Disorders of gut–brain interaction and the long-term risks of opioids

ABSTRACT

Prescription opioid abuse has become a public health crisis. It is often challenging to manage affected patients as their symptoms are often viewed through a prism of complex psychosocial issues. Clinicians are often unaware of the lack of evidence regarding opioid prescribing for non-cancer pain, and these trends in prescribing have been significantly escalated by pharmaceutical companies and prescribing culture in recent years. Opioid prescribing in the context of disorders of gut–brain interaction (formerly known as functional gastrointestinal disorders) can worsen conditions such as centrally-mediated abdominal pain syndrome and narcotic bowel syndrome. Opioids should not be prescribed to these patients as the harm is significantly greater than the benefit. However, in certain patients, such as those being investigated for organic abdominal pain, a trial of opioids may be indicated. In these groups, an opioid contract should be used, in addition to risk tools to identify those most vulnerable to the negative effects of these drugs. Prevention and treatment of the long-term effects of opioids requires a multidisciplinary approach and health-care professionals should all become 'opioid aware'.

As abuse of prescribed opioids is increasingly recognized as a public health crisis, there is renewed emphasis on how to manage and prevent the sequelae of opioid dependency. These patients present a clinical challenge as their symptoms are viewed through a prism of complex psychosocial issues. This article discusses the risks of opioids, especially in the context of disorders of gut–brain interaction (formerly known as functional gut disorders), and provides a basic approach to investigating and managing these patients, and to preventing new cases.

Background

Opioid overuse has become a prevalent public health issue (Dhalla et al, 2011). Following the increased use of prescription opioids since the 1980s, dependence, morbidity and mortality has increased at an alarming pace. While consumption of compounds derived from the opium poppy precedes documented history, the rise in opioids (i.e. synthetic and semi-synthetic compounds) began with the inception of diacetylmorphine in 1898 by Bayer. However, it was not until the late 1980s that prescribing opioids became common practice. In the 1990s new formulations were created by pharmaceutical companies, with claims of reduced potency and abuse potential. These promises, a programme to increase clinicians' prescribing of these drugs and direct-to-customer marketing led to the crisis that we are faced with today (Van Zee, 2009).

The liberalisation of opioid prescribing was typified by Margo McCaffery's definition of pain as 'whatever the experiencing person says it is, existing whenever and wherever the person says it does', in combination with the promotion of pain relief as a human right (Lipman, 2005) and aggressive 'marketing in the evidence void' by pharmaceutical companies (Dhalla et al, 2011). Now, prescription of opioids for chronic and non-cancer pain has become commonplace, and opioid prescriptions for chronic abdominal pain more than doubled in the USA between 1997 and 2008 (Dorn et al, 2011; Kurlander and Drossman, 2014). In the USA, deaths from prescribed opioids have tripled since 2000 and opiate overdose is now the second most common cause of accidental death (Weisberg et al, 2014; Rudd et al, 2016). Although the problem is certainly worse in the USA, the UK is following a similar trend (Stannard, 2013). Per capita, the UK has the tenth highest rate of increase in use of opioids worldwide with a six-fold increase in opioid prescriptions between 1991 and 2009 (Farias et al, 2017). Primary care saw double the prescription of weak opioids and a six-fold increase in prescriptions of stronger opioids between 2005 and 2012 (Foy et al, 2016).

This rise is despite a distinct lack of evidence for the efficacy of opioids in non-cancer pain and a growing body of literature describing their dangers. Most doctors are unaware that there are no high quality randomized controlled trials to support these prescribing patterns, and that opioids are often prescribed for inappropriate ailments, for longer durations and in too high doses (Noble et al, 2008; Stannard, 2013).

While many of the negative effects of opioids have been known for centuries (increased risk of falls, addiction, respiratory depression and death), they also have a multitude of lesser known side effects such as an increased risk of osteoporosis and immune suppression (Freynhagen et al, 2013). In addition, an increasing body of work suggests that opioids have a significant role to play regarding chronic abdominal pain, particularly in disorders of gut–brain interaction, or functional gastrointestinal disorders.

