REVIEW

Drug-induced gastrointestinal disorders

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ABSTRACT

Drug-induced gastrointestinal disorders can mimic conditions, such as inflammatory bowel disease (IBD) and irritable bowel syndrome (IBS) and, hence, recognition can prevent unnecessary investigations and treatment. While the knowledge and awareness relating to the adverse gastrointestinal effects of some medications, such as non-steroidal anti-inflammatory drugs are well established, other commonly prescribed drugs, such as antipsychotics, antidepressants and metformin are less well understood and warrant further study. This review attempts to integrate recent information regarding adverse drug reactions and place this in a useful clinical context.

INTRODUCTION

Medication-induced gastrointestinal (GI) symptoms and endoscopic pathology are commonly encountered in clinical practice.[1] While awareness of GI adverse effects of some medications are well recognised, other medications that are commonly used and cause GI symptoms frequently, such as metformin, antipsychotic and antidepressants, are arguably underappreciated.[2 3] Medication-induced GI disorders may closely mimic other GI conditions (eg, irritable bowel syndrome (IBS) and inflammatory bowel disease (IBD)), and failure to recognise drug-related symptoms may lead to unnecessary investigations and treatment.[4] Medications produce symptoms by altering GI physiology (eg, constipation induced by anticholinergic medication), by causing tissue toxicity and damage (eg, ulcers from non-steroidal anti-inflammatory drugs (NSAIDs)), by changing the intestinal microbiota (eg, antibiotics causing *Clostridium difficile* infection), or by unknown mechanisms, such as with metformin.[5 6] The pharmacologically active compound, as well as the excipient (or packaging) of the tablet or capsule can cause problems.[7] Nausea and vomiting may be caused by mechanisms remote from the GI tract.[8] This article reviews the clinical and pathophysiological features of many of the commonly encountered drug-related disorders of the GI system, and attempts to categorise them to increase practical awareness and to improve management. An attempt is made to place the potential (or theoretical) adverse physiological consequences in a clinical context, and advise on the actual significance to patients. Drug-induced liver damage, and dental and gingival conditions are beyond the scope of this review.

OESOPHAGEAL DISORDERS

Oesophageal disorders may be induced by medications that alter peristaltic contractions (eg, by altering smooth or striated muscle function), by altering lower oesophageal sphincter pressure, decreasing saliva production, or by causing direct oesophageal damage through ulceration or predisposing to infection.[9] Medications commonly implicated are shown in table 1.

Pill oesophagitis

Oesophageal injury as a result of taking prescription or over-the-counter tablets and capsules typically manifests pathologically as inflammation and ulceration of the junction between the proximal and middle thirds of the oesophagus, perhaps because the aortic arch compresses this region.[9] Clinically, odynophagia is typical, but frank and painless dysphagia has also been described. In the largest review of world literature numbering more the 1000 cases, the medications most likely to cause oesophagitis were tetracyclines, particularly doxycycline (256 cases), NSAIDS, especially naproxen (81 cases), and aspirin (21 cases), slow-release potassium chloride (33 cases),

Table 1 Drugs reported to cause problems in the oesophagus, together with their proposed mechanisms

Presentation	Putative mechanisms	Drugs commonly reported
Pill oesophagitis	Hold-up in clearance of the pill from the oesophagitis Caustic injury of locally released drug	Tetracyclines Bisphosphonates Potassium chloride NSAIDs Iron
Gastroesophageal reflux	Lower oesophageal sphincter pressure	Nitrates Calcium channel antagonists Dopamine/dopaminergic agents Anticholinergics (eg, tricyclic antidepressants, hyoscine, propantheline) Progesterone Methylxanthines (caffeine, theophylline) Progesterone Alcohol
Dysphagia	Inhibit striated muscle function	Antipsychotics (dopamine antagonist); often associated with parkinsonism Alcohol
	Inhibit smooth muscle function	Anticholinergics (eg, tricyclic antidepressants, hyoscine, propantheline) Calcium channel blockers Theophylline Alcohol
	Cause xerostomia	Anticholinergics (eg, tricyclic antidepressants, hyoscine, propantheline) Opiates Antipsychotics Antihistamines Clonidine

