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SMALL INTESTINE (D SACHAR, SECTION EDITOR)

Drug-Induced Small Bowel Injury: a Challenging and Often Forgotten Clinical Condition

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Abstract

Purpose of Review Most drugs are given by the oral route. Oral intake allows direct contact between the drug and the entire GI tract mucosa, exposing it to potential topical damage until absorption. Medication-induced GI symptoms and lesions are therefore commonly encountered in clinical practice. This review will examine the most common drugs or classes of drugs affecting small bowel function and/or structure.

Recent Findings Since non-steroidal anti-inflammatory drugs (NSAIDs) are among the most widely used medicines, NSAID enteropathy is highly prevalent and brings about considerable morbidity. Antimicrobials and proton-pump inhibitors profoundly modify intestinal microbiota, affecting gut sensory and motor functions, while other drugs (like iron and gold derivatives) impair intestinal permeability. Olmesartan (and likely ACE inhibitors) induce villous atrophy and consequent malabsorption. Mycophenolate mofetil, cancer chemotherapeutic agents, and immune checkpoint inhibitors cause intestinal inflammation, abdominal pain, and diarrhea. Potassium chloride supplements may induce small bowel ulceration, stenosis, and perforation while the cotraceptive pill and anticoagulants are associated with intestinal ischemia and spontaneous intramural hematoma, respectively.

Summary In clinical practice, a deep knowledge of clinical pharmacology and toxicology and a high degree of suspicion of drug-related adverse events are mandatory. Only then, the practicing physician will be able to diagnose medication-induced small bowel lesions correctly and will implement the best strategies to treat them.

Keywords : Drug-induced · Adverse events · NSAIDs · Small bowel · Injury

Introduction

Primum non nocere
First do not harm
Thomas Inman, 1980

Iatrogenic disease, which results from diagnostic and therapeutic procedures undertaken on a patient, is one of the most frequent causes of patient-physician interaction and represents a growing public health problem [1]. Diagnostic procedures (mechanical and radiological) and therapeutic regimens (drugs, surgery, and other invasive procedures) can bring about iatrogenic disorders. The most common type of iatrogenic disease is pharmacologic, and almost all the organs and systems can be affected [2]. The incidence of adverse drug events[1] is particularly relevant in the elderly, where comorbidities drive the prescription (often by multiple physicians) of a multitude of drugs to a single patient [3].

Among the many drug delivery and targeting systems, the oral route remains the most widely used [4]. Despite its ease of

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[1] An adverse drug event is defined by the World Health Organization as "a response to a drug which is noxious and unintended, and which occurs at doses normally used" (https://apps. who.int/medicinedocs/en/d/Jh2992e/2.html).

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use and convenience, it remains the most challenging in terms of absorption (sometimes erratic) and drug- and food-to-drug interactions [5]. Moreover, oral intake allows direct contact between the drug and the entire GI tract mucosa, exposing it to topical damage until absorption. In addition, injury may continue after drug absorption, if the mucosa is further exposed as a result of the enterohepatic circulation [6].

All medications are associated with adverse effects and the GI tract is a frequent target. Indeed, as shown by the annual Food and Drug Administration drug report [7], 10% of the drug-induced adverse effects concern the GI tract, a figure that—in hospital inpatients—can actually reach the 20–40% [8]. Because most drugs are taken by mouth, patients tend to blame medications for their GI symptoms, which may reduce patient compliance and also herald the development of drug-induced diseases [8].

There are several classes of commonly used drugs that have an adverse effect on the GI tract [9–12]. The consequences range from asymptomatic histologic changes in the GI mucosa to fatal complications. The injury can be specific or non-specific [10, 11] and local and/or systemic [7] and involve the esophagus [13], the stomach [14], and/or the (small and large) bowel [15, 16]. Many of these iatrogenic injuries, and especially their complications, are preventable. The gastroenterologist's challenge is to diagnose them correctly, so that the offending drug can be discontinued (many drug-induced effects will regress or heal on cessation of treatment) or replaced and a therapeutic strategy duly implemented. A detailed and accurate drug history should therefore be taken in patients presenting with GI complaints.

Drug-Induced Small Bowel Injury

With the ever-growing armamentarium of pharmacological agents, GI drug-induced adverse effects are increasingly seen. The small intestine is one of the most frequent sites of drug-induced undesirable effects, accounting for 20–40% of all adverse reactions [16]. These may be self-limiting and without serious sequelae, but of greater concern are drug-induced mucosal inflammation and ulceration, which can manifest as GI hemorrhage, stricture, and/or perforation.

