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Analgesic drugs and the gut – a reciprocal relationship

R Lawrence
Consultant Psychiatrist in Addictions, Royal Edinburgh Hospital, Edinburgh, UK

ABSTRACT Analgesic drugs, as well as providing pain relief, can cause a range of other symptoms and side effects, most notably on the gastrointestinal system. Conversely, gastrointestinal disease will often require analgesia, and this can be complicated by the fact that the gut is the site of absorption of oral drugs. This paper discusses some of the effects of common oral analgesic drugs on the gastrointestinal tract and their role in managing some of the most common, non-malignant, chronic gastrointestinal disorders in adults.

KEYWORDS analgesics, chronic pain, gastrointestinal tract, opioid-induced bowel dysfunction

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Correspondence to ***R Lawrence***
Royal Edinburgh Hospital
Morningside Terrace
Edinburgh EH10 5HF
UK

e-mail ***rebecca.lawrence@nhslothian.scot.nhs.uk***

Chronic non-cancer pain affects around 19% of adults,[1] and its management usually requires a broad biopsychosocial approach. Oral medications are frequently employed, and often expected by patients, and, while the type of pain can dictate choice of drug, there are a number of broad classes. These include non-steroidal anti-inflammatory drugs (NSAIDS) and paracetamol, antidepressants and anticonvulsants (gabapentin and pregabalin are often used for neuropathic pain) and opioids. Skeletal muscle relaxants are used less often for chronic pain, and more for musculoskeletal conditions.[2]

The balance of risk between efficacy and harm is challenging, and many of these drugs can cause significant gastrointestinal side effects. Philpott et al.[3] reviewed the effects of drugs on the gastrointestinal system, commenting that they can induce symptoms and signs that resemble common conditions, such as inflammatory bowel disease (IBD) or irritable bowel syndrome (IBS). NSAIDs, in particular, can cause severe ulceration of the stomach and small intestine. They act by inhibiting cyclo-oxygenase (COX) types 1 and 2, and the adverse gastrointestinal effects are mediated largely through inhibition of COX 1, causing a range of problems from mild discomfort and bloating to bleeding, ulceration and death.[4] Indeed, Thomsen et al.[5] showed that use of NSAIDS was associated with increased mortality in in-patients with peptic ulcer perforation, and that this occurred with both COX 1 and COX 2 inhibitors. COX 2 selective inhibitors were developed in an attempt to minimise gastrointestinal effects, but concerns, particularly regarding cardiovascular safety, have limited their use.[6] Marlicz et al.[7] reviewed the changes in gut permeability and bacterial growth with use of NSAIDs, suggesting that further, more subtle, inflammation and damage may occur in the small intestine. Proton pump inhibitors, such as omeprazole or lansoprazole, are often used to minimise upper gastrointestinal damage caused by NSAIDs, but there is emerging evidence that these may actually add to the harm inflicted by NSAIDs on the mucosa of the small intestine, possibly by causing bacterial overgrowth.[7] NSAIDs may also be helpful analgesics in acute pancreatitis, although they have also been implicated as a potential cause.[8] In addition, severe hepatic toxicity is a rare but potentially fatal complication of NSAID use.[9]

In contrast, as a clinician, one tends to view paracetamol as relatively innocuous as regards side effects when used at a therapeutic dose, despite its danger to the liver in overdose. There is also some limited evidence that likelihood of acute pancreatitis may be increased in paracetamol overdose, although the mechanisms are unclear.[10] However a recent literature review by Roberts et al.[11] questions the safety of paracetamol, with some studies showing an increased risk of cardiovascular and renal adverse events. One study demonstrated a possible dose-related increase of gastrointestinal adverse events or bleeds,[12] but there were a lot of potential confounders, including a probable higher rate of comorbidities, and conclusions were limited due to methodology. In addition, while there is already some evidence that analgesics such as paracetamol and NSAIDs are associated with IBS[13] as well as constipation,[14] the relationships remain unclear at present.

Given that there is an association between pain and depression, as well as other psychiatric disorders,[15] the increased risk of upper gastrointestinal bleeding when

TABLE 1 Analgesic drugs and some associated symptoms and conditions

Analgesic drug	Some common associated symptoms/ conditions
Non-steroidal anti-inflammatory drugs	Gastrointestinal discomfort/ bloating Gastrointestinal bleeding Ulceration stomach and small intestine Rare: cardiovascular or renal adverse events/severe hepatotoxicity
Paracetamol	At recommended dose, side effects are uncommon Severe hepatotoxicity in overdose Rare: Increased risk of cardiovascular/renal adverse events
Selective serotonin reuptake inhibitors antidepressants	Nausea Weight changes Sleep problems Dry mouth Dizziness Headache Agitation Sexual dysfunction
Serotonin and noradrenaline reuptake inhibitor antidepressants	Nausea Weight changes Sleep problems Dry mouth Dizziness Headache Agitation Sexual dysfunction Increased blood pressure
Tricyclic antidepressants	Anticholinergic effects, including constipation, often severe Weight gain Drowsiness Sexual dysfunction Tachycardia
Gabapentin/pregabalin	Drowsiness Dizziness Poor balance Poor memory/concentration/ confusion Oedema
Opioids	Constipation Abdominal pain Decreased gastric emptying Gallbladder contraction