NSAIDs, non-steroidal anti-inflammatory drugs.

iron tablets (ferrous sulfate or succinate (24 cases)) and alendronate (85 cases).[10] The precise mechanism whereby the ingested medications result in mucosal injury is speculative. However, physiological studies indicate that, in greater than 50% of healthy subjects swallowing gelatine-coated capsules, the pill will remain in the oesophagus for greater than 5 min.[10] Most individuals who develop pill oesophagitis will have normal premorbid oesophageal function (or rather report no clinical symptoms), although it is notable that increased patient age, decreased oesophageal peristalsis, increased tablet size and extrinsic compression are all described as risk factors for this phenomenon, and cases of oesophageal obstruction from ingested pills in a malignant or benign stricture are described.[11] It is plausible that the composition of some tablets and capsules may cause caustic injury to the oesophagus. This has been demonstrated using animal models whereby the dissolution of the medication may result in a local acid (in the case of tetracyclines or ferrous sulfate) or alkaline (phenytoin) environment-producing localised tissue damage.[9]

Preventive measures are recommended, particularly the instruction to take tablets with a glass of fluid and to remain upright for at least 30 min following the ingestion. The evidence-base for such a recommendation is poor, particularly the need to stand upright, since the passage of substances through the oesophagus is more dependent upon peristalsis than gravity.[12] However, they do highlight the risks associated with such medications. Over-the-counter preparations of iron, potassium and vitamin C have caused this phenomenon, and hence, careful advice to patients, even with these seemingly innocuous agents, is required.[13]

Other medication-induced oesophageal disorders

Medications (particularly those with anticholinergic or dopaminergic effects) may also cause physiological impairment to the lower oesophageal sphincter resulting in or worsening gastroesophageal reflux disease, or smooth or striated muscle function potentially resulting in the development or worsening of dysphagia.[13] Furthermore, the ability of some of these same medications to cause xerostomia and, hence, contribute to dysphagia via the loss of the lubricating effect of saliva is apparent.[9] The prevalence of dysphagia as a result of medications is not known, and a small number of case reports (not even case series) suggest this is uncommon. A key and frequently encountered feature in those presenting with dysphagia secondary to antipsychotic medications is drug-induced parkinsonism, manifesting as bradykinesia and rigidity.[14] Vulnerable populations with impaired physiological reserve, such as the elderly, appear to be particularly at risk.[11] Local or systemic immunosupression increase the risk of oesophageal infection most notably by viral or fungal agents. Inhaled corticosteroids and medication regimes used for transplant recipients (such as calcineurin inhibitors) can predispose to oesophageal candidiasis or viral infections, such as cytomegalovirus or human herpes virus.[15] Oesophageal candidiasis is especially common following the use of inhaled corticosteroids as used to treat asthma, and patients are

hence advised to gargle and rinse water as a means of potentially rinsing the steroid particles into the stomach and avoiding this complication.[15]

GASTRIC DISORDERS

Medications capable of causing localised damage to the oesophagus (pill oesophagitis) can also cause gastritis. With the exception of NSAIDs, the number of case reports published describing chemical gastritis is significantly less than that for pill oesophagitis.[16 17] Such injury may be asymptomatic; focal gastric injury is often observed at endoscopy in patients on NSAIDs or aspirin. The clinical manifestations of drug-related gastritis include nausea, abdominal pain, haematemesis and melaena (if the ulceration is severe). Nausea is a non-specific symptom and may be the result of local damage, gastroparesis, or even chemical effects on the central nervous system (see box 1). Medications capable of altering smooth or striated muscle function have been postulated to contribute to gastroparesis in the same way as they cause or contribute to dysphagia, although no physiological or clinical studies (case reports, case series or drug trials) support this assertion, aside from aerolised atropine which does delay gastric emptying.[18 19]

