloid Interface Sci* 2000; 232(2): 282–288.
1919 doi:10.1006/jcis.2000.7157.
- 1920 324. He L *et al.* Lack of effect of colesevelam HCl on the single-dose pharmacokinetics of aspirin,
1921 atenolol, enalapril, phenytoin, rosiglitazone, and sitagliptin. *Diabetes Res Clin Pract* 2014; 104(3):
1922 401–409. doi:10.1016/j.diabres.2013.12.033.
- 1923 325. al-Meshal MA *et al.* The effect of colestipol and cholestyramine on ibuprofen bioavailability in
1924 man. *Biopharm Drug Dispos* 1994; 15(6): 463–71. Available at:
1925 <http://www.ncbi.nlm.nih.gov/pubmed/7993984>. Accessed September 29, 2017.
- 1926 326. al-Balla SR *et al.* The effects of cholestyramine and colestipol on the absorption of diclofenac in
1927 man. *Int J Clin Pharmacol Ther* 1994; 32(8): 441–5. Available at:
1928 <http://www.ncbi.nlm.nih.gov/pubmed/7981930>. Accessed September 29, 2017.
- 1929 327. Weaver R, Jochemsen R. Nonclinical Pharmacokinetics and Toxicokinetics. In: *International*
1930 *Pharmaceutical Product Registration, Second Edition*. CRC Press, 2009: 336–376.
1931 doi:10.3109/9781420081831-24.
- 1932 328. Caldwell JH, Greenberger NJ. Interruption of the enterohepatic circulation of digitoxin by
1933 cholestyramine. *J Clin Invest* 1971; 50(12): 2626–2637. doi:10.1172/JCI106763.

- 1934 329. Malik MY *et al.* Role of enterohepatic recirculation in drug disposition: cooperation and
1935 complications. *Drug Metab Rev* 2016; 48(2): 281–327. doi:10.3109/03602532.2016.1157600.
- 1936 330. Stotzer P-O *et al.* Effect of Cholestyramine on Gastrointestinal Transit in Patients with Idiopathic
1937 Bile Acid Diarrhea: A Prospective, Open-Label Study. *Ashdin Publ Neuroenterology* 2013; 2(5).
1938 doi:10.4303/ne/235657.
- 1939 331. Donovan JM *et al.* Drug interactions with colesevelam hydrochloride, a novel, potent lipid-
1940 lowering agent. *Cardiovasc drugs Ther* 2000; 14(6): 681–90. Available at:
1941 <http://www.ncbi.nlm.nih.gov/pubmed/11300370>. Accessed September 29, 2017.
- 1942 332. Sinha V *et al.* Physiologically Based Pharmacokinetic Modeling: From Regulatory Science to
1943 Regulator Policy. 2014. doi:10.1038/clpt.2014.46.
- 1944 333. Kesisoglou F *et al.* Physiologically Based Absorption Modeling to Impact Biopharmaceutics and
1945 Formulation Strategies in Drug Development—Industry Case Studies. *J Pharm Sci* 2016; 105(9):
1946 2723–2734. doi:10.1016/j.xphs.2015.11.034.
- 1947 334. Duan P *et al.* Physiologically Based Pharmacokinetic (PBPK) Modeling of Pitavastatin and
1948 Atorvastatin to Predict Drug-Drug Interactions (DDIs). *Eur J Drug Metab Pharmacokinet* 2017;
1949 42(4): 689–705. doi:10.1007/s13318-016-0383-9.
- 1950 335. Chen Y *et al.* Development of a Physiologically Based Pharmacokinetic Model for Itraconazole
1951 Pharmacokinetics and Drug–Drug Interaction Prediction. *Clin Pharmacokinet* 2016; 55(6): 735–
1952 749. doi:10.1007/s40262-015-0352-5.
- 1953 336. Min JS *et al.* Application of physiologically based pharmacokinetic modeling in predicting drug-
1954 drug interactions for sarpogrelate hydrochloride in humans. *Drug Des Devel Ther* 2016; 10: 2959–
1955 2972. doi:10.2147/DDDT.S109141.