Functional gastrointestinal disorders and the Rome foundation

The term functional gastrointestinal disorder was historically used to describe medically unexplained abdominal symptoms. These symptoms have been described and characterized since the 1980s by the Rome Foundation, an organization which has been central in leading research and providing education about functional gastrointestinal disorders. The ROME IV criteria are a collection of conditions relating to any

Dr Sanjeev Sahota, Senior House Officer, Department of Intensive Care Medicine, Royal Cornwall Hospitals Trust, Truro, Cornwall

Dr Paul Fortun, Consultant Gastroenterologist, Department of Gastroenterology, Royal Cornwall Hospitals Trust, Truro, Cornwall TR1 3LQ

Correspondence to: Dr P Fortun (paulfortun@nhs.net)

combination of visceral hypersensitivity, altered mucosal function, altered motility, dysregulated gut microbiome and aberrant CNS processing (Drossman, 2016). There has been a move away from the term functional, in order to emphasize the complex interaction between the brain and the gastrointestinal tract. The preferred term is disorders of gut–brain interaction, although the term functional, which has become a non-specific phrase ironically meaning psychological in origin rather than a disorder of function or physiology, is still used in the literature (Drossman and Hasler, 2016).

Mechanisms of disorders of gut–brain interaction and the biopsychosocial model

There are many proposed mechanisms to explain why these symptoms and syndromes occur on a biochemical, histological and structural level. The emerging field of neurogastroenterology explores the associations between neural cells and immunological function, and has led to the term brain–gut axis. In addition to this physiological dysregulation, there is a significant contribution and interaction of psychological, environmental and social subsystems, the combination of which provide the backdrop for disorders of the brain–gut axis.

The biopsychosocial model presents the theory that many factors, such as genetics, childhood development and sociocultural influences, affect psychological development (Drossman, 2016). Essentially, a disorder of gut–brain interaction is the result of the interplay of neurogastroenterology and psychosocial influences via the brain–gut axis. The Rome IV criteria classifies these into anatomical regions and distinguishes paediatric-specific conditions (*Appendix 1*) (Schmulson and Drossman, 2017). Of these diagnoses, this article discusses centrally-mediated abdominal pain syndrome and narcotic bowel syndrome as long-term opioid use can exacerbate these conditions.

Centrally-mediated abdominal pain syndrome

Centrally-mediated abdominal pain syndrome is characterized by severe abdominal pain unrelated to gut function (i.e. ingestion or defecation), which is present for at least 6 months and which cannot be explained by dysfunction in mobility, metabolism or within the viscera. It is thought that centrally-mediated abdominal pain syndrome is caused by central neurological sensitization and disinhibition of pain signals, although there appear to be strong genetic and environmental components (Keefer et al, 2016). Association with psychiatric or somatic conditions (such as anxiety, fibromyalgia and chronic fatigue syndrome) is also strong, but this does not exclude a certain level of gastrointestinal dysfunction (Keefer et al, 2016).

Narcotic bowel syndrome

Narcotic bowel syndrome is also known as opioid-induced gastrointestinal hyperalgesia. It is defined by the paradoxical increase in abdominal pain associated with ongoing or increased dose of opioids (Grunkemeier et al, 2007). It is estimated that narcotic bowel syndrome has a prevalence of approximately 5% in chronic opioid users (Kurlander and Drossman, 2014). Pain is the predominant symptom, but narcotic bowel syndrome can be associated with nausea, abdominal distension, intermittent vomiting and constipation (Grunkemeier et al, 2007).

In patients with abdominal pain, opioids may appear helpful initially, but tachyphylaxis soon occurs, often resulting in prescribed or self-administered increases in dosages. This leads to an increase in symptoms and reduction in bowel motility (Grunkemeier et al, 2007). Although opioid cessation is typically very difficult in this patient group, most patients with narcotic bowel syndrome will experience an improvement in their pain once opioids have been withdrawn (Drossman et al, 2012).

