



## Module 1923

# Which medicines cause diarrhoea?

From this pharmacy CPD module you will learn about:

- The main mechanisms of action that cause this reaction
- The impact of the disruption of the normal intestinal flora
- When you should refer medicine-induced diarrhoea
- Treatment and management strategies you can recommend

### NADIRA CALLACHAND, PHARMACIST

Diarrhoea is defined as an increased frequency of bowel movements from what is considered normal ( $\geq 3$  in 24 hours) and/or decreased stool consistency, and/or increased stool weight ( $>200\text{g}$  per 24 hours) – although the latter may be more difficult to determine.

Diarrhoea can be categorised as acute (usually starts during the first few days of treatment and lasts less than 14 days) or chronic (lasts more than three or four weeks and may start a long time after drug treatment has been initiated).<sup>1</sup>

Drug-induced diarrhoea is the result of the disruption of the normal physiological process of digestion and fluid absorption. It can be caused by almost any drug, but some medications are more likely to cause it than others. These include:

- allopurinol
- angiotensin II receptor blockers (eg lisinopril, perindopril)
- antibiotics
- digoxin
- colchicine
- cytotoxic drugs (eg methotrexate, chemotherapy)
- H<sub>2</sub>-receptor antagonists
- laxatives
- magnesium-containing antacids

- metformin
- non-steroidal anti-inflammatory drugs (NSAIDs)
- proton pump inhibitors (PPIs)
- selective serotonin reuptake inhibitors (SSRIs)
- statins
- theophylline
- levothyroxine.<sup>3</sup>

### What are the mechanisms that cause the reaction?

Drug-induced diarrhoea can occur through several mechanisms. Often, two or more mechanisms are involved.

#### Osmotic diarrhoea

Osmotic medicines – such as laxatives and sorbitol – prevent the reabsorption of water from the bowel lumen. These drugs are generally used to treat constipation.

#### Secretory diarrhoea

This occurs when the normal secretion and absorption of ions in the small intestine is disrupted, leading to excess water in the intestinal lumen and stools. Examples of medicines which cause this include digoxin and colchicine. In addition, some medicines – such as bisacodyl – activate the enzyme adenylate

cyclase in the small intestine, which leads to increased levels of cyclic AMP (a biological messenger) and impaired fluid resorption.

#### Motility disturbance

This is a disturbance of intestinal motility, caused by the acceleration of the migrating motor complex (the four phased process of gut motility during fasting periods). An example of a medicine that causes this is erythromycin.

#### Exudative diarrhoea

NSAIDs and chemotherapy are two examples of treatments that cause inflammation of the gastrointestinal tract. This inflammation is associated with the exudation of blood and pus into the luminal content, resulting in increased stool volume and altered fluid absorption.

#### Malabsorption

Poor digestion and malabsorption of fats can cause steatorrhea (excretion of abnormal quantities of fat). The weight-loss drug orlistat works by this mechanism, but the resulting diarrhoea may be worse than intended if patients taking it don't adhere to strict dietary rules. Malabsorption is also a potential side effect of colchicine.

#### Disruption of normal intestinal flora

Disruption of normal intestinal flora explains antibacterial-associated diarrhoea. Most antibiotics (eg penicillins, macrolides, cephalosporins, clindamycin and quinolones) can induce diarrhoea. This happens because antibiotics not only kill the bacteria they are prescribed for, but normal, healthy gut flora as



Atorvastatin, digoxin, metformin and NSAIDs are medicines that have diarrhoea as a possible side effect



**Treatment includes oral rehydration therapy to replace fluid and electrolytes lost through diarrhoea**

well. Usually, these bacteria are re-established in a few days.

The problem comes when opportunistic pathogens such as *Clostridium difficile* proliferate, releasing toxins which cause inflammation, mucosal damage and produce lesions in the intestine wall. Diarrhoea results from a number of mechanisms, depending on the antibiotic involved.<sup>2,4</sup>

Most cases cause benign diarrhoea, but in severe cases, overgrowth of *Clostridium difficile* can cause inflammation of the colon (pseudomembranous colitis).