- 1956 337. Grillo JA *et al.* Utility of a physiologically-based pharmacokinetic (PBPK) modeling approach to
1957 quantitatively predict a complex drug-drug-disease interaction scenario for rivaroxaban during
1958 the drug review process: implications for clinical practice. *Biopharm Drug Dispos* 2012; 33(2): 99–
1959 110. doi:10.1002/bdd.1771.
- 1960 338. Mitra A *et al.* Using Absorption Simulation and Gastric pH Modulated Dog Model for Formulation
1961 Development To Overcome Achlorhydria Effect. *Mol Pharm* 2011; 8(6): 2216–2223.
1962 doi:10.1021/mp200062a.
- 1963 339. Qi F *et al.* Influence of different proton pump inhibitors on the pharmacokinetics of voriconazole.
1964 *Int J Antimicrob Agents* 2017; 49(4): 403–409. doi:10.1016/j.ijantimicag.2016.11.025.
- 1965 340. Cristofolletti R *et al.* Assessment of Bioequivalence of Weak Base Formulations Under Various
1966 Dosing Conditions Using Physiologically Based Pharmacokinetic Simulations in Virtual Populations.
1967 Case Examples: Ketoconazole and Posaconazole. *J Pharm Sci* 2017; 106(2): 560–569.
1968 doi:10.1016/J.XPHS.2016.10.008.
- 1969 341. Doki K *et al.* Virtual bioequivalence for achlorhydric subjects: The use of PBPK modelling to assess
1970 the formulation-dependent effect of achlorhydria. *Eur J Pharm Sci* 2017; 109: 111–120.
1971 doi:10.1016/J.EJPS.2017.07.035.
- 1972 342. Establishing Bioequivalence in Virtual Space: Are We Really There? | AAPS Blog. Available at:
1973 [https://aapsblog.aaps.org/2016/09/29/establishing-bioequivalence-in-virtual-space-are-we-](https://aapsblog.aaps.org/2016/09/29/establishing-bioequivalence-in-virtual-space-are-we-really-there/)
1974 [really-there/](https://aapsblog.aaps.org/2016/09/29/establishing-bioequivalence-in-virtual-space-are-we-really-there/). Accessed January 25, 2018.
- 1975 343. Litou C *et al.* The impact of reduced gastric acid secretion on dissolution of salts of weak bases in
1976 the fasted upper gastrointestinal lumen: Data in biorelevant media and in human aspirates. *Eur J*
1977 *Pharm Biopharm* 2017; 115: 94–101. doi:10.1016/j.ejpb.2017.02.009.

- 1978 344. Lee HT *et al.* Effect of prokinetic agents, cisapride and metoclopramide, on the bioavailability in
1979 humans and intestinal permeability in rats of ranitidine, and intestinal charcoal transit in rats. *Res*
1980 *Commun Mol Pathol Pharmacol* 2000; 108(5–6): 311–23. Available at:
1981 <http://www.ncbi.nlm.nih.gov/pubmed/11958284>. Accessed August 23, 2017.
- 1982 345. Bustos D *et al.* Effect of loperamide and bisacodyl on intestinal transit time, fecal weight and
1983 short chain fatty acid excretion in the rat. *Acta Gastroenterol Latinoam* 1991; 21(1): 3–9. Available
1984 at: <http://www.ncbi.nlm.nih.gov/pubmed/1811403>. Accessed September 25, 2017.
- 1985 346. Joo JS *et al.* Alterations in colonic anatomy induced by chronic stimulant laxatives: the cathartic
1986 colon revisited. *J Clin Gastroenterol* 1998; 26(4): 283–6. Available at:
1987 <http://www.ncbi.nlm.nih.gov/pubmed/9649012>. Accessed September 25, 2017.
- 1988
- 1989

1991 *Table 1: Reported Pharmacokinetic Interactions with Metoclopramide*

	Interaction with:	Effect				References
		Rate of absorption	Cmax	Tmax	AUC	
Drug-Drug Interactions with Metoclopramide	Acetaminophen	↑	↑	↓		Nimmo et al., 1973 ^[30]
	Cimetidine		↓		↓	Gugler et al., 1981 ^[36]
			↓			Lee et al., 2000 ^[344]
	Cyclosporine		↑	↓	↑	Wadhwa et al., 1986 ^[42]
	Digoxin			↓	↓ (only for tablet)	Johnson et al., 1984 ^[41]
			↓			Manninen et al., 1973 ^[40]
	Droxicam			↓		Sánchez et al., 1989 ^[33]
	Levodopa	↑	↑	↓		Morris et al., 1976 ^[35]
Lithium			↓		Crammer et al., 1974 ^[32]	

