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Medication Induced Constipation and Diarrhea



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Medication induced constipation or diarrhea is a frequent side effect that contributes to costs of health care for evaluation and management as well as patient morbidity. The diagnosis is often delayed due to poor association of symptom onset with the use of a medication. In most cases, symptoms resolve after the drug is discontinued. However, as with pseudomembranous colitis, discontinuing the medication is not always sufficient treatment. This article discusses the most common medications associated with constipation and diarrhea as well as diagnosis, treatment and prevention of the disorder; the diagnosis is especially important when the offending medication cannot be discontinued.

INTRODUCTION

Constipation and diarrhea as a side effect of medications is a frequent occurrence. Constipation is the most common gastrointestinal complaint that leads to physician visits, diagnostic tests and medications for treatment (1,2). Medication induced diarrhea accounts

for about 7% of all adverse drug effects and there are more than 700 drugs that have been implicated in causing diarrhea (3). Certain patient populations are more at risk for development of symptoms such as the elderly, residents of nursing homes or patients with prolonged hospitalization. There are several mechanisms that contribute to medication induced constipation and diarrhea and treatment is often directed at reversing or modifying these mechanisms. Once an offending medication is identified, the simplest treatment is to discontinue it. Unfortunately, some medications are not easily removed from a patient's regimen without exacerbating underlying illness. In this article we will identify the most common medications associated with constipation and diarrhea as well as methods of diagnosis and treatment.

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DEFINITION OF CONSTIPATION

The definition of constipation can be unclear because there are multiple symptoms associated with constipation and patients will often have different complaints that lead them to seek treatment. The ROME II criteria standardized what constitutes constipation for adults. In order to have a diagnosis of constipation an individual must have two or more of the following symptoms for at least 12 weeks (not necessarily consecutive) in the preceding 12 months: straining during bowel movements, lumpy or hard stools, sensation of incomplete evacuation, sensation of anorectal blockage or manual maneuvers to facilitate bowel movements (e.g., digital evacuation or support of the pelvic floor) 25% of the time; less than three bowel movements a week; loose stools are not present and there is insufficient criteria for irritable bowel syndrome.

Medication induced constipation is classified as an organic cause in the AGA Technical review on constipation (2). Other organic causes include mechanical obstruction (colon cancer, strictures, anal fissures); metabolic conditions such as diabetes mellitus, hypothyroidism, hypercalcemia, hypokalemia, hypomagnesemia, uremia; myopathies (amyloidosis, scleroderma); neuropathies (Parkinson's disease, spinal cord injury, MS, cerebrovascular disease). Other conditions include depression, degenerative joint disease, autonomic neuropathy, cognitive impairment, immobility and cardiac disease.

EPIDEMIOLOGY AND ECONOMIC IMPACT

Depending on the study cited the prevalence of constipation varies greatly from 2%–28%, a range based on the general unreliability of individuals reporting symptoms identified as constipation. There is likely a lack of understanding of what it means to be constipated. Stewart, et al estimated the prevalence to be 14.7% in 10,000 subjects. However they also found that 37% of women and 59% of men who met symptom criteria did not report that they were constipated (4). Sonnenberg and Koch reviewed data from four nationwide studies in 1989 and estimated the prevalence of constipation to be 2% or four million people. Constipation was the most common digestive complaint in the United States. Cathartics and laxatives are prescribed to two-to-three million patients

yearly. It is three times more common in women as opposed to men and there is a marked increase after the age of 65 years. It appeared to affect non-whites 1.3 times more frequently than whites. Constipation was more frequent in the South and in people from families with low income (5). Talley, et al further evaluated the prevalence of constipation in those age 65 and over and found the prevalence of any form of constipation was 40.1%. For functional constipation and outlet delay the prevalence was 24.4 and 20.5% (6). It accounts for 2.5 million physician visits a year, and almost all (85%) physician visits for constipation result in a prescription for laxatives or cathartics (1). An average cost of a constipation work-up including colonoscopy extrapolated to the number of physician visits was 6.9 billion dollars (2).

