# Drug-induced gastrointestinal disorders

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## Abstract

Adverse drug effects on the gastrointestinal (GI) tract can occur: (1) as a predictable result of a drug's mode of action; (2) by direct injury; (3) through compromising GI mucosal integrity; or (4) as a consequence of changes in colonic microbiota. Non-steroidal anti-inflammatory drugs are the most common cause of gastroduodenal injury, owing to inhibition of prostaglandin synthesis, and increase the risk of serious GI complications. Low doses of aspirin are associated with an increased risk of upper GI haemorrhage. Cyclooxygenase (COX)-2 inhibitors largely spare the GI mucosa from injury. Advancing technology for investigating the small bowel now allows the identification of subtle changes (such as ulceration and erosions) of the small bowel mucosa secondary to drugs. This can lead to occult iron deficiency anaemia, hypoalbuminaemia and protein-losing enteropathy. Drug-induced colitis is an important problem, with antibiotics the most common drug cause. Drugs can also worsen pre-existing inflammatory bowel disease. Strategies to minimize the adverse GI effects of drugs include drug avoidance or minimization, using the lowest doses for the shortest time, selective COX-2 inhibitors for high GI risk/low cardiovascular risk patients, and upper GI mucosal protection by co-prescription of proton pump inhibitors with GI irritants.

**Keywords** Adverse events; colon; drugs; gastrointestinal injury; MRCP; non-steroidal anti-inflammatory drugs; pill induced; small intestine

## Introduction

Almost any drug can affect the gastrointestinal (GI) tract. Studies have shown that up to 5% of hospital admissions are associated with drug-induced disorders, and 40% of adverse drug reactions affect the GI tract. This contribution highlights drug-induced GI disorders that are common, important or often missed. It is useful to consider drug effects on the GI tract in the four categories below.

*Consequences of pharmacological mode of action* — adverse drug effects can occur as a predictable result of a drug's mode of action. For example, drugs with anticholinergic effects (e.g. antidepressants) reduce oesophageal sphincter pressure, resulting in reflux and heartburn; they also reduce colonic transit, resulting in constipation.

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## Key points

- Treatment of head and neck cancer with radiotherapy and/or cytotoxic agents can cause mucositis primarily affecting the oral mucosa

- Consider drug-induced diarrhoea with commonly prescribed medications such as β-adrenoceptor blockers

- Narcotic bowel syndrome is characterized by cycles of abdominal pain and increasing dose escalation of opiates in chronic users and is associated with hyperalgesia and constipation. It is an important diagnosis to exclude in these patients

- Microscopic colitis has been associated with use of non-steroidal anti-inflammatory drugs and proton pump inhibitors

- Elderly patients can have multiple causes for single presenting gastrointestinal (GI) complaints. They can be particularly susceptible to drug-related GI injury, in particular gastroduodenal ulceration and colitis

*Impairment of GI mucosal integrity* — the best-known examples are non-steroidal anti-inflammatory drugs (NSAIDs), which act principally by inhibiting prostaglandin synthesis.

*Direct injury to the GI tract* — examples include oesophageal damage by potassium preparations, gastroduodenal ulcers caused by cytotoxic drugs, and the ulceration and colitis associated with NSAIDs independent of prostaglandin inhibition.

*Changes in colonic bacterial flora* — widespread use of antibiotics, particularly cephalosporins, is associated with an increased incidence of *Clostridium difficile* infection and pseudomembranous colitis.

## Oral disease

Few drugs cause significant problems to the oral mucosa. However, the use of head and neck radiotherapy or cytotoxic agents can lead to mucositis, which most commonly affects the oral mucosa but can affect the mucosal lining throughout the GI tract. Mucositis is diagnosed by temporal association and the presence of inflammatory or ulcerative lesions in the mucosal barrier. Therapy is largely conservative. Risk of sepsis is particularly increased in immunosuppressed patients because of loss of the mucosal barrier. Further damage to the mucosa should be minimized. Good oral and dental hygiene, topical and patient-controlled analgesia, and early nutritional assessment are recommended. In some cases, injury can be so severe as to impair intake of nutrition owing to severe pain. In these cases nutritional support can be required.[1]

## Oesophageal disease

### Heartburn

Drugs commonly associated with heartburn and/or oesophageal injury are listed in Table 1. Drugs that relax the lower

## Common drug causes of oesophageal problems

**Relaxation of lower oesophageal sphincter causing heartburn**
- Anticholinergic agents (e.g. procyclidine, trihexyphenidyl)
- Tricyclic antidepressants
- Calcium channel blockers
- Nitrates
- Phenothiazines

**Direct mucosal injury**
- Tetracyclines
- Bisphosphonates

**Association with strictures**
- Potassium chloride[a]
- Quinidine[a]
- NSAIDs

[a] Particularly modified-release preparations.