The high incidence of small intestinal drug untoward effects is explained by the highly delicate interaction between the enteric nervous system (ENS) and central nervous system (CNS), the high metabolic activity of cells involved in absorption and secretion, and the great microbiome abundance and diversity. In addition, the intestinal mucosa is exposed to high luminal drug concentrations, often prolonged by biliary delivery. The potential for a drug to adversely affect all these pathways is therefore substantial [16].

The untoward effects of drugs can manifest in a number of ways and may resemble other conditions such as inflammatory bowel disease (IBD) or malignancy. The clinical picture may range from subtle and innocent symptoms to life-threatening presentations [16]. An in-depth knowledge of the pharmacology and toxicology of the prescribed medications is essential for the awareness of potential adverse effects and for differential diagnosis. Although there is often a temporal relationship between drug intake and symptoms, in some cases (for instance NSAID enteropathy or metformin-associated diarrhea), the time sequence is inconsistent and unpredictable [17••]. Knowledge of the anticipated side effects is therefore mandatory. It is worth emphasizing that—together with de novo damage—an aggravation of a pre-existing disease (for instance IBD) can occur [16].

There is no universally accepted classification for drug-induced adverse effects or diseases on the intestine. A classification based on the drug mechanism of action fails because the mechanism is rarely simple and involves a combination of effects [17••]. A morphological classification is equally problematic as many of the untoward drug actions are functional and do not cause structural damage. This is, for instance, the case of drug used for treating constipation or diarrhea. As a consequence, in clinical practice, the diagnosis and management of intestinal adverse effects of drugs are based on the presenting symptoms, which may drive laboratory, endoscopic, and/or imaging investigations.

Drugs Affecting Intestinal Function

Gastric and pancreatic lipases are enzymes that play a pivotal role in the digestion of dietary fat. Orlistat, an antiobesity drug, is a potent and specific inhibitor of intestinal lipases [18]. Given with fat-containing foods, it partially inhibits hydrolysis of triglycerides, reducing in that way the absorption of monoglycerides and free fatty acids. As a consequence, mild-to-moderate oily stools, diarrhea, abdominal pain, and fecal spotting can occur after administration [19].

Motilin causes a marked acceleration of intestinal transit in humans, induces interdigestive motor complexes, and stimulates intestinal fluid secretion. Erythromycin and related 14-member macrolide compounds mimic the effects of motilin on GI motility, acting as motilin agonists [20]. GI adverse events (including nausea, vomiting, diarrhea, and abdominal cramps) with macrolide antibiotics are common, being 21–32% with erythromycin and 12–13% with azithromycin and clarithromycin [21].

Small intestinal motor disturbances are also associated with oral administration of amoxicillin-clavulanate combination (ACC). While no effect on intestinal motility was evident during the diurnal fast or fed state, this antibiotic combination significantly increased the motility index of the non-propagated contractions and tended to increase the duration and the amplitude of the propagated contractions during the

nocturnal fasting period [22]. The reported incidence of GI adverse effects during ACC treatment ranged between 3–6% (nausea, vomiting, and abdominal cramping) and 4–15% (diarrhea) [23].

It is important to realize that the above studies were performed before the "microbiome revolution" [24••]. When analyzing the action of a drug, it is important to consider that an alteration of the gut microbiome is possible. Indeed, even non-antimicrobial compounds (actually 24% of the commonly used drugs) display anticommensal activity at concentrations lower than those achieved in the small and large bowel [25•]. In addition, gut microbiome is one of the major determinants of drug pharmacokinetics and, as a consequence, pharmacodynamics [26•].

In addition, both sensory and motor functions of the GI tract, including intestinal peristalsis, are dependent on the number and composition of intestinal microflora that—in their turn—is controlled by the intestinal motility, which clears the lumen from excessive bacteria [27]. Antimicrobials adversely affect intestinal microbiome (e.g., reducing bacterial diversity and expanding or collapsing membership of specific indigenous taxa), that is of rapid onset and often long-lasting [28], in which case full recovery may not be observed [28]. The alterations in microbial communities lead to changes in intestinal motility and secretions, which might well explain the observed adverse events of antibiotics, such as macrolides or ACC.