Complications related to constipation are more pronounced in the elderly. Fecal impaction can occur which can lead to intestinal obstruction, stercoral ulceration, mental disturbances, urinary retention and overflow diarrhea. Other complications in the elderly include cerebrovascular effects of straining such as transient ischemic attacks or syncope. Chronic constipation can result in megacolon leading to sigmoid volvulus, ischemic colitis, cecal perforation. It can lead to rectal prolapse and hemorrhoids, and chronic laxative use or abuse (7).

RISK FACTORS

Several medications are known to cause constipation. Prescription drugs that cause constipation include opiates, anti-cholinergic agents, tricyclic antidepressants (amitriptyline more than nortriptyline), calcium channel blockers such as verapamil, antiparkinsonian drugs, sympathomimetics (ephedrine, terbutaline), antipsychotics (chlorpromazine), diuretics (furosemide), and antihistamines (diphenhydramine). Non-prescription drugs include antacids especially calcium containing, calcium supplements, iron, antidiarrheal agents (loperamide, attapulgite), and NSAIDs such as ibuprofen (Table 1).

Talley, et al found that after adjusting for age, gender and other symptoms, an increased usage of aspirin was associated with functional constipation but not outlet delay (8). In a study of constipation in older adults (>65 y/o) aspirin, NSAIDs and medicines classified as constipating were associated with a small but signifi-