**Table 1**

oesophageal sphincter are particularly likely to cause problems because of the increased acid exposure of the oesophagus (often without mucosal injury). For most drugs, the precise mechanism by which dyspepsia arises is unknown, although there are a few exceptions (e.g. erythromycin, which causes pain as a consequence of its prokinetic activity as a motilin receptor agonist). Drugs such as cytotoxic agents and pivampicillin have been associated with peptic ulceration, although the evidence for the association is often informal. Calcium channel antagonists have also been implicated in peptic ulcer bleeding.

Patients should be managed by drug withdrawal when possible, although a few require acid suppression. Endoscopy is not usually required if the onset is clearly related to the drug and the condition settles on drug cessation.

*Candida oesophagitis* is a common cause of dyspepsia (heartburn) or odynophagia (painful swallowing) in patients taking corticosteroids (either systemic or inadvertently swallowed inhaled preparations), antibiotics or immunosuppressive drugs. The characteristic appearance at endoscopy is the formation of discrete white plaques.

### Mucosal injury and strictures

NSAIDs and tetracyclines, particularly doxycycline, are relatively common causes of erosive or 'pill' oesophagitis. There are case reports of other drugs such as fluoxetine, iron supplements, rifampicin and oral contraceptives causing similar problems. Potassium chloride and quinidine are more strongly associated with strictures, often in the mid-oesophagus, with modified-release preparations a particular problem. Bisphosphonates, now commonly prescribed, can cause reversible oesophagitis. Risk of drug injury can be minimized by correct administration while remaining in the upright position for 30 minutes, accompanied by plenty of fluids.

### Dyspepsia and gastroduodenal ulcers

Virtually any drug can cause dyspepsia, most commonly without oesophagitis or gastroduodenal ulceration (non-ulcer dyspepsia). Some drugs have been associated with ulceration or ulcer complications. Most attention has focused on NSAIDs, which have been responsible for up to 30% of adverse drug reaction admissions. This burden may be reducing as their use is declining and the use of protective measures (principally prescribing of proton pump inhibitors (PPIs)) is increasing. Aspirin is an NSAID that is rarely used at anti-inflammatory dosage. It is now predominantly used at low doses for cardiovascular protection and, more recently, cancer prophylaxis and therapy.

### NSAID ulcers and non-ulcer dyspepsia

Non-ulcer dyspepsia is the most common GI adverse effect of NSAIDs. Uncomplicated ulceration is also common (Figure 1) but often (relatively) silent. Dyspepsia is thus a poor guide to management, and patients often present with an unheralded ulcer complication. NSAIDs cause ulcers principally because of inhibition of prostaglandin synthesis.

*Estimation of risk* − the use of traditional NSAIDs increases the risk of serious GI complications. Case-control studies and a meta-analysis have shown that the average relative risk of developing uncomplicated or complicated peptic ulcer is 4-fold and 5-fold in NSAIDs users compared with non-users.

### Risk factors

**Patient-associated risk factors:** the main concomitant risk factors for ulcer complications are age and previous GI bleeding. Some studies suggest that NSAID-induced dyspepsia is particularly common in patients infected with *Helicobacter pylori*. Whether the same is true for ulceration is controversial.