Proton-pump inhibitors (PPIs) represent a very effective class of drugs, widely prescribed in all age populations. The widespread, often lifelong, use of these medications raises growing concern for potential adverse effects resulting from long-term therapy [29]. Almost all studies found a significant reduction in intestinal microbial diversity after (even short-term) use of PPIs [30•, 31]. During PPI treatment, significant changes in taxa associated with *Clostridioides difficile* infection (increased Enterococcaceae and Streptococcaceae, decreased Clostridiales) and taxa associated with small intestine bacterial overgrowth (increased Micrococcaceae and Staphylococcaceae) were observed. As a consequence, long-term PPI users present a higher risk of both incident [32–34] and recurrent [35, 36] *C. difficile* infection as well as small intestinal bacterial overgrowth [37, 38] compared with non-users. Through alterations in intestinal microecology, PPIs will exacerbate non-steroidal anti-inflammatory drug (NSAID)–induced small intestinal injury [39] and may nullify the better small bowel tolerability of selective COX-2 inhibitors (see below) [40•].

Most oral iron supplements have been associated with erosive mucosal injury in the upper GI tract as well as metallic taste, nausea, vomiting, and epigastric discomfort, and other GI symptoms such as diarrhea and constipation [41]. A recent systematic review [42], including several thousands of patients receiving ferrous iron salts, has reported GI adverse effects in 30–70% of patients. Iron adverse effects are likely due to direct toxicity of unabsorbed iron (less than 10% of the oral iron salts is absorbed) on the intestinal mucosa. After iron oral supplementation in children, an increased intestinal permeability (determined by urinary lactulose-to-mannitol ratio) has been documented [43], which may be one of the mechanisms of intestinal damage.

More than 35 years ago, Auranofin® (triethylphosphine gold, AF) was developed for the treatment of rheumatoid arthritis as a substitute for the injectable gold compounds—gold thiomalate and gold thioglucose [44]. With this gold derivative, both systemic and GI toxicity is uncommon [44]. However, nearly half of the patients taking this drug complain of abdominal cramps and occasional diarrhea [44], which can be troublesome and lead 4% of patients to discontinue chrysotherapy. Two thorough studies [45, 46] investigated the pathophysiology of AF-induced diarrhea. Despite several reports of gold colitis and proctitis, no evidence of colitis was found in AF-treated patients with diarrhea [46]. Although a case report of malabsorption with partial villous atrophy at duodenal biopsy [47] has been reported, no infection or signs of malabsorption were found in this patient population [45]. AF increased the transit through the GI tract as a whole [46], and an involvement of prostaglandins in the pathogenesis of diarrhea has been suggested [48]. The more than twofold increase in stool weight was associated with an increased sodium concentration in fecal water, without significant changes in potassium and bicarbonate concentrations. However, bicarbonate concentrations and fecal pH decreased [46]. In addition, an increase in intestinal permeability and protein loss (evaluated by the clearance of alpha-1 antitrypsin from the circulation into the GI tract) was found [46].

Many compounds lead to diarrhea. The main mechanisms include exaggerated pharmacologic effects on intestinal motility and/or interference with water absorption/secretion pathways [16, 49]. The growing list of drugs belonging to different pharmacological classes is reported in some detailed reviews [50•, 51] to which the reader is referred. Identification of a drug as a cause of chronic diarrhea is not always easy and may be a challenge in patients taking multiple medications. Drug-induced diarrhea is rarely associated with malabsorption of nutrients, and a clinical improvement may occur within days of discontinuation of the drug or may take longer when associated with mucosal injury.

Besides inadequate lifestyle habits (insufficient intake of fluids and dietary fibers, reduced activity of daily living) and diseases [52••], drugs have also been reported as one of the most important causes of constipation [53, 54]. Presumably, the age association reflects a higher prevalence of other causes of constipation, such as medication use. Drugs and polypharmacy are indeed important risk factors for constipation in the elderly [52••].

Drugs Causing Intestinal Damage

Diarrhea is a common consequence of many medications. Conversely from that caused by drugs increasing GI motility, such as erythromycin or other macrolides, which has an acute onset shortly after starting the medication, diarrhea illness may appear late and be chronic if the drug induces inflammation or enteropathy, like that described with olmesartan and mycophenolic acid.