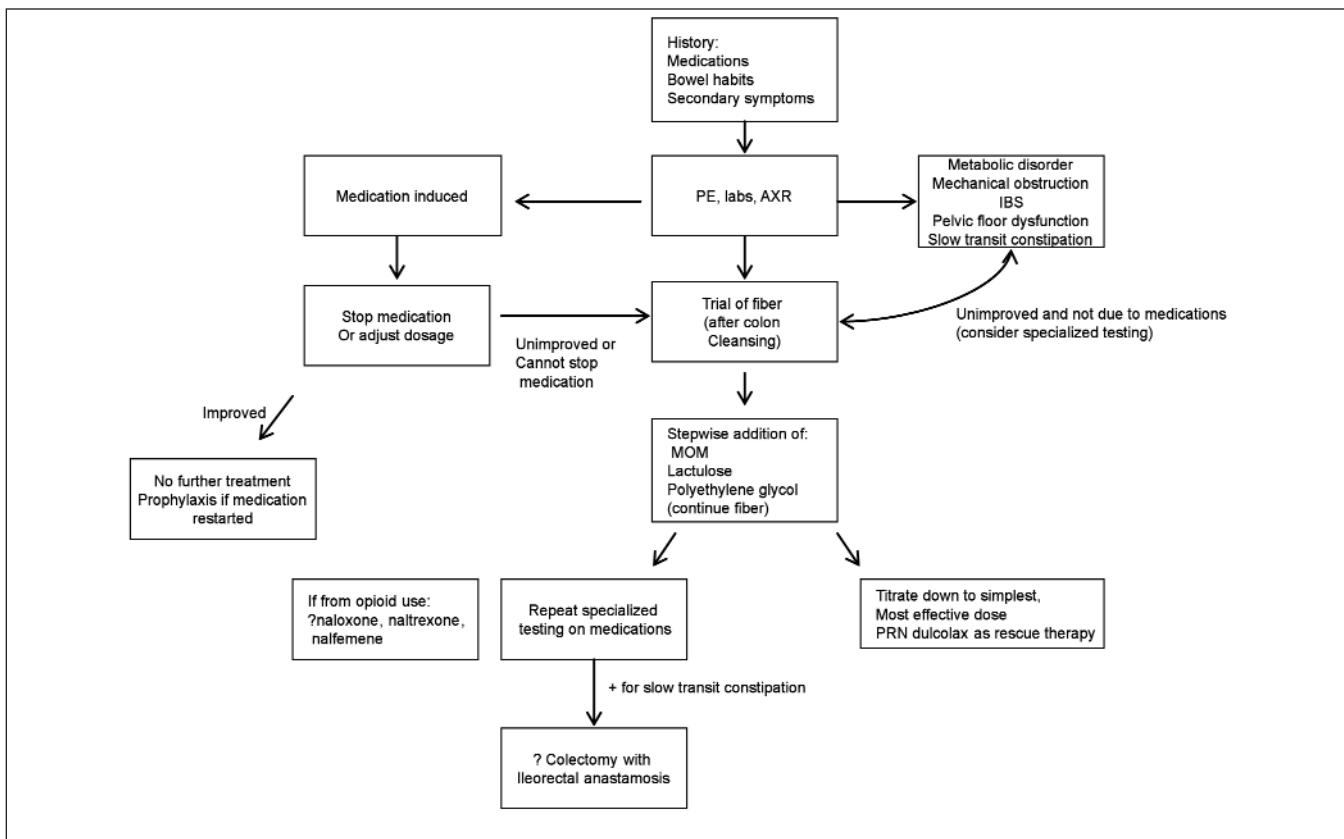


Figure 1. Management of Medication Induced Constipation. History: stool consistency, frequency, straining, manual maneuvers, sensation of blockage, abdominal pain/bloating, incontinence, diarrhea. Secondary symptoms: weight loss/gain, skin rashes/dryness, fatigue. Specialized testing: anorectal manometry, colonic transit testing, balloon expulsion, defecography. MOM—milk of magnesia, PE—physical exam, AXR—abdominal x-ray

cantly increased risk in patients with functional constipation and outlet delay, after adjusting for age and gender (6). They expressed uncertainty if this is a cause and effect relationship or reflects NSAID use for intestinal or extraintestinal symptoms associated with the different constipation categories. A cohort study of 2,355 nursing home patients found that a relative risk of 1.59 (95% CI = 1.24–2.04) was associated with moderately to strongly constipating drugs. It was suggested that the high prevalence of constipation among nursing home residents is only partly due to adverse drug effects (9). Based on his findings it can be inferred that chronic constipation has several etiologic factors, with the elderly likely to have more risk factors and an increased risk of constipation compared to the young.

Narcotics are probably the most well known medication class that causes constipation and often stool soften-

ers are prescribed in order to prevent constipation. However, it is not well known whether one narcotic analgesic is less constipating than the other. Staats, et al examined 1,836 patients without a prior diagnosis of constipation that received three different types of long acting opioids for malignant and non-malignant pain. After adjusting for race, supplemental opioid usage and number of days of opioid exposure, it was found that transdermal fentanyl was associated with the lowest risk of constipation compared to oxycodone CR and morphine CR. The increased risk of constipation with oxycodone compared to transdermal fentanyl was statistically significant (10).

DIAGNOSIS

An algorithmic approach to the diagnosis of constipation is recommended and guided by the response to first