Management strategies to mitigate opioid dependency

Managing these complex patients presents a clinical challenge, and it is important to make a distinction between those already established on opioids, and new patients being investigated for organic abdominal pain who are opiate naïve. The first group require a strategy of opioid deprescribing or containment, and for the second, prevention of dependency is vital. In both subgroups, a multidisciplinary approach should be used, involving primary and secondary care in addition to community nursing and psychologists.

In disorders of gut–brain interaction, it is inappropriate to use opioids even in the short term for the reasons discussed above, although there may be circumstances in patients with organic abdominal pain where opioids could temporarily ease severe symptoms. In this group it is important to counsel patients about the goals of treatment, the short- and long-term risks of opioids, and to set clear boundaries about consequences of aberrant drug-taking behaviour (e.g. opioid supply from multiple sources, requests for 'lost' medication and parenteral administration). A useful way to achieve this is using an opioid contract, which includes an explicit agreement that if the treatment does not show benefit in reasonable doses (120 mg of oral morphine equivalent per day), that this constitutes treatment failure and that the opioid prescribing will end (Freynhagen et al, 2013).

The initiation of opioids should be considered a trial with realistic goals and expectations (e.g. pain reduction, rather than cessation) and an improved quality of life. It is important that benzodiazepines are stopped before initiating a trial of opioids, and patients should be thoroughly assessed for concomitant illicit drug use, which can be common in this group. An opioid risk tool has been developed in order to estimate the probability of aberrant behaviour in patients on long-term opioid therapy (*Table 1*) (Webster and Webster, 2005).

The potential for future dependency should also be assessed, and several characteristics have been identified in patients at risk of long-term opioid use: female gender, middle age, socioeconomic deprivation, obesity, multiple comorbidities, pre-existing mental health disorders, and patients already on benzodiazepines, anticonvulsants or antidepressants (Foy et al, 2016). Given that opioids are more likely to be prescribed in higher doses and for a longer duration to vulnerable patients with mental health and substance abuse comorbidities, clinicians should pause to consider whether they are simply trying to alleviate and comfort a 'broader range of distress' with the blunt and unproven instrument of a narcotic prescription (Sullivan and Ballantyne, 2012).

If prescribing opioids is necessary, it is important to coprescribe laxatives to reduce the risk of opioid-induced constipation. It is also advisable to avoid cyclizine as an

Table 1. Opioid risk tool

Item		Mark each box that applies	Item score if female	Item score if male
1. Family history of substance abuse	Alcohol	❑	1	3
	Illegal drugs	❑	2	3
	Prescription drugs	❑	4	4
2. Personal history of substance abuse	Alcohol	❑	3	3
	Illegal drugs	❑	4	4
	Prescription drugs	❑	5	5
3. Age (mark box if 16–45 years)		❑	1	1
4. History of preadolescent sexual abuse		❑	3	0
5. Psychological disease	Attention deficit disorder, obsessive-compulsive disorder, bipolar, schizophrenia	❑	2	2
	Depression	❑	1	1
Total		—	—	
Total score risk category: low risk: 0–3; moderate risk: 4–7; high risk: ≥8				

From Webster and Webster (2005)

Table 2. Summary of opioid strategies

Opioids are very good analgesics for acute pain and for pain at the end of life but there is little evidence that they are helpful for long-term pain
A small proportion of people may obtain good pain relief with opioids in the long term if the dose can be kept low and especially if their use is intermittent (however, it is difficult to identify these people at the point of opioid initiation)
The risk of harm increases substantially at doses above an oral morphine equivalent of 120 mg/day but there is no increased benefit: tapering or stopping high-dose opioids needs careful planning and collaboration
If a patient has pain that remains severe despite opioid treatment it means the opioids are not working and should be stopped, even if no other treatment is available
Chronic pain is very complex and if patients have refractory and disabling symptoms, particularly if they are on high opioid doses, as very detailed assessment of the many emotional influences on their pain experience is essential
From Faculty of Pain Medicine (2019)

antiemetic, as this has strong anticholinergic and opioid-potentiating activity, as well as sedative effects (Thursby-Pelham et al, 2009). An important preventative measure in the authors' experience is to restrict inpatient intravenous opioid prescribing to 48 hours. This allows time to review previous tests and consultations, thus avoiding unnecessary duplication and contradictory messages. It also gives the clinician the opportunity to reassess symptoms and discuss ongoing management with pain specialists. Designating a named responsible clinician avoids the 'collusion of anonymity' where patients navigate a path from one specialist to another. A good summary of key strategies has been made by the Faculty of Pain Management of the Royal College of Anaesthetists (*Table 2*).