Olmesartan is a selective, competitive, and long-lasting angiotensin-1 receptor antagonist used for the treatment of hypertension. A celiac-like enteropathy associated with olmesartan was first described in 2012, and a number of cases have since been reported [55•]. It is an uncommon adverse effect, likely molecule- rather than class-specific (one single case has been described with irbesartan and valsartan [15]), and may be difficult to recognize because of its clinical and histologic similarities to other clinical entities, including celiac disease and autoimmune enteropathy [55•]. The clinical features include chronic diarrhea (proportional to the duration of exposure), abdominal pain, and vomiting, with negative celiac serology and villous atrophy (often accompanied by intraepithelial lymphocytosis and infiltration of the lamina propria) on duodenal biopsy. Withdrawing the offending agent is the mainstay of treatment, while gluten-free diet is ineffective. Topical budesonide has also been used, with most patients improving under this therapy [55•]. A recent epidemiologic study found a similar incidence of malabsorption in ACE inhibitor–treated patients, suggesting that also this drug class can cause iatrogenic enteropathy [56].

Mycophenolate mofetil (MMF), a pro-drug of mycophenolic acid, is an immunosuppressive agent, which inhibits de novo purine synthesis, resulting in antiproliferative effects on T and B lymphocytes. The most common adverse effects of mycophenolate mofetil are GI complaints (such as diarrhea), which are frequent and lead to MMF dose reduction or withdrawal in 40–50% of cases [57]. Several cases of villous atrophy in patients treated with MMF have been reported [58], likely underlying the diarrhea, seen however in only 16% of patients [58]. A recent case report described—in a 45-year-old on MMF, presenting with abdominal pain and weight loss but macroscopically normal duodenoscopy—an extensive enteropathy jejunum and ileum revealed by video capsule endoscopy and confirmed on a push enteroscopy with biopsies [59]. Because GI adverse effects of MMF are well known and expected, colonoscopy is seldom performed in patients presenting with diarrhea. It should be remembered, however, that MMF-related colitis, which can sometimes display a late onset [60, 61], has been reported, especially in kidney transplant recipients [62]. Endoscopy showed patterns of colonic mucosal injury mimicking a host of conditions [63], including non-specific colitis (31.3%), IBD-like colitis (25.0%), normal/near-normal findings (18.8%), and graft-versus-host disease–like (18.8%) and ischemia-like colitis (12.5%) [62]. Crypt distortion and loss as well as increased apoptosis constituted the main histological features [64]. As shown by several clinical studies, conversion to enteric-coated mycophenolate sodium (EC-MMF sodium) [65, 66] or switching to another immunosuppressive agent [67] may be an effective option to reduce GI-related symptom burden (enteropathy and colopathy, respectively). However, a few cases of villous atrophy have been reported even after the EC formulation [58].

Approximately 5–15% of patients subjected to conventional cancer chemotherapy develop intestinal mucositis. This condition is associated with impairment of quality of life, increased health care costs, hospital admission (one-third of patients), and even death. The symptoms of intestinal mucositis include diarrhea, bleeding, nausea, vomiting, abdominal pain, malnutrition, infections and sepsis due to bacterial translocation (which can be life-threatening), dehydration, and fatigue [68]. Among the many cytotoxic drugs, irinotecan and 5-fluorouracil (5-FU) are the most widely studied. It is now well established that development of mucositis induced by these agents is a complex pan-tissue phenomenon, involving multiple pathways interacting at all mucosal levels [69]. The diarrhea associated with mucositis has been investigated and shown to be related not only to inflammatory (structural and functional) changes in the small intestine and colon (crypt hypoplasia, altered absorptive function) [69] but also to changes in the gut microbiota (with, most frequently, decrease in *Bifidobacterium*, *Clostridium* cluster XIVa, and *Faecalibacterium prausnitzii*; and increase in Enterobacteriaceae and *Bacteroides*) [70]. Animal studies have shown that crypt apoptosis, dysbiosis, and overexpression of inflammatory cytokines are sequential events in the development of intestinal mucositis after exposure to 5-FU. Vomiting and diarrhea are also common with capecitabine (an oral 5-FU prodrug), after which use severe ileitis with diffuse submucosal edema of the small bowel wall has been reported [71, 72].