INTESTINAL DISORDERS

Symptoms or pathology attributed to the use of medication are reported less frequently in the small intestine, perhaps explained by a relative deficiency, at least until the recent advent of capsule endoscopy, in access and visualisation compared with other areas.[1 20] NSAIDs often cause mucosal lesions (see above and below), and iron and potassium chloride can also cause abnormalities similar to those described in the stomach and oesophagus (see above).[20] Symptoms that are not attributable to overt pathological damage, such as diarrhoea or constipation, may relate to the ability of a medication to alter GI transit per se, which could obviously involve the small and/or large bowel. Dedicated physiological or transit studies are, however, not forthcoming.

Box 1 Drugs reported to cause nausea and vomiting along with their proposed mechanisms

A. Via tissue damage
- Potassium chloride
- NSAIDs
- Iron
- Chemotherapeutic agents

B. Via chemoreceptors in the central nervous system
- Digoxin
- Dopaminergic agents (eg, levodopa, bromocriptine)
- Opiates
- Digoxin
- Chemotherapeutic agents (eg, cyclophosphamide, cisplatin)

Medication-induced constipation and diarrhoea

Case reports and case series are the major sources of data that link medications to abnormalities in GI transit, although the known pharmacological action of some agents may explain the resultant symptoms. Given that the 'normal transit time' of the small bowel (proximal duodenum to caecum) is 2–6 h, and for the large bowel it is 12–36 h, it may be that the effect on colonic propulsive motor activity by medications is of greater significance.[21 22]

Two recent large epidemiological studies suggest that medication-induced diarrhoea and constipation may be more common than previously recognised. In a community survey of 4622 patients, drug use per se, and polypharmacy, were independently associated with the report of constipation and diarrhoea.[3] In particular, frusemide, levothyroxine and ibuprofen were independently associated with constipation, and carbamazepine and lithium with diarrhoea (see discussion of individual agents below).[3] Interestingly, previous literature has reported frusemide and ibuprofen as causes of diarrhoea and not constipation.[23 24] In a nursing home-based study of 5622 elderly individuals, polypharmacy was associated with diarrhoea, and the medications that were implicated were antibiotics, psychotropics, allopurinol and angiotensin-2 inhibitors. Psychotropic medications that affect cholinergic and serotonergic pathways are known to cause GI symptoms (see discussion).[25 26] Cardiovascular medications used in the treatment of hypertension may also cause constipation (such as the calcium channel blocker, verapamil) and diarrhoea (such as β blockers), presumably related to their pharmacodynamic actions.[27 28] In clinical practice, the authors note that verapamil frequently causes constipation, and this effect has been used to treat diarrhoea caused by microscopic colitis, whereas diarrhoea due to β blockers is seldom encountered, perhaps highlighting the distinction between physiological studies (eg, demonstrating increased sigmoid contractility with β blockers) and clinically relevant effects.[28] Interestingly, ACE inhibitors have also been noted to cause diarrhoea. In rare patients, this is due to intestinal angioedema and associated with abdominal pain, thought to be related to bradykinin metabolism. In others, watery diarrhoea alone is described, but the mechanism is unknown.[29 30] Intriguingly, the effect of ACE inhibitors in modulating vagal tone and downstream effects in limiting the stimulation of angiotensin-2 receptors has been proposed as a treatment for constipation in some patients, although arguably, diarrhoea induced by ACE inhibitors is seldom encountered in clinical practice.[31]

Opiates are well known to cause constipation, occurring in around 40% of patients.[32] It is likely to be mediated through inhibition of the opiate-specific μ receptors located on the intestinal wall, in addition to their locations throughout the central and peripheral nervous system.[32 33] Opiate-induced constipation can be significant and result in cessation of the medication. In some cases where opiates are used long-term for chronic non-malignant pain, narcotic bowel syndrome (NBS) may result. This is characterised by abdominal pain that does not improve, but worsens despite escalating disease of opiates, resulting in a self-perpetuating cycle.[32] Fortunately, some relief of both the constipation and the NBS appears possible with the use of new pharmacological strategies including the opiate antagonist, naltrexone, and the peripherally restricted μ receptor antagonists methylnaltrexone and alvimopan.[33] The preferred management approach in patients with NBS is opiate withdrawal, although this is very challenging in patients with chronic pain. Prevention is the key by avoiding the use of, and if needed, increasing doses of opiates in patients with chronic pain where constipation may be a contributing factor.