For patients with symptoms consistent with disorders of gut–brain interaction, it is important to develop and maintain a strong doctor–patient relationship, which includes validation of the patient's symptoms and experiences. Allocation of a named physician allows continuity of care and avoids multiple, confusing and often contradictory opinions. This 'joined-up' coordinated approach will be essential if deprescribing is to be achieved. Discussions should include an explanation of the experience of visceral hypersensitivity and how it can be caused by opioid-related dysfunction of the brain–gut axis, and therefore the rationale for de-escalation (Grunkemeier et al, 2007).

Cessation of opioids is associated with reduced abdominal pain in those taking them long term, and those who do not relapse continue to improve their symptoms over time. Opioid detoxification has an 89.7% success rate initially with rapid dose reduction between 10–30% per day, but this has a high relapse rate – two thirds restarted narcotic medication after an average of 3 months (Drossman et al, 2012). The authors' practice has been to deprescribe in an outpatient setting by 10% at intervals ranging between weekly and monthly with a fixed timetable agreed with the patient.

While details of pharmacological adjunctive therapy during opioid cessation are beyond the scope of this article, their purpose is to prevent symptoms of withdrawal, lessen anxiety and provide analgesia for the underlying pain (Grunkemeier et al, 2007). Examples include tricyclic antidepressants (such as amitriptyline) and serotonin-noradrenaline reuptake inhibitors (duloxetine and venlafaxine), clonidine, gabapentin, pregabalin and even a short course of benzodiazepines. A multidisciplinary approach is essential to prevent relapse. Those who are successful in stopping opioids report significant improvements in their pain (Drossman et al, 2012).

CURRICULUM CHECKLIST

This article addresses the following requirements from the general internal medicine training curriculum

- Managing an acute specialty-related take
- Managing patients in an outpatient clinic, ambulatory or community setting (including management of long-term conditions)
- Managing medical problems in patients in other specialties and special cases.

Conclusions

Improved awareness of the risk of opioids, particularly in disorders of gut–brain interaction, makes the prevention of new cases of opioid-dependent patients, and deprescribing in existing patients, timely and urgent. Clinicians all need to become opioid aware. A multidisciplinary approach is essential to set realistic goals about symptom relief, work with patients to reduce opioids, and to educate patients and colleagues to prevent new cases. **BJHM**

Conflict of interest: none.

Dhalla IA, Persaud N, Juurlink DN. Facing up to the prescription opioid crisis. BMJ. 2011 Aug 23;343 aug23 1:d5142. https://doi.org/10.1136/bmj.d5142

Dorn SD, Meek PD, Shah ND. Increasing frequency of opioid prescriptions for chronic abdominal pain in US outpatient clinics. Clin Gastroenterol Hepatol. 2011 Dec;9(12):1078-85.e1. https://doi.org/10.1016/j.cgh.2011.08.008

Drossman DA. Functional gastrointestinal disorders: history, pathophysiology, clinical features, and Rome IV. Gastroenterology. 2016 Feb 19. pii: S0016-5085(16)00223-7. https://doi.org/10.1053/j.gastro.2016.02.032

Drossman DA, Hasler WL. Rome IV—Functional GI Disorders: Disorders of Gut-Brain Interaction. Gastroenterology. 2016 May;150(6):1257–1261. https://doi.org/10.1053/j.gastro.2016.03.035

Drossman DA, Morris CB, Edwards H et al. Diagnosis, characterization, and 3-month outcome after detoxification of 39 patients with narcotic bowel syndrome. Am J Gastroenterol. 2012 Sep;107(9):1426–1440. https://doi.org/10.1038/ajg.2012.142

Faculty of Pain Medicine. 2019. Opioids Aware: A resource for patients and healthcare professionals to support prescribing of opioid medicines for pain. (accessed 6 September 2019)https://www.rcoa.ac.uk/faculty-of-pain-medicine/opioids-aware

Farias JC, Porter L, McManus S, Strang J, Hickman M, Reed K, Smith N. 2017. Prescribing patterns in dependence forming medicines. London: National Centre for Social Research.