Immune checkpoint inhibitors (ICIs) are a novel group of monoclonal antibodies with proven effectiveness in a wide range of malignancies, including melanoma, renal cell carcinoma, non–small cell lung cancer, urothelial carcinoma, and Hodgkin's lymphoma. Currently, there are two main targets for manipulation of immune checkpoint signaling: signaling mediated by cytotoxic T lymphocyte antigen-4 (CTLA-4) or by programmed cell death 1 (PD1) receptors [73••]. Several molecules (ipilimumab as anti-CTLA-4 and nivolumab, pembrolizumab, atezolizumab, durvalumab, and avelumab as anti-PD1 agents) have been specifically designed to target these pathways. These drugs could be able to reverse immune tolerance of cancer cells and generate a long-term antitumor immune response [73••]. ICIs have the potential to improve the treatment of advanced malignancies, but they are also

associated with a substantial risk of immune-related adverse events. The hallmark symptom of ICI enterocolitis is diarrhea, seen in up to 30% of patients, which is likely due to an abrupt triggering of acute inflammation in the small (and large) bowel [74••]. Many patients also experience abdominal pain, nausea, and vomiting, while hematochezia and fever are less frequent. In a series of 39 patients with anti-CTLA-4 enterocolitis, 4 patients had symptoms reminiscent of Crohn's disease: 1 patient had aphthous mouth ulcers and 3 patients had anal lesions (2 fistulas and abscesses, 2 fissures) [74••]. Enterocolitis is the most frequent but not the only GI immune–related adverse effects induced by anti-CTLA-4. Indeed, two case reports have described enteric neuropathy induced by ipilimumab, as revealed by severe constipation [75, 76]. According to a recent systematic review [74••], GI adverse effects induced by anti-CTLA-4 are frequent, potentially severe and resemble IBD, whereas those induced by PD-1 blockade seem to be less frequent and clinically more diverse. The main differences between the untoward effects of these two classes of ICIs are summarized in Table 1.

Potassium replacement is the cornerstone of therapy for hypokalemia [77]. In most cases, a chloride deficiency and some degree of metabolic alkalosis accompany potassium deficiency, so potassium chloride is the most commonly used supplement. The major risks of therapy with potassium supplements are hyperkalemic cardiac arrest and small bowel ulceration [77]. This adverse effect (the estimated risk of which is 40–50 per 10,000 patient-years) has mainly been reported with ingestion of enteric-coated potassium chloride tables [78] and enteric-coated combinations of thiazide diuretics and potassium chloride [79]. Ulceration can be stenosing and progress to necrosis and perforation. Experimental studies in monkeys and dogs have shown that high concentrations of potassium, causing local irritation and vasoconstriction, represent an important factor for the development of lesions. Enteric coating itself did not contribute to damage since EC placebo tablets were without effect [80]. Newer slow-release tablets (i.e., a wax matrix formulation and a microencapsulated formulation) are much safer, and intestinal damage is nowadays rare, albeit not absent. Indeed, ulceration of the small bowel has been reported also with a wax-core potassium formulation [81]. It should then be emphasized that the safest approach to minimizing hypokalemia is to ensure adequate dietary potassium intake.

Non-steroidal anti-inflammatory drugs (NSAIDs) are among the most frequently prescribed and used medications worldwide. They confer important clinical benefits across multiple indications. Unfortunately, however, their use is associated with a broad spectrum of adverse reactions involving the liver, kidney, cardiovascular system, skin, and gut. Gastrointestinal adverse effects are the most common and cover a wide clinical spectrum, ranging from dyspepsia, heartburn, and abdominal discomfort to more serious events, such as peptic ulcer with life-threatening ulcer complications of bleeding and perforation [82].

While the perception of NSAID-associated damage has long been held, the appreciation that it can extend to the lower GI tract is more recent [103, 104]. In the first large prevention study (i.e., the MUCOSA trial) [83] and the recent VIGOR trial [84], more than 40% of NSAID-related events occurred in the small bowel and colon. On the other hand, the overall pattern of GI events leading to hospitalization has recently shown a decreasing trend in upper gastrointestinal events and a slight, but significant, increase in lower gastrointestinal events [85].

Technology advancement (i.e., the availability of video capsule endoscopy (VCE)) has contributed to our knowledge of NSAID enteropathy, which appears to be site-dependent. Indeed, VCE studies [105, 106] have shown that about 75% of NSAID users display intestinal mucosal injury. These range from denuded areas (seen mainly in the proximal small bowel) to the so-called mucosal breaks (erosions and ulcers), observed in its distal part [107] (Fig. 1). Like non-selective compounds, COX-2 selective NSAIDs damage the small bowel, but the frequency and severity of events are generally lower [108]. The improved intestinal tolerability of the selective agent, celecoxib, persisted even when compared to a ns-NSAID combined with a PPI [109, 110]. In healthy volunteers [106, 109, 110] and patients [105], omeprazole did not prevent NSAID-associated small intestinal damage, as evaluated by