### Who is most likely to be affected?

Elderly patients are more likely to develop drug-induced diarrhoea, and polypharmacy in this population puts them at greater risk. Older

people also have reduced immune response and gut acid secretion.<sup>5</sup>

In addition, immunocompromised patients, patients in residential care and those who have had a recent admission to hospital are at increased risk of antibiotic-associated diarrhoea.<sup>6</sup>

### Will it pass with continued use?

Acute diarrhoea may resolve spontaneously without the need to withdraw the culprit drug. In more severe cases, withdrawal may be necessary, and diarrhoea usually subsides within a few days once the causative drug has been stopped. In some cases, reducing the dose may be enough to alleviate symptoms.<sup>1</sup>

### When is referral necessary?

If drug-induced diarrhoea is suspected when

the patient is taking a long-term medication, they should be referred so a suitable alternative can be found. Chronic diarrhoea may lead to electrolyte imbalance, which can be particularly harmful in elderly patients. Acute diarrhoea which lasts for more than three days for adults (two days for elderly patients) requires referral. Other symptoms which require referral include:

- associated fever or vomiting
- blood or mucus in the stools
- signs of dehydration (drowsiness, dry mouth, sunken eyes, weakness or passing little urine).<sup>7</sup>

You should take into account the severity of symptoms and the patient's age (eg elderly or very young) when deciding to refer to the GP or to A&E.

### How can it be treated?

The most effective way to resolve the diarrhoea is often to stop the culprit medication, after which symptoms usually resolve within a few days. However, in some cases treatment may be needed to treat symptoms or stop diarrhoea.

Symptomatic treatment includes diet modification and oral rehydration therapy (ORT). ORT replaces fluid and electrolytes (sodium and potassium) lost through diarrhoea. ORT solution also contains citrate and/or bicarbonate to correct acidosis, as well as glucose to aid transportation of water across the intestinal mucosa. ORT is suitable for all ages, although patients with diabetes should carefully monitor their blood glucose levels if using it. ORT consists of a powder, which is dissolved in fresh drinking water (usually 200ml). Any unused portion can be kept in the fridge for up to 24 hours.<sup>7</sup>

Antiperistaltic agents, such as loperamide and codeine, can be used to slow intestinal transit. This decreased intestinal motility enhances fluid and electrolyte reabsorption and reduces the volume of intestinal contents, reducing discomfort for the patient. Codeine carries a risk of dependency, so should only be used with caution.

Loperamide is a synthetic opioid analogue

that rarely causes side effects associated with opioids. Two 2mg capsules of loperamide should be taken initially, followed by 2mg after each loose bowel movement (with a maximum of eight capsules in 24 hours).

Antiperistaltic agents are not recommended for severe diarrhoea, due to the risk of colonic retention of the causative toxins and bacteria.<sup>2</sup>

### What advice should you provide to patients?

It's important to familiarise yourself with the medications that commonly cause diarrhoea and counsel patients on this potential side effect when appropriate. You should advise patients who experience this symptom after starting a new medication on when it is appropriate to return to their doctor to seek an alternative medication.

For symptomatic relief, provide advice on OTC remedies, such as ORT and loperamide, when appropriate, emphasising the need to stay hydrated.

Some pharmacies sell bacteria cultures or so called 'probiotics' for antibiotic-induced diarrhoea. However, there is limited evidence of a proven benefit.

C+D clinical editor Kristoffer Stewart spoke to Professor Simon Gaisford from University College London's school of pharmacy, to find out more about the appropriate use of probiotics, what advice you can provide to patients, and his latest research into probiotic therapy. Listen to the podcast at [bit.ly/cd\\_podcast](http://bit.ly/cd_podcast).