Diarrhoea as a result of antibiotic ingestion can manifest both as the severe, at times life threatening, colitis due to infection by *C difficile*, as well as milder cases of watery antibiotic-associated diarrhoea.[34 35] *C difficile*-associated colitis is a well-recognised condition often caused by the ingestion of antibiotics (HR for cephalosporins and clindamycin is particularly high) resulting in overgrowth of this pathogen, a decrement of commensal 'good' bacteria and the production of *C difficile* toxins that have a direct lytic effect on enterocytes resulting in inflammation and necrosis. Less well recognised and researched is the much more common syndrome of watery diarrhoea shortly after the ingestion of antibiotics. Notably, an estimated 80–90% of cases of antibiotic-associated diarrhoea fall into this category, although its pathogenesis is mostly unknown. The β-lactam class of antibiotics are known to cause diarrhoea, although a higher risk in combination with calvulanate (as in amoxicillin-clavulanate) suggests that clavulanate may have an additional effect.[34] Erthryomycin and related macrolides can cause diarrhoea via stimulating motilin receptors and, hence, have been used in cases of gastroparesis with limited success because of tachyphylaxis.[8] Colchicine can cause diarrhoea (the mechanism is not known) in a dose-dependent fashion, and has been proposed as treatment for constipation.[36]

Proton pump inhibitors have been implicated in causing diarrhoea, the mechanisms proposed including small bowel bacterial overgrowth (shown in one study of 42 patients), microscopic colitis (case reports) and an increased rate of *C Difficile* (see above and below).[37–39]Arguably, the evidence linking proton pump inhibitor use to *C Difficile* infection is the strongest of these propositions, supported by a recent meta-analysis incorporating some 300 000 patients and revealing an increase in relative risk of between 1.5 and 2.7.[39]

Several other medications have been implicated as causes of diarrhoea (see box 1). Interestingly, all the agents that deliver 5-aminosalicylic acid (mesalazine) to the colon can cause diarrhoea. However, olsalazine is most notable, where the increase in intestinal transit has been demonstrated and found to be related to the stimulation of intestinal secretion resulting in clinically significant diarrhoea in 10–20% of patients.[40]

Drug-induced IBD

The use of several medications have been proposed to cause, precipitate or perpetuate ulcerative colitis (UC), Crohn's disease (CD) or conditions closely resembling these diseases.[4] The relationship between NSAIDs and IBD is discussed below. Antibiotics have been proposed to increase the risk of subsequent development of IBD, both for UC and CD, in children and adult populations.[4] Large (retrospective) case-control studies consistently associate the ingestion of antibiotics in the years leading up to the diagnosis of IBD.[4] Two large retrospective studies have been published recently in this area; an increased risk of IBD was reported with exposure to tetracyclines in 94 487 patients treated for acne in the UK, and previous use of antibiotics, except clindamycin, were linked to later development of IBD in 2234 subject and 22 346 controls in Canada.[41 42] Together with the association of the development of CD in those prescribed antibiotics for pneumonia in the first 5 years of life, these studies are increasing the case that antibiotic use may cause, and/or precipitate IBD, but how large the risk is, and how this should influence clinical decision making, is unknown.[43]