Table 1 Differences in anti-PD-1 and anti-CTLA-4 GI immune adverse events (from ref. [68])

	Anti-CTLA-4	Anti-PD-1
Incidence of diarrhea/colitis	30.2%/5.7%	12.1%/0.7%
Incidence of grade 3–4 diarrhea/colitis	7.4%/4.1%	1%/0.4%
Immunopathological features	Predominance of colonic mucosal CD4+ T cells and high TNF secretion	Predominance of colonic mucosal CD8+ T cells
Time to onset after first infusion	1 month	2–4 months
Time to resolution of GI irAE	0.5–1.6 months	1.1–4.2 months
Response rate to corticosteroids	80%	80%

CTLA-4 cytotoxic T lymphocyte-associated protein-4, *irAE* immune-related adverse effects, *PD-1* programmed death-1, *TNF* tumor necrosis factor

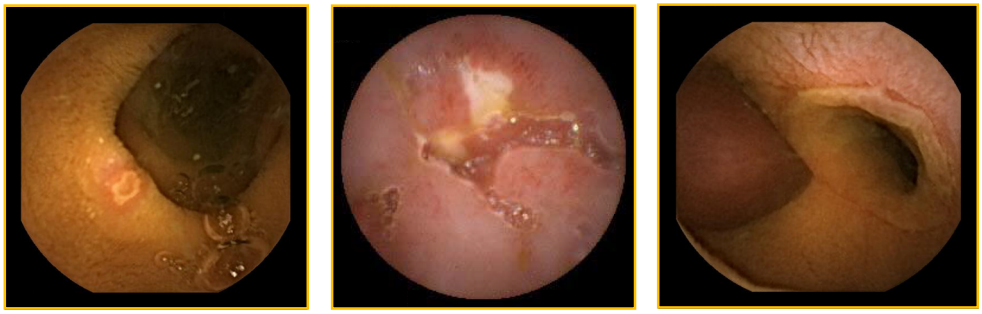

Fig. 1 Video capsule images of NSAID-associated small bowel lesions

video capsule and/or fecal calprotectin measurement. Experimental (for review, see [111]) and clinical [40•, 107] evidence suggests that PPIs may actually aggravate NSAID injury in the small bowel.

The pathogenesis of small intestinal damage has not been completely elucidated. NSAID-induced inhibition of mucosal prostaglandin synthesis along the entire digestive tract may well be implicated, but there is a concurrence of other pathogenic factors that add to mucosal damage. Among them, enterobacteria and bile are the most important ones. At the level of the distal GI tract, they indeed trigger specific NSAID-induced pathogenic mechanisms [100, 111, 112].

Bile acids [113] and inhibition of cyclooxygenase activity [114] are important factors in the pathogenesis of NSAID enteropathy. However, current concepts focus mainly on alterations in gut microbiota and the consequent pathological activation of the innate inflammatory cascade [101]. Recent evidence (for review, see [115]) has established the key role of the NLRP3[2] inflammasome in the dynamic interaction between microbiota, intestinal epithelium, and the innate immune system. This interplay forms an integrated network, capable of regulating the maintenance/breakdown of intestinal homeostasis.

Antimicrobials can prevent or lessen NSAID enteropathy (for review, see [100, 111, 112]). These findings (derived mainly from experimental studies) support the pathogenic role of enteric bacteria. In the only human study [116], metronidazole (an antimicrobial targeting most Gram-negative and Gram-positive anaerobic bacteria [102]) reduced inflammation and blood loss in patients taking NSAIDs. Although these results suggested a therapeutic potential for antimicrobials in this clinical setting, potential adverse effects of systemic drugs and the possible occurrence of drug resistance have so far precluded this interesting approach [100]. However, rifaximin (a poorly absorbed antibiotic) was found to prevent NSAID enteropathy in both animals [117, 118•] and humans [119••]. This drug is also endowed with intrinsic anti-inflammatory [118•] and eubiotic [87] properties, leading to an increase in relative abundance of *Lactobacilli* and *Bifidobacteria*. Both activities might contribute to its enteroprotective effect. Indeed, NSAID-driven intestinal damage is associated with significant mucosal inflammation, which is easily detected by the increase in fecal calprotectin [91, 106, 110], and probiotics appear to be capable of preventing both increased intestinal permeability and damage [92].