**Drug-related risk factors:** the main drug-related risk factors are dose and choice of NSAID, co-prescription of corticosteroids and co-prescription of warfarin. The risk of ulcer complications increases with dose. Several meta-analyses have suggested a hierarchy of risk from a low level with low doses of ibuprofen, through an intermediate level with diclofenac, to a high level with ketoprofen, piroxicam, naproxen, indometacin. In addition,
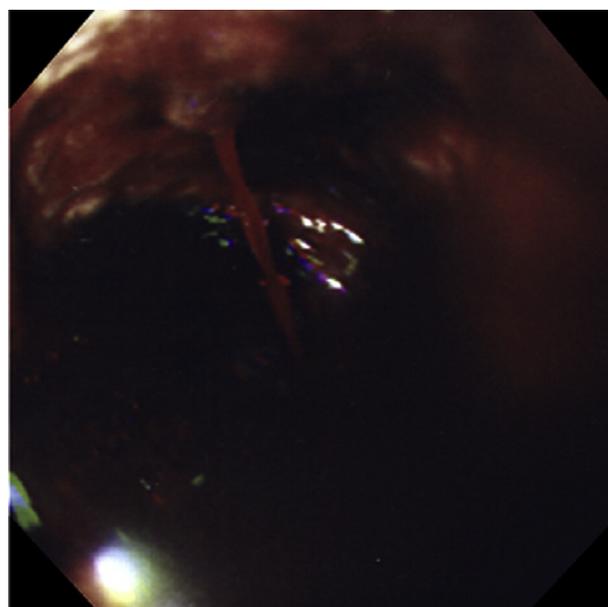


**Figure 1** NSAID-induced gastric ulcer with active bleeding. Source: Courtesy of *Clinical Gastroenterology and Hepatology*, Mosby, 2005.

there was an up to 8-fold variation in risk across the recommended dose ranges for each drug. It now seems likely that corticosteroids do not increase the risk of ulceration, except in patients taking NSAIDs.

**Aspirin anticoagulants and other anti-haemostatic agents:** the GI risks of low-dose aspirin are becoming a major cause of ulcer complications as its use becomes more widespread. The 2015 National Confidential Enquiry into Patient Outcome and Death of UK patients with acute upper GI bleeding (AUGIB) that followed the 2007 UK audit into AUGIB found that peptic ulceration remained the most common cause identified (44% of recorded endoscopic diagnoses). Of patients admitted with AUGIB, 34% were taking aspirin compared with 13% taking warfarin, 13% clopidogrel and 6% NSAIDs. AUGIB continues to carry significant mortality, with almost 10% of patients dying during their hospital stay.[2]

Aspirin is estimated to increase the risk of upper GI haemorrhage 2−3-fold. At low doses, aspirin has a limited effect on the gastroduodenal mucosa, and its anti-haemostatic properties are thought to be the dominant mechanism by which it causes ulcer bleeding. However, a large double-blind, placebo-controlled outcomes study is, at the time of writing, investigating whether the risk of ulcer bleeding is reduced in patients on aspirin if *H. pylori* has been eradicated, which may change our understanding of the mechanism of ulcer bleeding in these individuals.[3]

Clopidogrel, warfarin and direct-acting oral anticoagulants (DOACs), including the thrombin inhibitor dabigatran, and the factor Xa inhibitors apixaban and rivaroxaban, have been associated with GI bleeding. Risks are higher if aspirin is used in combination with NSAIDs or clopidogrel.

### Reducing risk
#### Proton pump inhibitors:
*NSAIDs* − it is cost-effective for all patients taking an NSAID or a cyclooxygenase (COX)-2 inhibitor to be offered ulcer prophylaxis with a PPI. This is based largely on primary prophylaxis endoscopic studies and secondary prevention studies that have used ulcer bleeding as an endpoint.

*Aspirin* − data are fewer than for NSAIDs, but most authorities would recommend a PPI-based strategy, especially in patients >75 years of age.[4]

*Clopidogrel* − there are pharmacokinetic data showing that PPIs can inhibit the activation of clopidogrel, although it seems that this is not clinically significant. In a randomized controlled trial, patients taking omeprazole had a significant reduction in upper GI complications with no difference in cardiovascular events compared with placebo. On current evidence, the decision to administer PPIs to patients treated with clopidogrel should be individualized based on the patient's bleeding and cardiovascular risk.

*Oral anticoagulants* − there are few definitive data in this area. Observational studies suggest that PPIs may reduce the risk of upper GI bleeding. Omeprazole and possibly other PPIs may increase anticoagulation by inhibiting warfarin metabolism, but the clinical impact of this is limited and can be managed by careful monitoring. PPIs do not interact with DOACs, but their role in preventing associated bleeding has not been established.

***Helicobacter pylori* eradication:** the role of *H. pylori* in drug-induced GI ulceration is complex and there are few systematic trial data. Some studies have shown that eradication of *H. pylori* before NSAID use reduces the risks of endoscopic ulcers. Others have shown no difference or that individuals with continuing *H. pylori* infection have better rather than worse outcomes when acid-suppressing drugs are used.