Exposure to the oral contraceptive pill among women has been linked to the development of both CD and UC, with a relative risk of between 1.5 and 2.5. The risk is greatest for current exposure, and appears to return toward baseline when the medication is ceased.[44] Discussion of this issue with women of reproductive age who develop IBD should be considered. Several other medications have been implicated as causes or precipitants of IBD or IBD-like conditions (table 2). Isotretinoin (a synthetic analogue of vitamin A) has been implicated as a cause of UC and CD, although the number of recorded cases is small (85 reported to the Food and Drug Administration (FDA) between 1986 and 2008) and the significance is still questioned. The American Academy of Dermatology position statement currently is that the evidence is insufficient to claim causality exists.[4]

Drug-induced microscopic colitis

The cause or precipitation of microscopic colitis (both lymphocytic and collagenous) by medications is supported by case reports, case series and a case-control

Table 2 Drugs implicated in the cause of lower gastrointestinal symptoms and/or conditions

Symptom/condition	Implicated medications
Diarrhoea	Metformin Iron Fibrates (less with fenofibrate) Antibiotics (especially amoxicillin-clavulinate) ACE inhibitors β-blockers Angiotensin-2 antagonists Lithium Carbamazepine NSAIDs Frusemide 5-ASA (especially olsalazine) Proton pump inhibitors
Constipation	Opiates Anticholinergics Iron Antipsychotics (especially newer atypical agents eg, clozapine) Verapamil Frusemide Levothyroxine Cholestyramine
Inflammatory bowel disease	Antibiotics Oral contraceptives Mycophenolate mofetil Etenercept Ipilimumab Rituximab
Microscopic colitis	SSRIs (especially sertraline) NSAIDs Ticlopidine Lansoprazole Carbamazepine Acarbose Ranitidine

ASA, aminosalicylic acid; NSAIDs, non-steroidal anti-inflammatory drugs.

study.[45 46] The medications implicated by the greatest body of literature are the NSAIDS and SSRIs (particularly sertraline).[46] Ticlopidine, lansoprazole, ranitidine, lisinopril, acarbose and carbamazepine have also been implicated. It is of interest that some of these agents (such as carbamazepine and lisinopril) have been noted as a cause of diarrhoea in observational studies, raising the possibility that the development of microscopic colitis may have been the underlying mechanism for the diarrhoea.[3]

SPECIFIC DRUG EFFECTS

Metformin-induced GI symptoms

Up to one in three patients who use metformin for the treatment of type 2 diabetes or other conditions (such as polycystic ovarian syndrome) will develop GI symptoms, with diarrhoea and nausea being most frequently reported.[47] In a review of 956 patients using oral hypoglycaemic agents for type 2 diabetes, those using metformin, but not other hypoglycaemic medications, were significantly more likely to report diarrhoea and faecal incontinence.[48]

The pathogenesis of metformin-induced GI symptoms is unknown, although several hypothesis and potential pathophysiological mechanisms have been suggested and studied. Relevant animal studies and case reports in humans have not identified pathologically evident lesions, strongly suggesting that a physiological (functional) disturbance underlies the symptoms. The malabsorption of bile salts (and vitamin B12) in the ileum is one putative mechanism that could cause diarrhoea.[49] A direct action of metformin on enterocytes that reduces the absorption of bile salts and enhances the secretory effect of conjugated bile salts on the colonic epithelium is hypothesised.[49] Other theories include the ability of metformin to act as an agonist at 5-hydroxytryptamine-3 (HT_3) receptors within the GI system, as well as altering the levels of other peptides important in GI function including ghrelin, VIP and GLP-1.[50]

Given the common use of metformin as a first-line agent in treating type 2 diabetes and the growing prevalence of this condition, as well as the potential for patients to discontinue their medication based on GI side effects (at least 5%), this would seem a clinically significant problem worthy of further study.[48] For example, the effect of bile acid sequestrants on metformin-induced diarrhoea has not been reported.