	Methotrexate				↓ (pediatrics)	Mahony et al., 1984 ^[37]
	Mexiletine	↑				Wing et al., 1980 ^[31]
	Morphine				↓	Manara et al., 1988 ^[34]
	Salicylic acid		↑ plasma levels (in patients with migraine attacks)			Volans et al., 1975 ^[28]
	Tetracycline				↓	Gothoni et al., 1972 ^[29]
	Tolfenamic acid	↑				Tokola et al., 1984 ^[27]

1992

1993 *Table 2: Classification of laxatives and antidiarrheal agents* ^[43–45]

	Class	Subgroup	Examples
Laxatives	Osmotic laxatives	Indigestible disaccharides	Lactulose
		Sugar alcohols	Sorbitol
		Synthetic macromolecules	Polyethylene glycol 4000
		Saline laxatives	Sodium sulphate Magnesium sulphate

	Stimulant laxatives		Bisacodyl Senna Phenolphthalein Casanthranol Sodium picosulfate
	Bulk laxatives		Wheat bran Isphagula Sterculia
	Others		Linaclotide
Antidiarrheal agents	Opioids		Loperamide Diphenoxylate Codeine phosphate
	Adsorbents/Bulking agents		Kaolin Isphagula Methylcellulose
	Miscellaneous		Racecadotril

1994

1995 *Table 3: Effects of laxatives and antidiarrheal agents on gastrointestinal conditions*^[45,46,49,51–54,58–60,65,345,346]

Drug category	Implication on gastrointestinal conditions	
Laxatives	↓Gastrointestinal transit time	Small intestinal transit time (bisacodyl) Colonic transit time (bisacodyl, linaclotide, lactulose, polyethylene glycol)

		Whole gastrointestinal transit time (wheat bran, senna, bisacodyl)
	pH in the colon	↓ pH (lactulose, senna, wheat bran, sodium sulphate) ↑ pH (magnesium sulphate)
	Fecal short chain fatty acids	↑ (bisacodyl, senna, wheat bran)
	Differences in gut microbiota	↑ Anaerobes, Bifidobacteria (lactulose) ↓ Bifidobacteria (polyethylene glycol-4000)
	Haustra (small pouches in the colon)	↓ (chronic use of stimulant laxatives)
Antidiarrheal agents	↑ Gastrointestinal transit time	↑ intestinal transit time (loperamide)
	Fecal short chain fatty acids	↑ (loperamide)

1996

1997 *Table 4: Drug-Drug Interactions with concomitant administration of bile acid sequestrants*

Implication on gastrointestinal conditions	Associated risk for co-medication	Reported interactions
Binding of weakly acidic drugs	↓ Bioavailability of co-administered drug	Furosemide ^[312] warfarin, ^[313] phenprocoumon, ^[314,315] sulindac, ^[316] cerivastatin, ^[317] levothyroxine, ^[318] glipizide, ^[319] mycophenolic acid, ^[320] folic acid, ^[321] valproate ^[322]

Disruption of enterohepatic recirculation of drugs	↑ Excretion of co-administered drug	Anticoagulants, ^[313-315] cardiac glycosides, ^[328] mycophenolate mofetil ^[320]
Possible impact on gastrointestinal transit time	↓ ↑ Time available at gastrointestinal absorption site, effect on tmax	Sustained-release formulation of verapamil ^{[331]*}
Reduced concentrations of bile acids for drug solubilization	↓ Absorption of low-soluble compounds	

1998 **not clinically significant due to high variability in the pharmacokinetics of verapamil*

1999

2000 **Figure Captions**

2001

2002 **Figure 1:** Gastrointestinal drugs discussed in this review.

2003

2004 **Figure 2:** Gastric emptying results in twelve gastroesophageal reflux patients with delayed basal
2005 emptying rates (A) and in fourteen gastroesophageal reflux patients with normal basal emptying rates
2006 (B), in a two-way crossover design consisting of a control phase and a phase in which 10 mg
2007 metoclopramide was ingested orally. The data are expressed as the mean percent (\pm 1 SEM) isotope
2008 remaining in the stomach for a period of 90 min after ingestion of an isotope-labeled test meal.^[25] Figure
2009 reprinted from Fink et al. with permission from Springer Nature.