**Cyclooxygenase-2 inhibitors:** selective COX-2 inhibitors were heralded as 'safer NSAIDs' because they carried the anti-inflammatory benefits of COX-2 inhibition while retaining the gastroprotective benefits of COX-1. Four large outcome studies have considered rofecoxib (VIGOR study), celecoxib (CLASS study), lumiracoxib (TARGET study) and etoricoxib (MEDAL programme). TARGET showed a 5-fold reduction in ulcer complications to very low levels that were similar to those seen in the background population in patients not taking aspirin. All studies have similarly shown reductions in complicated and uncomplicated ulcers or in close surrogate measures to a greater or lesser extent in non-users of aspirin. In all studies, aspirin use was associated with a loss of most, if not all, of the benefits of the COX-2 inhibitor.

Recent studies have raised concerns about increased cardiovascular risk with the use of COX-2 inhibitor drugs, which has somewhat tarnished their reputation within the UK. However, further evidence suggests that their cardiovascular risk profile may be comparable to standard NSAIDs. The National Institute for Health and Care Excellence (NICE) still recommends their use, suggesting that COX-2 inhibitors be reserved for patients at 'high risk' of GI adverse effects.

### Recommendations for prophylaxis
- Patients with one or more risk factors for NSAID-associated ulcers (80% of patients) should be advised to take preventive treatment, although this is often neglected.
- PPIs have been shown to prevent aspirin- and NSAID-induced upper GI injury. There remains some concern over their use in patients treated with clopidogrel because of abrogation of the antiplatelet effect.
- $H_2$-receptor antagonists can be used to protect against NSAID damage, but there is good evidence to suggest that, at a conventional dosage, these agents prevent only duodenal ulceration.
- COX-2 inhibitors are associated with fewer GI events than traditional NSAIDs. This benefit is lost in aspirin users. However, unlike NSAIDs, COX-2 inhibitors do not interfere with aspirin's ability to inhibit platelet aggregation. Although there is concern about the effects of COX-2 inhibitors (and NSAIDs) on cardiovascular outcomes, a combination of a COX-2 inhibitor with aspirin may prove to be a more reliable anti-haemostatic strategy than a combination with a non-selective NSAID.
- For those at high risk of GI ulceration, addition of a PPI to a COX-2 inhibitor offers even greater GI protection.

### Management
NSAID-induced ulcers have been shown to heal with all standard anti-ulcer drug regimens. Healing is faster if the NSAID is

stopped. PPI therapy is the recommended first-line treatment for effective ulcer healing.

## Nausea and vomiting

Nausea and vomiting are common adverse drug reactions that can occur as a direct effect of the drug or as a result of gut damage, including ulceration. The more common drug causes are listed in Table 2. Many drugs (e.g. levodopa, opioids, cisplatin, digoxin) induce symptoms by directly stimulating the chemoreceptor trigger zone in the area postrema (located on the dorsal surface of the medulla oblongata at the caudal end of the fourth ventricle). Chemotherapeutic agents probably cause nausea and vomiting by stimulating serotonin release from enterochromaffin cells within the gut, which activates the vagus. Drugs such as potassium chloride, iron preparations and NSAIDs probably act via direct gastric irritation. In a few patients, these symptoms are accompanied by gastric or duodenal ulceration. Dopamine receptors in the area postrema are the target for antiemetic drugs such as chlorpromazine, haloperidol, domperidone and metoclopramide.

Nausea is a challenging symptom to investigate, and no drug should be judged blameless until the effect of stopping it has been assessed. Use of several drugs at one time, particularly in elderly patients, can cause nausea, and it is important to simplify drug regimens in such patients. Chronic use of other substances such as alcohol or cannabis can lead to significant symptoms and should be enquired about directly during the history. Cannabis use has been shown to cause a syndrome similar to cyclical vomiting syndrome, so called cannabinoid-induced hyperemesis. Cyclical vomiting syndrome presents with episodic and sometimes severe vomiting episodes of unidentified cause, which can lead to electrolyte disturbance and dehydration, and can require hospitalization.