Since NSAID enteropathy is not a pH-dependent phenomenon, PPIs are ineffective in preventing NSAID injury to lower GI tract [93]. On the contrary, mucosal protective compounds could be an alternative, as suggested by many experimental studies [94, 95]. Among the different compounds, whose efficacy was evaluated with the VCE, only misoprostol [96] is available in Europe and North America and approved for treatment and prevention of NSAID injury, while rebamipide [88, 89, 97–99], irsogladine [90, 120], and teprenone (geranylgeranylacetone) [86, 121] are only available in Asia. Although effective in the treatment of intestinal lesions associated with low-dose, enteric-coated aspirin [122–124] and NSAIDs [124], misoprostol is presently approved only for treatment and prevention of NSAID-associated gastroduodenal ulcers [125, 126]. It is not devoid of adverse effects (e.g., diarrhea, loose stool, abdominal discomfort) and is contraindicated in women, pregnant, or those wishing to conceive [125]. An alternative strategy to lessen NSAID enteropathy is represented by the use of a non-acidic, selective COX-2 inhibitor. Indeed, switching patients with rheumatoid arthritis on long-term conventional NSAIDs to celecoxib resulted in a significant reduction of small bowel injury [127]. A summary of currently available strategies for prevention and/or treatment of NSAID- or aspirin-induced enteropathy is given in Table 2.

Clofazimine is a riminophenazine dye that, due to its antibacterial and anti-inflammatory properties, has been used for several diseases, including multibacillary leprosy. In over 40 years of use in leprosy, several cases of a unique pathology, i.e., a crystal-storing histiocytosis [128], producing an exudative enteropathy [129], have been reported. Symptoms include diarrhea, (sometimes severe) abdominal pain, and weight loss are improved by a gluten-free diet, after stopping the offending drug. Sometimes symptoms can be intractable and

[2] *NLRP3* = nucleotide-binding oligomerization domain leucine-rich repeat and pyrin domain–containing protein 3

Table 2 Strategies for prevention and/or treatment of small bowel lesions induced by NSAIDs or aspirin

Therapy	References	Remarks
Non-acidic COX-2 selective agents (i.e., celecoxib)	[83–86]	Less damaging agent than non-selective NSAIDs
Misoprostol	[87–90]	Consistent results for both prevention and healing. High doses needed and potential adverse events
Rebamipide	[91–95]	Effective in both prevention and treatment of NSAID enteropathy
Irsogladine	[96, 97]	Effective in both prevention and treatment of NSAID enteropathy
Teprenone	[98, 99]	Effective only in prevention of NSAID-induced small bowel lesions
Metronidazole (systemic antimicrobial)	[100]	Reduces inflammation and blood loss in patients taking NSAIDs. Preventive effect on intestinal lesions not yet demonstrated
Rifaximin (poorly absorbed antibiotic)	[101]	Proof-of-concept study in healthy volunteers positive. Studies in OA/RA patients taking NSAIDs needed
Probiotics	[102]	Attractive approach but evidence is limited. More studies are needed to identify the most suitable strain(s)

OA osteoarthritis, *RA* rheumatoid arthritis

severe, leading to death [130, 131]. The only study evaluating intestinal function found an increased fecal fat excretion but normal Schilling's and D-xylose tests [132]. In those patients submitted to explorative laparotomy, all tissues were stained bright orange-yellow and histological examination showed clofazimine birefringent crystals deposited in the small bowel mucosa and submucosa as well as in mesenteric lymph nodes [128, 129, 131]. This crystal histiocytosis produced infiltrative lesions, mimicking—in radiological studies—malignant lymphoma or other infiltrative disorders [128]. In patients under long-term clofazimine, this condition must be considered to avoid misdiagnoses and unnecessary laparotomy.

Cough and upper airway angioedema are well-recognized adverse reactions of angiotensin-converting enzyme (ACE) inhibitor therapy. Angioedema occurs in 0.1 to 0.7% of patients taking these drugs, and it can affect about 1 of 2500 patients during the first week of exposure [133]. It usually manifests as swelling of the face, tongue, and lips, and in rare cases, the gastrointestinal wall. Thus, visceral angioedema is a rare and often unrecognized complication of ACE inhibitor therapy [134]. Indeed, since angioedema is less obvious when it involves abdominal organs, it presents a diagnostic challenge. When angioedema involves, the gastrointestinal tract symptoms can mimic an acute abdomen. Most patients complain of abdominal pain, while emesis, diarrhea, and ascites are frequent accompanying symptoms. Laboratory results are mostly non-specific, with up to half of the patients showing leukocytosis and elevated serum creatinine levels [134]. CT findings consist of circumferential small bowel wall thickening, which may be segmental. Mucosal enhancement is seen with prominence of the mesenteric vessels. The precise mechanisms of action of ACE inhibitors in relation to visceral angioedema are not fully understood. It has been suggested that bradykinin-associated vasodilation and altered vascular permeability cause the edema seen with ACE inhibitors [134].