2010

2011 **Figure 3:** Impact of laxatives on colonic transit times of a) healthy subjects and b) patients, measured by
2012 scintigraphy (¹), metal detector (²) or radiopaque markers method (³); patterned bars represent
2013 controls.^[45,47–49,53,54]

2014

2015 **Figure 4:** Effect of loperamide on gastrointestinal transit time after oral administration in healthy
2016 subjects.^[46,70–72]

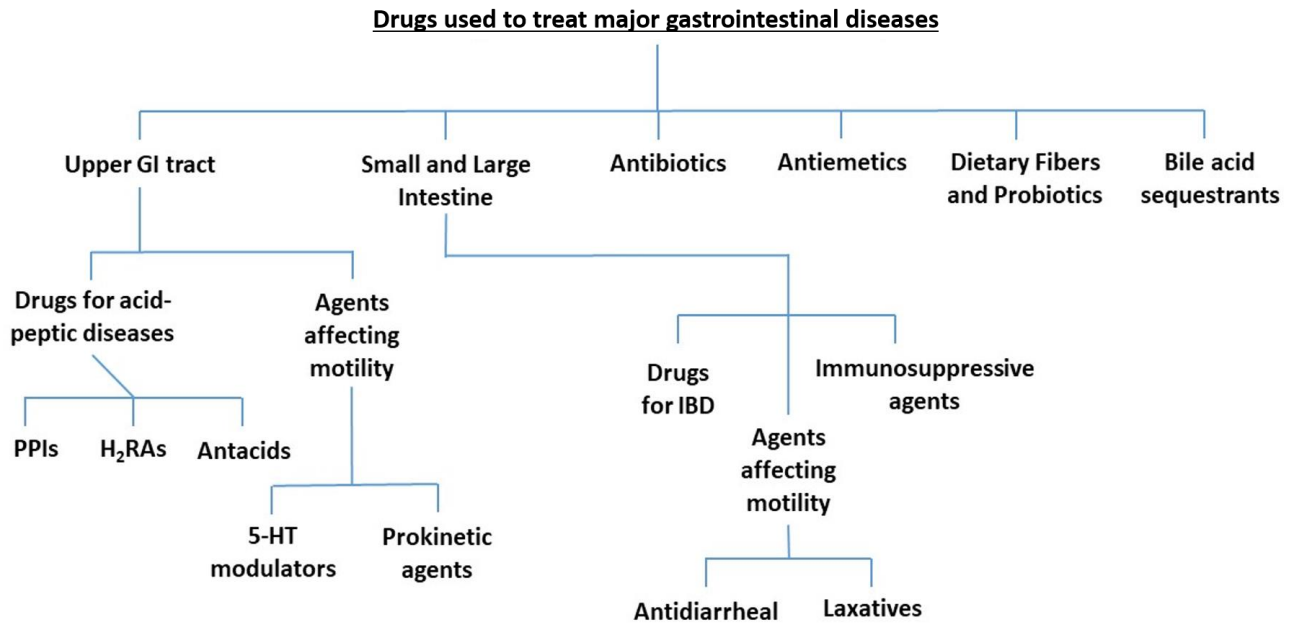
2017

2018 **Figure 5:** pH in the stomach of fasted healthy adults as a function of time, after administration of 240 mL
2019 table water into the antrum of the stomach. Key: (From left to right boxes) White boxes, Phase 1 (control
2020 phase); Light pink boxes, Phase 2 (pantoprazole phase); Dark blue boxes, Phase 3 (famotidine phase).
2021 Each box was constructed by using 7–8 individual values.^[119]