## Pancreatitis

Alcohol is a common cause of pancreatitis. Other drug-related causes are uncommon, but the main culprits are:
- diuretics (thiazides, furosemide)

- angiotensin-converting enzyme inhibitors
- statins
- sulfonamides
- azathioprine and 6-mercaptopurine
- corticosteroids
- NSAIDs
- sodium valproate
- exenatide and liraglutide
- L-asparaginase (about 7% of recipients).

## Constipation

Opioids and drugs with antimuscarinic effects are the main causes of drug-induced constipation (Table 3). Opiate combinations increase ileocaecal and internal sphincter tone while weakening GI motility movements and lessening the susceptibility of rectal dilation to stimulation; this prolongs the duration of excretion in the intestine, causing constipation. Pharmacological therapies have been developed that selectively antagonize peripheral opioid receptors to relieve constipation. One such example is naloxegol, which has been approved by NICE to treat opioid-induced constipation not responding to laxatives. Combined preparations of opioids and opioid antagonists are now available in an attempt to prevent constipation in particularly susceptible patients, such as those with palliative care needs.

Reduced bowel frequency also occurs with selective serotonin reuptake inhibitors (e.g. fluoxetine) and locally acting

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**Common drug causes of nausea and vomiting**

**Locally irritant**
- Potassium chloride
- Iron preparations
- NSAIDs
- Theophyllines
- Azathioprine
- Metronidazole

**Act via the central nervous system**
- Levodopa
- Bromocriptine
- Opioids
- Digoxin
- Chemotherapeutic agents (e.g. cisplatin, mustine, dacarbazine, cyclophosphamide)

Table 2

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**Common drug causes of constipation and diarrhoea**

**Constipation**
- Drugs with antimuscarinic effects (e.g. atropine, phenothiazines, tricyclic antidepressants)
- Opioids
- Mebeverine
- Peppermint oil
- Aluminium-containing antacids
- Sucralfate
- Gaviscon®
- Iron
- Laxatives (chronic)
- Loperamide
- Ondansetron

**Diarrhoea**
- β-Adrenoceptor blockers
- Misoprostol
- Antibiotics
- Magnesium-containing antacids
- Olsalazine and other aminosalicylates (5-ASAs)
- Mefenamic acid
- Iron
- Laxatives (acute)
- Metformin
- Angiotensin-converting enzyme inhibitors
- Statins
- NSAIDs
- PPIs

Table 3

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antispasmodics (e.g. mebeverine, peppermint oil). Aluminium-containing antacids, sucralfate and alginates (e.g. Gaviscon®) also commonly cause constipation, as does iron (although this can also cause diarrhoea). Drug-induced megacolon from enteric neurotoxicity caused by vincristine or (possibly) laxatives is an uncommon but important cause of drug-induced constipation. Some constipating drugs (such as ondansetron) are now being recognized as a useful therapy for diarrhoeal illnesses.

A number of newer treatments are now available for constipation. These include prucalopride, which is a highly selective serotonin 5-HT$_4$ receptor agonist that acts as a prokinetic in the gut, and linaclotide, which is an agonist that activates the cell surface receptor of guanylate cyclase 2C (GC-C), which in turn increases intracellular cyclic guanosine monophosphate (cGMP). Elevated cGMP stimulates the secretion of chloride, bicarbonate and water into the intestinal lumen, resulting in increased intestinal fluid and accelerated transit. Finally, lubiprostone is a bicyclic fatty acid medication derived from prostaglandin E1 that acts by specifically activating ClC-2 chloride channels on the apical aspect of GI epithelial cells, producing a chloride-rich fluid secretion. These secretions soften the stool, increase motility and promote spontaneous bowel movements.

Although fibre (dietary and prescribed) is used to treat constipation, it can cause pain, bloating and, occasionally, impaction if excessive amounts are ingested unaccompanied by adequate volumes of liquid. Soluble fibre (porridge, bananas, ispaghula husk) is better tolerated than insoluble fibre by many patients.

**Narcotic bowel syndrome** is an important diagnosis to exclude in chronic opioid users. This describes cycles of abdominal pain and increasing dose escalation of opiates in chronic users. It can be associated with hyperalgesia and constipation. The treatment required is opiate withdrawal.[5]

### Melanosis coli

Anthraquinone laxatives (e.g. senna) are widely used laxatives of natural origin that pass unabsorbed to the large bowel, where they are metabolized to aglycones. These aglycones exert their laxative effect by damaging epithelial cells, which leads directly and indirectly to changes in absorption, secretion and motility. Damaged epithelial cells can be found as apoptotic bodies in the pigmented colonic mucosa, characteristic of pseudomelanosis coli. The belief that laxatives cause enteric neuronal damage leading to chronic megacolon is probably misplaced.