selective serotonin reuptake inhibitors (SSRIs) are prescribed with NSAIDs is also of importance to the clinician.[16] Duloxetine, a serotonin and noradrenaline reuptake inhibitor that is often prescribed for neuropathic pain as well as depression, might be expected to have similar effects; however an analysis of placebo-controlled trial and post-marketing adverse event reports suggests that duloxetine does not increase the already raised risk of bleeding caused by NSAIDs.[17] Nevertheless, clinical experience suggests that duloxetine is not always well tolerated due to nausea, especially initially. Tricyclic antidepressants are also used to treat neuropathic pain, and their anticholinergic effects on the gastrointestinal system can cause significant constipation.[3] This may, however, contribute to their use in treating IBS, which will be discussed later. Antidepressants may also affect the liver, more commonly raising aminotransferases but occasionally leading to severe hepatotoxicity.[18]

Both gabapentin and pregabalin have been shown to be effective in treating neuropathic pain,[19] with their action considered to be due to their effect on voltage gated calcium channels.[20] There is some evidence that they may be beneficial in IBS, possibly by decreasing sensitivity of the rectum, but these studies are small and further investigation would be helpful.[21,22] Gabapentin and pregabalin are excreted by the kidneys, without being metabolised in the liver, so may be safer in liver disease.[23]

Opioid drugs are also being increasingly used in chronic non-cancer pain. They have long been supported by the World Health Organization for their role in cancer pain,[24] but their position in non-cancer pain is less clear. Many concerns have been raised regarding tolerance and addiction when used long-term, despite their established efficacy in the shorter term.[25] There are a number of guidelines recommending careful prescribing, with ongoing monitoring, and discontinuation if there is no benefit, and use of particular caution where there is a history of substance misuse.[26]

When withdrawing from opioids, patients predominantly complain of gastrointestinal symptoms, including abdominal pain, diarrhoea, nausea and vomiting, and it can be difficult, in some circumstances, to differentiate the underlying pain condition from the withdrawal syndrome. Conversely, one of the major side effects of opioid use is constipation, with prevalences calculated between 15%[27] and 41%.[25] Opioids have different effects throughout the bowel, including decreased gastric emptying and increased duodenal motility. They cause an increase in gastric secretions but, lower down the gut, decrease secretions and increase tone. They can also cause the gallbladder to contract, leading to pain and spasm of the sphincter of Oddi, delaying digestion.[28]

However constipation remains the most common problem and, such is its effect on quality of life and

health, that many attempts have been made to counter this. These include use of laxatives, and reducing opioid dose or changing opioid and, more recently, combining an opioid agonist, such as long acting oxycodone, with naloxone, an agonist that can reverse peripheral effects on the gut caused by opioids.[29,30] The effects of opioids on the bowel can be extremely severe, leading to significant abdominal pain and even hospitalisation, which may be made worse by giving additional opioids, or increasing doses to manage pain. Concerns have been raised that the symptoms produced, which can resemble those of IBS, are on the increase.[31,32] Caution should therefore be exercised when prescribing opioids for gastrointestinal disorders such as IBS and IBD, particularly in the overall context of increasing prescribing of opioids, notably in the USA. Opioids also require to be used with caution in chronic liver cirrhosis as they are metabolised by the liver and may worsen the symptoms of encephalopathy.[33]

Moving away from individual drugs to approach this issue from a disease perspective, there are a number of common disorders of the gastrointestinal system that may require analgesia. One of the foremost of these is IBS, which is seen frequently in both primary and secondary care. It is considered to be a functional disorder, in that clear evidence of organic pathology is not found, but it can cause distressing and disabling pain and altered bowel function, and is thought to be present in up to 20% of the adult population.[34] Biopsychosocial factors usually contribute to its development, and psychological interventions, such as cognitive behavioural therapy are an important component of therapy. Analgesia remains a key concern and various pharmacological approaches exist. Tricyclic antidepressants (TCAs) can be used for both pain and depression, and SSRIs can help the often-associated symptoms of depression and anxiety. These drugs are thought to work primarily by centrally inhibiting reuptake of brain noradrenaline and serotonin, respectively, with regulatory effects on the gut, but both drug classes can have gastrointestinal side effects. A 2008 NICE guideline provides a broad framework for managing IBS; pharmacological recommendations include antispasmodics, laxatives, linaclotide and loperamide, all of which may reduce pain despite not being classified as analgesics. TCAs (at low doses) and SSRIs are advised only after these agents have been tried.[35]