2022

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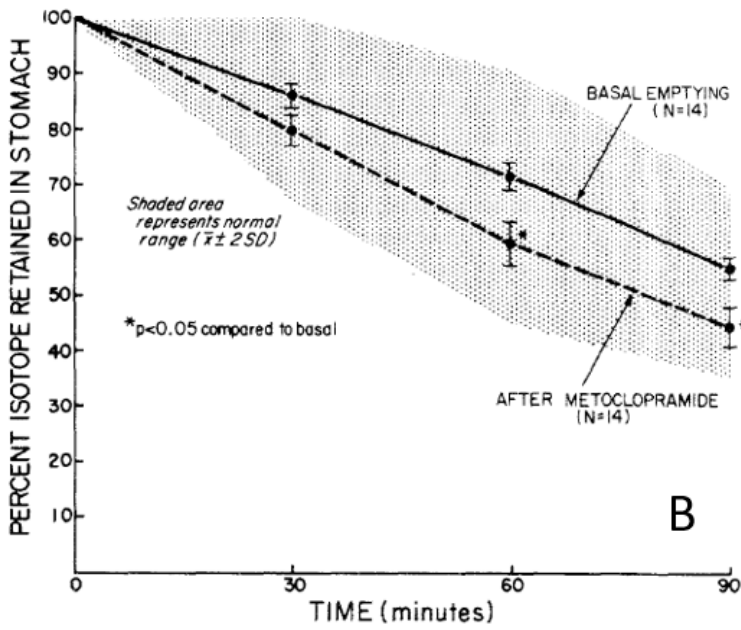
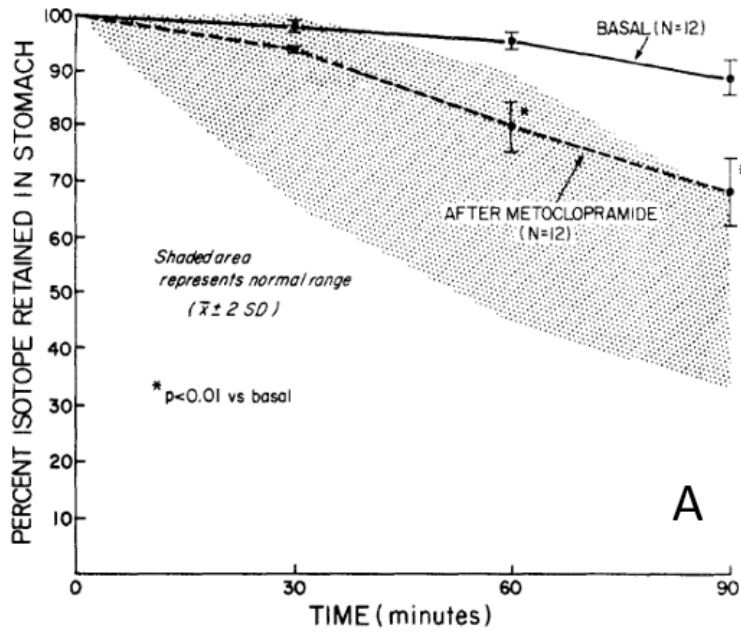
2025