### Diarrhoea

Drug-induced diarrhoea (Table 3) is common. The main causes are:
- antibiotics, which disturb the colonic flora and tend to select *C. difficile* (responsible for pseudomembranous colitis; Figure 2)
- β-adrenoceptor blockers, which act by antagonizing anti-peristaltic adrenergic stimulation
- bile acids, which have a direct irritant action in the colon
- misoprostol, which stimulates intestinal secretion and motility.

Metformin is associated with a number of GI adverse effects, diarrhoea being the most common. However, modified-release
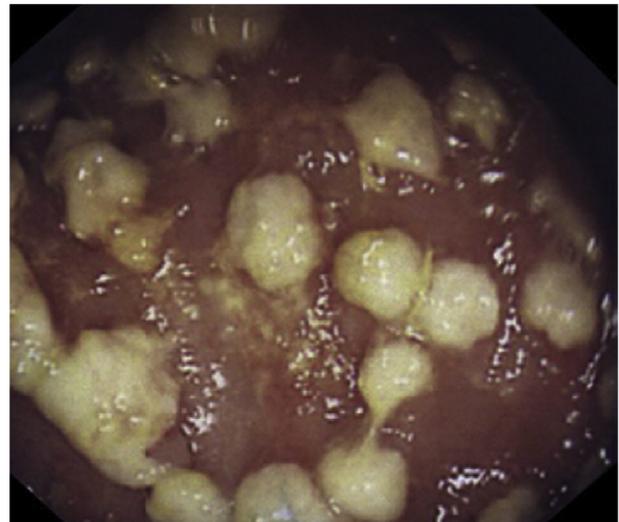


**Figure 2** Appearance of pseudomembrane in sigmoid colon after broad-spectrum antibiotics (cephalosporin), with proven *Clostridium difficile* toxin on stool testing. Source: Courtesy of *Clinical Gastroenterology and Hepatology*, Mosby, 2005.

preparations have been found to have better GI tolerability than immediate-release preparations. Magnesium-containing antacids (available over the counter) can be an unrecognized cause and may not be detected in the initial history. Deliberate use of laxatives should always be considered in patients with diarrhoea, particularly when the serum potassium level is low. All salicylates can cause diarrhoea, but it is particularly likely with olsalazine, which has been shown to stimulate small intestinal secretion. Azathioprine occasionally causes diarrhoea, sometimes in the context of toxic shock-like syndrome, and can cause diagnostic confusion when the drug is used for inflammatory bowel disease. It is increasingly recognized that drugs that suppress acid production (PPIs and H$_2$-receptor antagonists) predispose to enteric superinfection.

### Malabsorption

Many drugs (e.g. colchicine, methotrexate, laxatives) can cause malabsorption, although this is usually of little clinical significance. Sulfasalazine and phenytoin commonly cause folate malabsorption.

### Small intestinal injury

The small intestine may be a more common site for NSAID toxicity than the stomach and duodenum, which are well recognized. However, the small bowel effects may be more occult, and usually arise only after chronic (e.g. 6 months') use. Small bowel enteropathy, a combination of increased intestinal permeability and mild mucosal inflammation, is suggested by hypoalbuminaemia and iron deficiency. This occurs from direct mucosal toxicity. Capsule endoscopy has allowed the demonstration that NSAIDs cause mucosal erosions (Figure 3).

### Colonic ulcers
NSAIDs are also recognized to cause sporadic colonic ulcers. Increasingly, the use of nicorandil, which has long been
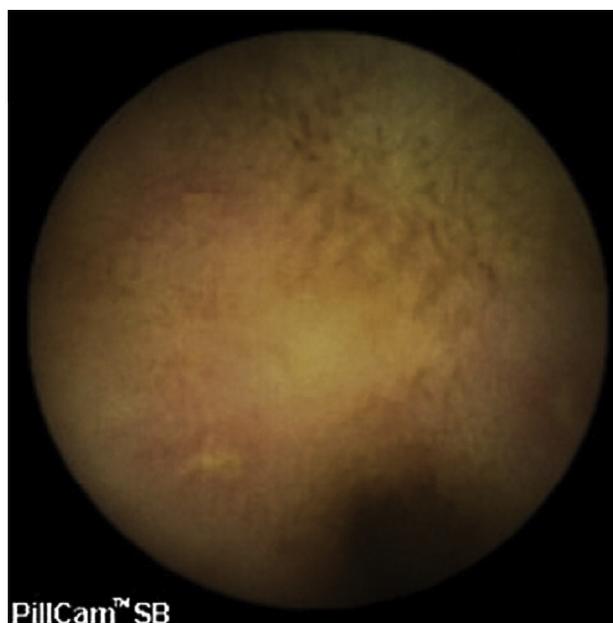
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**Figure 3** Typical small bowel erosions in the terminal ileum of a healthy volunteer taking NSAIDs, with a red halo resulting from hyperaemia, and a pale centre.