IBD also causes significant pain, and this can be directly caused by the inflammatory process and its consequences; however, pain can persist in periods of apparent remission, and this may have an overlap with the more functional pain experienced in IBS.[36] Psychosocial interventions may be helpful both for this aspect, and also to help cope with an ongoing debilitating and painful disorder. Disease modifying therapies, as well as steroids and antibiotics, are used in IBD, and may reduce pain by addressing pathology but are outwith the scope of this paper. Both NSAIDs and selective COX 2 inhibitors have been used to manage pain, although there are concerns they may actually worsen disease.[36,37] Opioids are often prescribed, but tolerance and dependence remain a risk, and opioid-induced hyperalgesia is being increasingly acknowledged as a potential contributor to pain. They can also cause side effects, including constipation and ileus and, at worst, narcotic bowel syndrome.[37] TCAs may also alleviate inflammatory pain, as well as acting centrally, and both TCAs and SSRIs can be used to address the psychological aspects of IBD. Both gabapentin and pregabalin may offer benefits by their effect on calcium channels, but this is likely to be less effective in the acute inflammatory stages.[37]

Chronic pancreatitis is another painful condition that is thought to be increasing in prevalence in developed countries, possibly due to increased alcohol consumption.[38] Many patients will have exocrine pancreatic insufficiency, and the use of replacement therapy to relieve symptoms is established.[39] In addition, simple analgesics, such as NSAIDs and paracetamol can be used, but more severe pain will often require use of weak, and sometimes strong, opioids. Misuse and dependence on opioids is a risk, which may be increased in patients who have previously misused alcohol. There are also additional challenges in this patient group when using oral medication. Many gastrointestinal disorders will cause problems with drug absorption, and pancreatic insufficiency will add to this. Patients with chronic pancreatitis can also have abnormalities of gut motility and bacterial overgrowth, and may continue to drink alcohol (sometimes to manage pain), which can interact with prescribed drugs. Opioids can decrease gut motility, further interfering with effects on absorption, as well as contributing their usual gastrointestinal side effects.[40] As regards choice of opioid, Paisley and Kinsella[38] consider tramadol to be a useful starting point, causing less constipation and neuropsychological side effects than morphine; they also comment that oxycodone may be particularly useful, due to its K-agonist effect in alleviating visceral pain. There may, however, also be some advantage in using transdermal preparations to avoid problems with absorption. Alternatively, buprenorphine (which is also licensed for use in opioid dependency) can be taken sublingually, and may have less severe side effects. Pergolizzi et al.[41] comment on buprenorphine's antihyperalgesic effect and good safety profile, which may also be an advantage.

Finally, pain management in liver disease, and particularly in cirrhosis, also poses challenges. Mortality from cirrhosis throughout Britain (especially in Scotland) increased from 1950 to 2002,[42] probably reflecting an increase in alcohol consumption, although possibly also an increase in obesity and prevalence of hepatitis C (particularly in combination with heavy alcohol

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consumption). In patients who are currently alcohol dependent (or, indeed, dependent on other substances), oral analgesia will be complicated by potential interactions. Chandok and Watt[43] advise a cautious approach, even in non-dependent patients with normal renal function, with lowered doses of most analgesics, and avoidance of NSAIDs in cirrhosis, due to the risk of renal failure following inhibition of prostaglandins. Care is also required with opioids due to the risk of precipitating encephalopathy.[33] If opioids are given, laxatives must be used to minimise this risk.[23] However a broad and individualised approach is necessary as patients can experience both visceral and musculoskeletal, as well as neuropathic, pain. Neuropathic pain can be treated with gabapentin or pregabalin, neither of which is significantly metabolised by the liver, nor will cause the same anticholinergic effects on the gut as TCAs.[23] The liver plays a major role in the metabolism of many drugs and, while caution is necessary, most drugs (other than NSAIDs) can be used at lower doses, and it is important not to undertreat significant pain due to fear of exacerbating liver disease.[33,44]

CONCLUSIONS

The relationship between disorders of the gut and common analgesics is complex, and drugs can play a role in the aetiology or maintenance of some disorders. This is perhaps most obvious in the case of NSAIDs and the upper gastrointestinal tract – but their effect on the small intestine may be more insidious and less well recognised by the clinician. Opioids are frequently used in severe pain, but cause particular problems with constipation and dependence, and require careful introduction and monitoring of risk versus benefit. Common disorders of the gastrointestinal system will often require analgesic therapy, but this needs to be considered very carefully and it can be difficult to differentiate symptoms caused by the disease from those caused by drugs. Finally, many of these disorders have a strong psychosocial component and, while this paper has focused on the use of drugs, the importance of taking these factors into account during assessment and treatment cannot be overemphasised.

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