Foy R, Leaman B, McCrorie C et al. Prescribed opioids in primary care: cross-sectional and longitudinal analyses of influence of patient and practice characteristics. BMJ Open. 2016 May;6(5):e010276. https://doi.org/10.1136/bmjopen-2015-010276

Freynhagen R, Geisslinger G, Schug SA. Opioids for chronic non-cancer pain. BMJ. 2013 May 29;346(may29 4):f2937. https://doi.org/10.1136/bmj.f2937

Grunkemeier DMS, Cassara JE, Dalton CB, Drossman DA. The narcotic bowel syndrome: clinical features, pathophysiology, and management. Clin Gastroenterol Hepatol. 2007 Oct;5(10):1126–1139, quiz 1121–1122. https://doi.org/10.1016/j.cgh.2007.06.013

Keefer L, Drossman DA, Guthrie E, Simrén M, Tillisch K, Olden K, Whorwell PJ. Centrally mediated disorders of gastrointestinal pain. Gastroenterology. 2016 May;150(6):1408–1419. https://doi.org/10.1053/j.gastro.2016.02.034

Kurlander JE, Drossman DA. Diagnosis and treatment of narcotic bowel syndrome. Nat Rev Gastroenterol Hepatol. 2014 Jul;11(7):410–418. https://doi.org/10.1038/nrgastro.2014.53

Lipman AG. Pain as a human right. J Pain Palliat Care Pharmacother. 2005 Jan;19(3):85–100. https://doi.org/10.1080/J354v19n03_16

Noble M, Tregear SJ, Treadwell JR, Schoelles K. Long-term opioid therapy for chronic noncancer pain: a systematic review and meta-analysis of efficacy and safety. J Pain Symptom Manage. 2008 Feb;35(2):214–228. https://doi.org/10.1016/j.jpainsymman.2007.03.015

Rudd RA, Aleshire N, Zibbell JE, Gladden RM. Increases in drug and opioid overdose deaths—united States, 2000–2014. MMWR Morb Mortal Wkly Rep. 2016 Jan 01;64(50-51):1378–1382. https://doi.org/10.15585/mmwr.mm6450a3

Schmulson MJ, Drossman DA. What is new in Rome IV. J Neurogastroenterol Motil. 2017 Apr 30;23(2):151–163. https://doi.org/10.5056/jnm16214

Stannard C. Opioids in the UK: what's the problem? BMJ. 2013 Aug 15;347:f5108. https://doi.org/10.1136/bmj.f5108

Sullivan MD, Ballantyne JC. What are we treating with long-term opioid therapy? Arch Intern Med. 2012 Mar 12;172(5):433–434. https://doi.org/10.1001/archinternmed.2011.2156

Thursby-Pelham FW, De Silva AN, Stroud MA, Fine DR. Cyclizine dependence in patients with complex nutritional requirements. Proc Nutr Soc. 2009;68 OCE1:E21. https://doi.org/10.1017/S0029665109001621

KEY POINTS

- Functional abdominal pain is now referred to as disorders of gut–brain interaction.
- Disorders of gut–brain interaction can present as complex and demanding clinical challenges.
- Opioid dependency and side effects including narcotic bowel syndrome are a potential risk in vulnerable patient groups.
- Opioids should not be started in patients with a disorder of gut–brain interaction.
- If intravenous morphine is required on admission to hospital, consider limiting its use to no more than 48 hours, while assessing for organic pathology.
- If a trial of opioids is appropriate, they should only be started with prior discussion of risks with the patient, with an understanding that they will be stopped and not escalated if ineffective.
- Successful opioid de-escalating requires a multidisciplinary team approach.
- Opioid awareness is key to preventing new cases.