**Drugs that cause colitis**

**Antibiotics – leading to pseudomembranous colitis**
- Amoxicillin
- Ampicillin
- Clindamycin
- Erythromycin and clarithromycin
- Cephalosporins

**Drugs causing ischaemic colitis**
- Oral contraceptive pill
- Chemotherapeutic agents – 5-fluorouracil, cisplatin danazol
- Vasopressin
- Clindamycin
- Atypical antipsychotics

**Miscellaneous**
- NSAIDs
- Methyldopa
- Penicillamine
- Mycophenolate
- Ipilimumab

**Table 4**

associated with oral and anal ulceration, is being recognized as a cause of colonic ulceration. However, the mechanism has yet to be established, although it has been hypothesized that there is probably a potassium channelopathy. In terms of clinical manifestations, the patient can develop anaemia, diarrhoea or weight loss.

## Colitis

The most common drug-related causes of colitis are shown in Table 4. Endoscopic examination and biopsy can be useful if the clinical cause of colitis is uncertain or patients are immunosuppressed. Providing the histologist with as much information as possible about patient background, medication and endoscopic views is likely to yield the most useful histology reports. Other common causes such as ischaemic colitis should be considered if infective, drug-induced, pseudomembranous and inflammatory conditions have been excluded.

Whereas many chemotherapeutic agents can cause colitis (Table 4), capecitabine colitis requires a particular mention. This oral 5-fluorouracil pro-drug, commonly used as a chemotherapeutic agent against colorectal cancer, is recognized as a significant cause of chemotherapy-associated diarrhoea, which can be severe or even life-threatening. Depending on severity, treatment can involve antidiarrhoeal medications, fluid balance assessment and replacement, withdrawal of chemotherapy and nutritional support. Ipilimumab, a biological agent used in the treatment of malignant melanoma, can cause an immune-mediated colitis, which can present similarly to ulcerative colitis and can respond to infliximab therapy.

### Pseudomembranous colitis

Despite improvements in *C. difficile* infection rates in recent years, antibiotic-induced *C. difficile* infection leading to pseudomembranous colitis remains one of the most common drug-related colitis complications. In patients presenting with new-onset diarrhoea, direct enquiry should be made regarding recent antibiotic usage, recent hospital stay or possible contact history (such as nursing home residents). Although the antibiotics listed in Table 4 are the most common culprits, any recent history of any antibiotic usage should raise suspicion.

Toxin-positive patients are commonly treated with metronidazole or oral vancomycin, depending on the severity of the episode. Rarely, severe cases require prolonged or other antibiotic courses, immunoglobulins, faecal transplant or surgery. Polymerase chain reaction testing can now identify carriers of *C. difficile*. These non-toxin producing patients do not usually require treatment, but can be at risk of future toxigenic episodes. They can still pose a cross-infection risk.

### Microscopic colitis

The term 'microscopic colitis' encompasses both lymphocytic and collagenous colitis. These conditions are diagnosed histologically on colonic biopsy of an otherwise normal-appearing colon, in a patient with symptoms of watery diarrhoea. The exact cause is unknown, although the condition has been associated with a variety of medications, including NSAIDs and PPIs, and some autoimmune conditions such as coeliac disease. It is more common in elderly individuals. Treatment options include withdrawal of trigger medications, and trials of treatment with budesonide or loperamide.