2026

2027 Figure 1

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2029



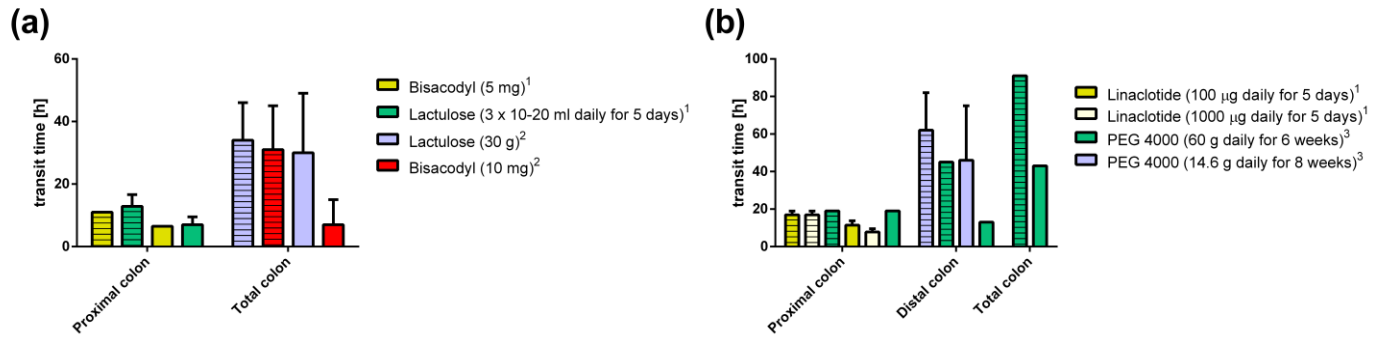
2030

2031 Figure 2

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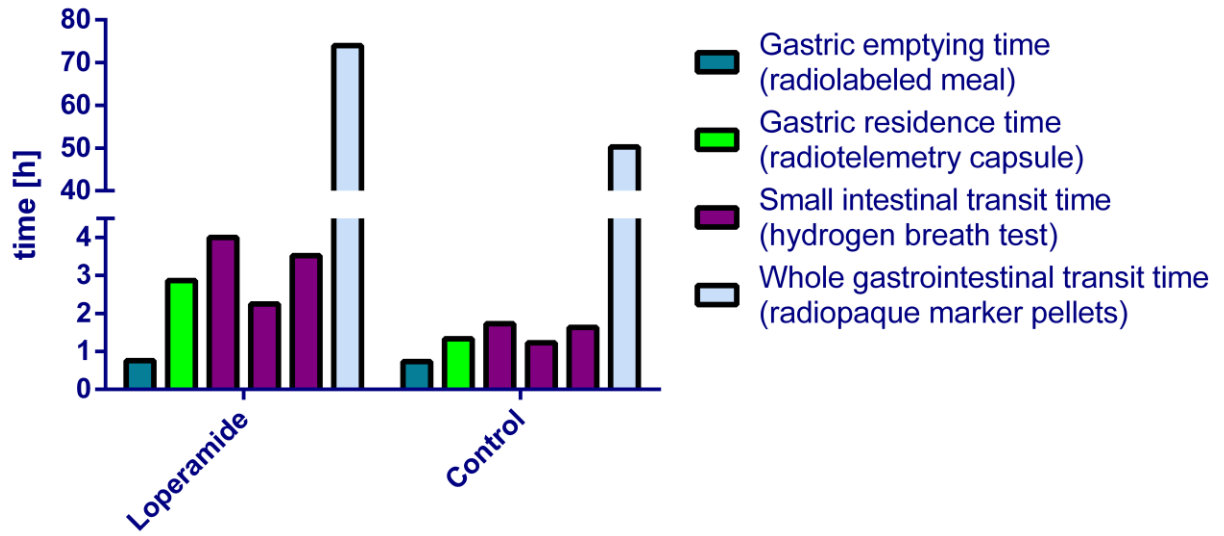
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2037 Figure 3

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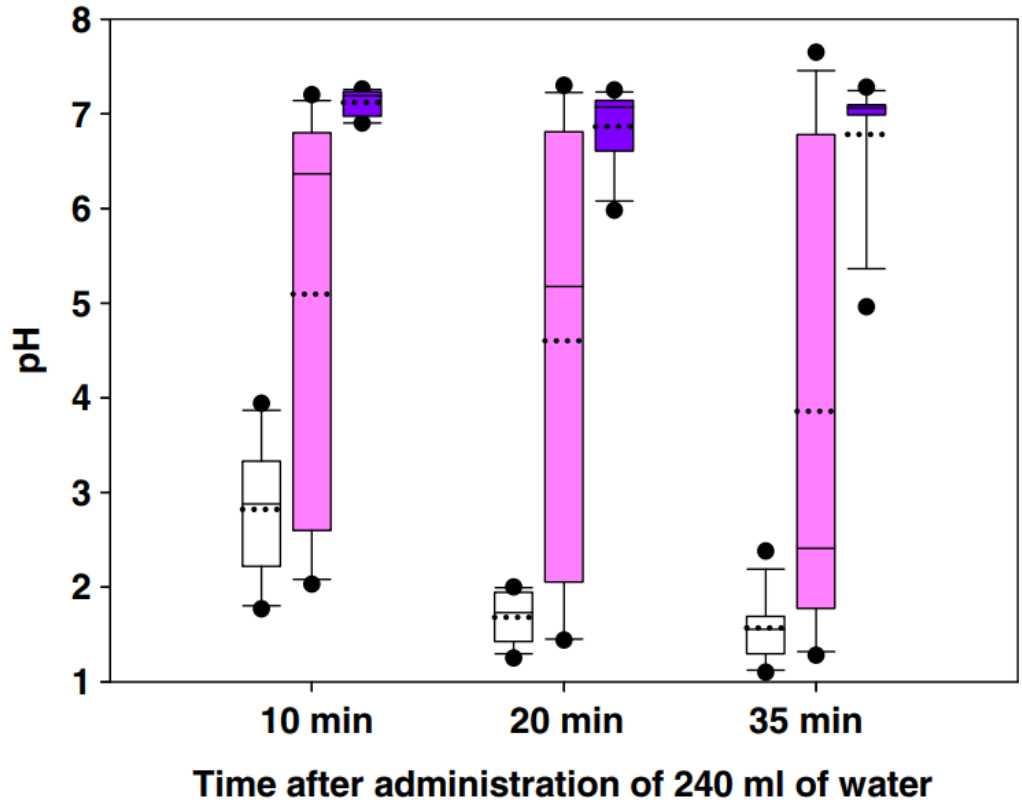
2042

2043 Figure 4

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2048

2049 Figure 5