Among the many cardiovascular complications of the contraceptive pill, one of the least familiar is small bowel ischemia, but one associated with a high mortality rate and much morbidity [135]. "Reversible" ischemic enterocolitis or colitis and intestinal infarction represent the two clinical and pathologic presentations of this infrequently seen complication [136]. The clinical presentation is in all instances abdominal pain, usually colicky in nature, lasting from hours to weeks and associated with bloody diarrhea or gross hematochezia in 87% of patients. Nausea and vomiting are less consistently reported (33%). Fever and elevated leukocyte count (the only laboratory study with consistently abnormal results) could be present [136]. Plain radiographs of the abdomen were normal in most patients, although occasional reports of non-specific large or small bowel ileus or bowel wall thickening have been reported. The pathophysiology of this iatrogenic complication is unclear, complex, likely multifactorial, and connected to the "pro-thrombotic state." Contraceptive pill has long been suspected of being able to predispose to classic IBD. This assumption has been supported by early studies [16] and a recent meta-analysis [137], showing a significant association between the contraceptive pill use and Crohn's disease.

Non-traumatic spontaneous small bowel intramural hematoma (IMH) is one of the potential complications of oral anticoagulation therapy. Once considered a rare event, it is now being reported with increasing frequency. Clinical series of spontaneous IMH involving a high number of patients are quite rare, and the literature data mainly consist of case reports. The classical triad of clinical symptoms comprises abdominal pain, small bowel obstruction, and multiple hemorrhagic symptoms (hematuria, hematomas, ecchymoses, hematemesis, and melena) [138, 139]. While leukocytosis is frequently reported, the presence of anemia is not a constant finding. Although suspected, the diagnosis can only be confirmed by abdominal imaging or an exploratory laparotomy.

Ultrasonography in patients with acute intramural small bowel hematoma will show a thickened and echogenic submucosal layer [140]. It should be considered, however, that this finding is not specific for intestinal tract hematomas and can be seen in a wide spectrum of lower GI disorders, including IBD. The diagnosis is more evident on CT examination, which reveals included circumferential bowel wall thickening, luminal narrowing, and intestinal tract obstruction. Intramural hyperdensity can be seen in some patients. A stacked-coin appearance can also be evident [140]. The most important etiologic factors appear to be overanticoagulation with vitamin K antagonists (the thromboplastin time is prolonged in over 70% of cases) or correct oral anticoagulation associated with additional impairment of hemostasis, due to the administration of antiplatelet drugs [140]. It is worth mentioning that spontaneous intramural small bowel hematoma has also been described during therapy with low molecular weight heparin (LMWH) [141].

Conclusions

The ever-increasing number of drugs on the market, allowing more effective treatments for a variety of diseases, is a welcome witness to medical progress. There is however the other side (the dark one) of the coin. Sir William Osler famously commented that "no drug has a single effect" and these side actions range from the mildly inconvenient to the frankly dangerous [142]. Since most drugs are given by oral route, medication-induced GI symptoms and lesions are commonly encountered in clinical practice. Oral intake allows direct contact between the drug and the entire GI tract mucosa, exposing it to topical damage until absorption. The large surface area of the small bowel and prolonged exposure time increase the risk of drug-mediated damage, which is often further increased by impairment of intestinal permeability.

There is an ever-growing list of medications, including several drug classes, which are potentially able to affect adversely the GI tract [9–12]. The injury can be specific or non-specific [10, 11] and local and/or systemic [7], and the outcome can range from asymptomatic histologic changes in the GI mucosa to fatal complications. Drug-induced GI disorders may closely mimic other GI conditions (both functional and organic), and failure to recognize medication-driven symptoms may lead to unnecessary investigations and treatment. It is therefore mandatory to have an in-depth knowledge of clinical pharmacology and toxicology and maintain a high degree of awareness of drug-related adverse events. Only then, the practicing physician will be able to diagnose medication-induced small bowel lesions correctly and implement the best strategy to treat them.

Compliance with Ethical Standards

Conflict of Interest Ingvar Bjarnason declares no conflict of interest.

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Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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