NSAID-induced GI disorders

The effect of NSAIDs in causing upper GI ulceration, most often in the stomach, is well recognised.[17] Inhibition of cyclooxygenase (COX), particularly of the constitutively expressed COX-1, leads to the reduction of bicarbonate and mucous production, as well as a decrease in blood flow and epithelial repair. Furthermore, NSAIDs are acidic and capable of causing local caustic damage.[1] The adverse effects are dose-related, and drugs within this class have variable ulcerogenic potential, probably related to the degree of COX-1 inhibition.[51] A new class of NSAIDs, namely COX-2 inhibitors such as rofecoxib and later celecoxib, attempted to minimise the GI side effects, and indeed the largest trial using rofecoxib demonstrated a 50% reduction in peptic ulcers compared with non-selective COX inhibitors.[51] However, the significant increase in cardiovascular events meant that this drug was declared unsafe.[52] A second large study using celecoxib with low-dose aspirin did not demonstrate a reduction in GI complications (although there was no increase in cardiovascular events), probably explained by the loss of GI protection induced by the aspirin.[53]

Small intestinal inflammation and ulceration as a result of NSAID use is frequent, and can be severe as documented by the more recent advent of capsule endoscopy[20] In one case series, the ingestion of diclofenac resulted in detectable new lesions in greater than 60% of subjects, although the majority were

asymptomatic.[20] The pathology induced by NSAIDS can be non-specific; for example, small erosions or red dots), but, in other cases, characteristic (intestinal diaphragm formation by some considered pathognomonic of NSAID-induced) and, in severe, rare cases, florid neutrophilic inflammation leading to ulceration, protein losing enteropathy and perforation.[20] Once again, the dose and the degree of COX-1 inhibition appear related to the likelihood of adverse events.[17]

Case reports and case series suggest that NSAIDS may cause damage to the large bowel with resultant lesions including ulceration, mucosal diaphragm formation and even perforation. Based on the relatively small number of case reports, and the lack or specific research dedicated to this topic, it would seem likely that colonic lesions directly attributable to NSAIDS are less frequent than those observed in the upper GI system.[23] More controversial is the assertion that NSAIDS may precipitate or cause IBD (both UC and CD). A recent large prospective study, using data derived from a trial that had a primary endpoint of cardiovascular outcomes, revealed an increased risk for the development of CD in those using low-dose aspirin (OR 6.14).[54] A case-control study of 200 cases of colitis (UC or CD) newly diagnosed between 1989 and 1993 demonstrated an OR of 1.77 for the recent exposure to NSAIDs.[55] The ability of NSAIDs to precipitate previously diagnosed cases of IBD has also been described in case reports.[4] The safety of COX-2 inhibitors may be superior in this regard, with a placebo-controlled trial of celecoxib failing to demonstrate an increased risk of disease exacerbation (either endoscopically or via clinical symptoms) in 222 patients with IBD, albeit over the short drug exposure interval of 2 weeks.[56]

GI symptoms induced by psychotropic medications

Psychotropic medications, such as antidepressant and antipsychotics are frequently used by patients presenting to gastroenterologists, yet the literature pertaining to the adverse effects of these agents is limited and resides mainly in psychiatry and not gastroenterology journals.[57] In a review of literature relating to second-generation antipsychotics, De Hert *et al*[57] noted that constipation was reported in 20% of patients receiving these agents. The constipation can be profound and, in the case of clozapine in particular, life threatening and associated with the need for intervention to prevent potential perforation or necrosis.[58] Many of the newer agents, including olanzapine, risperidone, quetiapine and ziprasidone cause constipation in at least one-quarter of patients.[25] The mechanism of constipation is not known, but is postulated to be due to anticholinergic, antihistaminergic and serotonergic effects, as well as possibly the lack of physical activity among the patients taking these sedating medications.[59] Given the propensity to the development of constipation and the potential for this to be severe, further study, particularly instituting prophylactic management strategies, should be undertaken.