### Exacerbation of ulcerative colitis

There is evidence that analgesic drugs (paracetamol and NSAIDs, including COX-2 inhibitors) provoke relapse of colitis in some patients. The mechanism is unknown. Interestingly some of the 5-aminosalicylic acid (5-ASA) medications used to treat colitis, such as mesalazine, are recognized to, paradoxically, worsen

diarrhoea. Immunosuppressant medications used in the therapy of colitis can also predispose to other infections, such as cytomegalovirus, which should be excluded in colitis not responding to conventional therapy.

## Drug-related gastrointestinal complications in elderly individuals

With an increasing elderly population and often a need for polypharmacy in this age group, this group of patients can be particularly susceptible to the problems of drug-related GI injury. Oesophageal injury can be seen in those with pre-existing oesophageal disease or massive left atrial enlargement, and is more likely to occur when patients swallow their medication in a reclining position. This group remains susceptible to ulcer disease, with 28% of patients who present with AUGIB being aged >80 years. Chronic diarrhoea can be multifactorial in this age group and should be investigated carefully. Elderly patients are at higher risk of *C. difficile* infection and other conditions such as microscopic colitis (collagenous or lymphocytic colitis) or ischaemic colitis. Long-term bowel injury from previous conditions, such as radiation proctitis from pelvic radiotherapy, should be excluded.

## In summary − minimizing the adverse gastrointestinal effects of drugs

To minimize adverse effects from drug therapy, ensure that tablets and capsules are taken with adequate fluid volumes to avoid getting stuck in the oesophagus. Modified-release preparations should be avoided. NSAID toxicity can vary depending on drug choice and dosage. Where possible, minimize the dosage, cover with a PPI or consider a COX-2 inhibitor. Be aware when

prescribing PPIs (and H$_2$-receptor antagonists) that enteric infection should be excluded should diarrhoea develop. Drugs can be a common cause of diarrhoea, and medication triggers such as β-adrenoceptor blockers can in particular not be appreciated by prescribers. In patients with inflammatory bowel disease, drug-induced diarrhoea, drug-induced disease relapse and secondary infection from immunosuppression require careful consideration. Elderly patients can have multiple causes for a single presenting feature such as diarrhoea. ◆

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# TEST YOURSELF

To test your knowledge based on the article you have just read, please complete the questions below. The answers can be found at the end of the issue or online here.

## Question 1
A 42-year-old woman presented with increasing abdominal pain, bloating and constipation. She had a history of three caesarean deliveries, laparoscopy for lysis of adhesions, and irritable bowel syndrome for 23 years that had been relatively well controlled. She had initially been treated with morphine sulphate (MST) 10 mg 12-hourly for her pain. However, the symptoms had worsened. The dosage of MST was therefore increased over time but, although it initially provided her with some relief, her abdominal pain became increasingly worse.

### What is the most appropriate action?
A. Increase the dose of MST
B. Gradually reduce the dose of MST to zero
C. Treat with antispasmodics such as buscopan
D. Treat the constipation with laxatives
E. Advise dietary changes

## Question 2
A 43-year-old man presented with a 6-month history of diarrhoea. He had up to 10 explosive watery stools a day with occasional faecal incontinence. There was no associated bleeding or pain. He had not lost any weight. There was no previous history of bowel problems. He had a past medical history of a cholecystectomy, hypertension and hypercholesterolaemia, and a recent onset of type 2 diabetes mellitus. He had not recently travelled abroad. His medications included metformin, ramipril, simvastatin, loperamide and buscopan.

### What is the most likely cause of his diarrhoea?
A. Infection
B. Ramipril
C. Simvastatin
D. Metformin
E. Bile acid malabsorption

## Question 3

A 78-year-old man presented with a 3-day history of melaena, abdominal discomfort and a feeling of lethargy and shortness of breath. Prior to this, he had suffered intense pain in his hip for which he had been self medicating with over the counter ibuprofen. He also had had a recent myocardial infarction whilst also being known to have atrial fibrillation, hypertension and type 2 diabetes mellitus. He was currently taking regular aspirin, clopidogrel, rivaroxban, ramipril and simvastatin.

On clinical examination, the abdomen was generally tender, with no guarding. Rectal examination confirmed melaena.

### Investigations

- Haemoglobin 87 g/litre (13.0−18.0) (previously 12.5)
- Urea 17.3 mmol/litre (2.5−7.0) (previously 6.1)

### Which is the most likely drug to have caused this event?

A. Ibuprofen
B. Simvastatin
C. Aspirin
D. rivaroxban
E. Clopidogrel