Van Zee A. The promotion and marketing of oxycontin: commercial triumph, public health tragedy. Am J Public Health. 2009 Feb;99(2):221–227. https://doi.org/10.2105/AJPH.2007.131714

Webster LR, Webster RM. Predicting aberrant behaviors in opioid-treated patients: preliminary validation of the Opioid Risk Tool. Pain Med. 2005 Nov;6(6):432–442. https://doi.org/10.1111/j.1526-4637.2005.00072.x

Weisberg DF, Becker WC, Fiellin DA, Stannard C. Prescription opioid misuse in the United States and the United Kingdom: cautionary lessons. Int J Drug Policy. 2014 Nov;25(6):1124–1130. https://doi.org/10.1016/j.drugpo.2014.07.009

Appendix 1. Functional gastrointestinal disorders: disorders of gut–brain interaction

A. Oesophageal disorders	A1. Functional chest pain		F. Anorectal disorders	F1. Fecal incontinence	
	A2. Functional heartburn			F2. Functional anorectal pain	F2a. Levator ani syndrome
	A3. Reflux hypersensitivity				F2b. Unspecified functional anorectal pain
	A4. Globus				F2c. Proctalgia fugax
	A5. Functional dysphagia			F3. Functional defecation disorders	F3a. Inadequate defecatory propulsion
B. Gastroduodenal disorders	B1. Functional dyspepsia	B1a. Postprandial distress syndrome			F3b. Dyssynergic defecation
		B1b. Epigastric pain syndrome	G. Childhood functional gastrointestinal disorders: neonate/toddler	G1. Infant regurgitation	
	B2. Belching disorders	B2a. Excessive supragastric belching		G2. Rumination syndrome	
		B2b. Excessive gastric belching		G3. Cyclic vomiting syndrome	
	B3. Nausea and vomiting disorders	B3a. Chronic nausea vomiting syndrome		G4. Infant colic	
		B3b. Cyclic vomiting syndrome		G5. Functional diarrhoea	
		B3c. Cannabinoid hyperemesis syndrome		G6. Infant dyschezia	
	B4. Rumination syndrome			G7. Functional constipation	
C. Bowel disorders	C1. Irritable bowel syndrome (IBS)		H. Childhood functional gastrointestinal disorders: child/adolescent	H1. Functional nausea and vomiting disorders	H1a. Cyclic vomiting syndrome
	C2. Functional constipation IBS with predominant constipation (IBS-C)				H1b. Functional nausea and functional vomiting
	C3. Functional diarrhoeal IBS with predominant diarrhoea (IBS-D)				H1b1. Functional nausea
	C4. Functional abdominal bloating/distension IBS with mixed bowel habits (IBS-M)				H1b2. Functional vomiting
	C5. Unspecified functional bowel disorder IBS unclassified (IBS-U)				H1c. Rumination syndrome
	C6. Opioid-induced constipation				H1d. Aerophagia
D. Centrally-mediated disorders of gastrointestinal pain	D1. Centrally-mediated abdominal pain syndrome			H2. Functional abdominal pain disorders	H2a. Functional dyspepsia
	D2. Narcotic bowel syndrome or opioid-induced gastrointestinal hyperalgesia				H2a1. Postprandial distress syndrome
E. Gallbladder and sphincter of Oddi disorders	E1. Biliary pain	E1a. Functional gallbladder disorder			H2a2. Epigastric pain syndrome
		E1b. Functional biliary sphincter of Oddi disorder			H2b. Irritable bowel syndrome
	E2. Functional pancreatic sphincter of Oddi disorder				H2c. Abdominal migraine
					H2d. Functional abdominal pain – not otherwise specified
				H3. Functional defecation disorders	H3a. Functional constipation
					H3b. Non-retentive fecal incontinence

From Drossman (2016)