Antidepressant-related GI adverse effects appear class-specific; the older tricyclic agents are typically associated with constipation secondary to their anticholinergic activity, while the newer selective serotonin reuptake inhibitors (SSRIs) are sometimes associated with nausea and diarrhoea on commencement, which is generally a short-lived phenomenon.[26] In one of the few physiological studies of antidepressant medications, Chial *et al*[60] found no difference in colonic transit using the antidepressant agents, paroxetine, venlafaxine or buspirone, compared with placebo. Upper GI transit appeared more rapid with paroxetine, and postprandial gastric volumes larger with venlafaxine.[60] A later study investigating the therapeutic use of venlafaxine in treating functional dyspepsia failed to demonstrate a change in gastric volumes.[61] Hence, it is apparent that the research in relation to these medications that have the potential to alter GI function is limited and, given the frequent prescription and potential for therapeutic use in GI disorders, further research is warranted.

The use of the mood-stabiliser medication, lithium, as well as carbamazepine has been associated with the development of diarrhoea, although neither the mechanism of action nor the relationship to the dose or duration of treatment have been elucidated. In a cross-sectional survey of 4622 individuals, 33% of patients taking lithium and 25% taking cabamazepine had diarrhoea.[3] As with other psychotropic medications, adverse GI side effects appear to warrant further study.

GI symptoms induced by excipients

Excipients, the fillers or 'vehicle' that transport the drug in a capsule or tablet, can potentially cause symptoms.[5] For example, small amounts of wheat starch containing gluten can potentially be harmful to patients with coeliac disease.[7] Lactose may also be found in ingested medications and could, theoretically, trouble those with lactose intolerance. However, the quantity of this sugar is likely to be very small, unless large volumes of syrup preparations are ingested. Artificial sweeteners, such as sorbitol, may be found in cough syrups and other elixirs as a sweetener, and may potentially cause abdominal bloating and diarrhoea in a dose-dependent fashion. Such poorly absorbed short-chain carbohydrates can trigger GI symptoms, particularly in patients with IBS.[62]

Preventing medication-induced adverse effects

Old age and polypharmacy have been recognised as risk factors for the development of diarrhoea and constipation, and hence, awareness and caution in the prescription of medication is required in these groups. It is apparent that some adverse effects are predictable and may warrant routine preventive strategies, including the use of other pharmacotherapies to ameliorate

the effects of the culprit agent. Two examples supported by high-level evidence are lessening the risk of *C difficile* infection associated with antibiotic exposure by the coadministration of probiotics at the time of antibiotic prescription (in an attempt to maintain or enhance the 'friendly' commensal bacteria such as lactobacillus, and reduce the growth of clostridium and production of clostridium toxin),[63] and the coprescription of a proton pump inhibitor to reduce the chance of NSAID-related peptic ulcer disease.[17] In the same way, it seems only reasonable that routine prescription of laxatives be considered when antipsychotic medications that cause constipation in approximately 1/5 of patients, although this is not current practice.[57] A knowledge of and further research into the prevention of medication-induced adverse effects remains an important area of investigation.

Therapeutically utilising medication-induced GI side effects

Knowledge of the adverse effects of some medications may allow the physician to use these agents for therapeutic purposes other than their principal pharmacological purpose in that patient. For example, in a patient with poorly controlled diarrhoea due to microscopic colitis who also has hypertension, the use of verapamil for the hypertension might be a wise decision due to its prominent constipating effect. Similarly, many patients with UC, particularly with distal disease or proctitis alone, develop troublesome constipation, variably described as 'proximal constipation'. Since the vast majority of such patients require maintenance therapy with a mesalazine (5-ASA)-delivering drug, it may be prudent to use olsalazine, since this has a net secretory effect in the small intestine and may mitigate the constipation. Given the multitude of medications available to the modern clinician and scientist, it is conceivable that a number of existing drug classes may be employed in treating GI symptomatology in patients with other indications for those drugs. Clearly, this is a fertile ground for research.

Summary

Medications may induce GI symptoms and, in some cases, cause mucosal injury. While some agents have known pathogenic actions and are well described, other widely used medications appear capable of causing symptoms in a relatively high proportion of patients. However, they remain under-recognised and, hence, warrant further study. Greater awareness and understanding of medication-induced GI symptoms may limit unnecessary, invasive and expensive diagnosis and treatment.

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