## References

1. Drugs and therapies perspectives (2001) Drug-induced diarrhoea: A far from rare adverse event. [Online] Available at: <https://www.medscape.com/viewarticle/406463>
2. Chassany O. et al (2000) Drug-induced diarrhoea. [Online] Available at: [https://www.researchgate.net/profile/Olivier\\_Chassany/publication/12666553\\_Drug-Induced\\_Diarrhoea/links/57053d0e08ae44d70ee30f94/Drug-Induced-Diarrhoea.pdf?origin=publication\\_detail](https://www.researchgate.net/profile/Olivier_Chassany/publication/12666553_Drug-Induced_Diarrhoea/links/57053d0e08ae44d70ee30f94/Drug-Induced-Diarrhoea.pdf?origin=publication_detail)
3. Nice clinical knowledge summaries (2018) Diarrhoea – adult’s assessment. [Online] Available at: <https://cks.nice.org.uk/diarrhoea-adults-assessment#!backgroundSub:2>
4. Johnson D.A. (2017) A pharmacy of suspects: drug-induced diarrhoea’s likeliest causes. [Online] Available at: [https://www.medscape.com/viewarticle/879541#vp\\_4](https://www.medscape.com/viewarticle/879541#vp_4)
5. Ratnaike R., Jones TE. (1998) Mechanisms of drug-induced diarrhoea in the elderly. [Online] Available at: <https://www.ncbi.nlm.nih.gov/pubmed/9789728>
6. Barbut F., Meynard J.L (2002) Managing antibiotic associated diarrhoea. [Online] Available at: <https://www.bmj.com/content/324/7350/1345.full>
7. Kennedy E, CPPE, NHS Scotland (2009) Responding to minor ailments. [Online] [https://www.nes.scot.nhs.uk/media/360683/responding\\_to\\_minorailmentsloresweb.pdf](https://www.nes.scot.nhs.uk/media/360683/responding_to_minorailmentsloresweb.pdf)

## Which medicines cause diarrhoea CPD

### What are you planning to learn?

I want to learn more about how diarrhoea is defined, the commonly prescribed medicines that cause it and the mechanisms by which this occurs. I also want to improve my knowledge of how drug-induced diarrhoea can be managed and the advice I can give to my patients.

This learning will help me to improve my knowledge of the medicines that cause diarrhoea and how it can be managed, and to be able to confidently provide advice to patients and carers.

### How are you planning to learn it?

- I plan to read more about the symptoms and treatment of diarrhoea and advice for patients on the NHS Inform website at [tinyurl.com/medicinesanddiarrhoea](https://www.nhs.uk/healthcareprofessionals/CPD/OTC-Guide-to-Medicines-and-Diagnostics).
- I plan to revise my knowledge of the OTC medicines available for the treatment of diarrhoea from the C+D *OTC Guide to Medicines and Diagnostics*.

### Give an example of how this learning has benefited the people using your services

A patient who had received counselling about how her prescribed antibiotic might cause diarrhoea returned to say that she was suffering from this side effect. I was able to advise her about treatment and, as she was elderly and had been suffering for two days, referred her back to the GP. She felt reassured, as she had been uncertain whether to bother the GP, and made an appointment for that day.

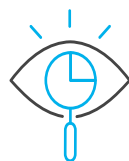
## Take the 5-minute test online

1. Diarrhoea is classed as chronic if it lasts for more than three weeks.  
**True or false**
2. Allopurinol, digoxin, metformin, statins and levothyroxine can all have diarrhoea as a side effect.  
**True or false**
3. Erythromycin causes diarrhoea by disrupting the secretion and absorption of ions in the small intestine.  
**True or false**
4. Digoxin and colchicine can cause diarrhoea, as they disturb intestinal motility.  
**True or false**
5. Acute diarrhoea lasting for more than three days in adults requires referral.  
**True or false**
6. Oral rehydration therapy is not suitable for use in diabetics.  
**True or false**
7. Any unused portion of oral rehydration therapy can be kept in the fridge for 48 hours.  
**True or false**
8. Loperamide and codeine act by slowing intestinal transit, which enhances fluid and electrolyte reabsorption.  
**True or false**
9. The maximum adult dose of loperamide 2mg capsules is six in 24 hours.  
**True or false**
10. Antiperistaltic agents are not recommended for severe diarrhoea.  
**True or false**

You can complete the quiz and logsheet by visiting [bit.ly/UPDATE-PLUS](https://bit.ly/UPDATE-PLUS) and searching: 1923



**An Update Plus subscription gives you...**



### Update module

A typical module that allows you to read the content and then complete the short 5 minute quiz to test.



### Practical approach

A pharmacy-based clinical scenario asks what you would do and provides expert advice.



### Podcast

Listen to expert interviews on speciality areas, from Alzheimer’s to the Zika virus.



### Interactive quiz

Try our interactive quizzes and see where you rank against your peers.