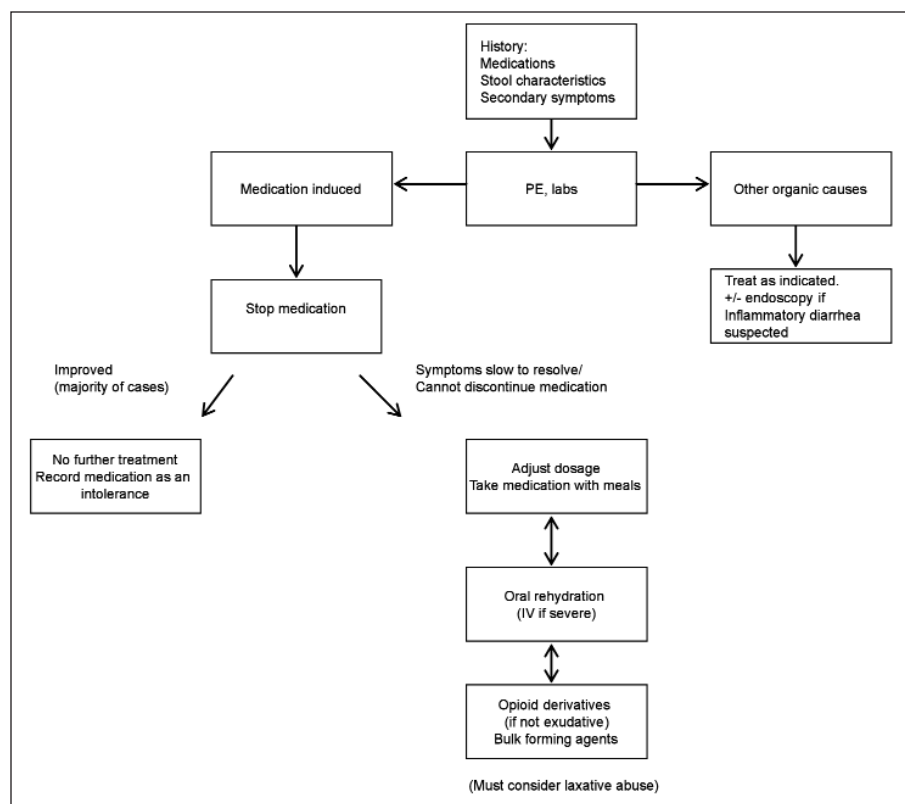


Figure 2. Management of Medication Induced Diarrhea. History: Medications and time of use relative to onset of diarrhea. Laxative use. Stool characteristics: volume, frequency, presence of blood/mucus. Secondary symptoms: fevers, chills, weight loss, dehydration, abdominal pain. Review of systems- rules out diabetes mellitus, hyperthyroidism, HIV, IBD. Physical exam: Anorectal exam- rule out impaction, anal fissures/abcess, assess sphincter tone. Presence of thyromegaly, lymphadenopathy, wheezing, abdominal masses. Nutritional and volume status
*Many cases of chronic diarrhea can be due to laxative abuse.

tone of the external anal sphincter, whether there is puborectalis muscle pain on palpation to suggest spasm and finally if the patient is able to

line therapies (Figure 1). First, a detailed history and physical examination is required with questions regarding stool frequency and consistency, straining, pain or bloating, the sensation of incomplete evacuation, the use of manual efforts for successful defecation as well as the use of laxatives. In order to diagnose constipation due to medications one should obtain a detailed medication list including over the counter medications as well as the time of their initial use. It should be noted if the patient developed constipation symptoms after starting a particular medication. The presence of abdominal pain or bloating that is relieved with defecation is suggestive of irritable bowel syndrome.

A rectal examination should start with an inspection of the perineum to rule out fissures, external hemorrhoids, fistulas or scars. The physician should observe the degree of perineal descent during simulated defecation, which is normally between 1–3.5 cm. Reduced descent suggests inability to relax the pelvic floor while excessive descent suggests laxity which could be due to childbirth or several years of excessive straining which can lead to incomplete evacuation (11). On digital exam, one should note the

expel the examining finger with valsalva.

Standard laboratory tests to exclude a treatable cause such as hypothyroidism should be obtained. The presence of alarm symptoms (age >50, sudden change in stool caliber, anemia, weight loss or rectal bleeding) warrant a referral for a colonoscopy to rule out colon cancer as a structural cause for constipation.

A trial of fiber with or without osmotic laxatives should be initiated. It should be noted that if pelvic floor dysfunction is suspected, the patient should be referred for further testing as fiber supplements will not improve their condition. If these early interventions do not improve symptoms, the patient should be referred for specialized testing to rule out slow transit constipation or pelvic floor dysfunction, and consider balloon expulsion, defecography, colonic transit and anorectal manometry.

Balloon expulsion quantifies the patient's ability to evacuate a balloon filled with 50 cc of water and serves as a simple screening test to rule out dysfunctions of defecation. It can also be used to assess response to biofeedback. Defecography involves

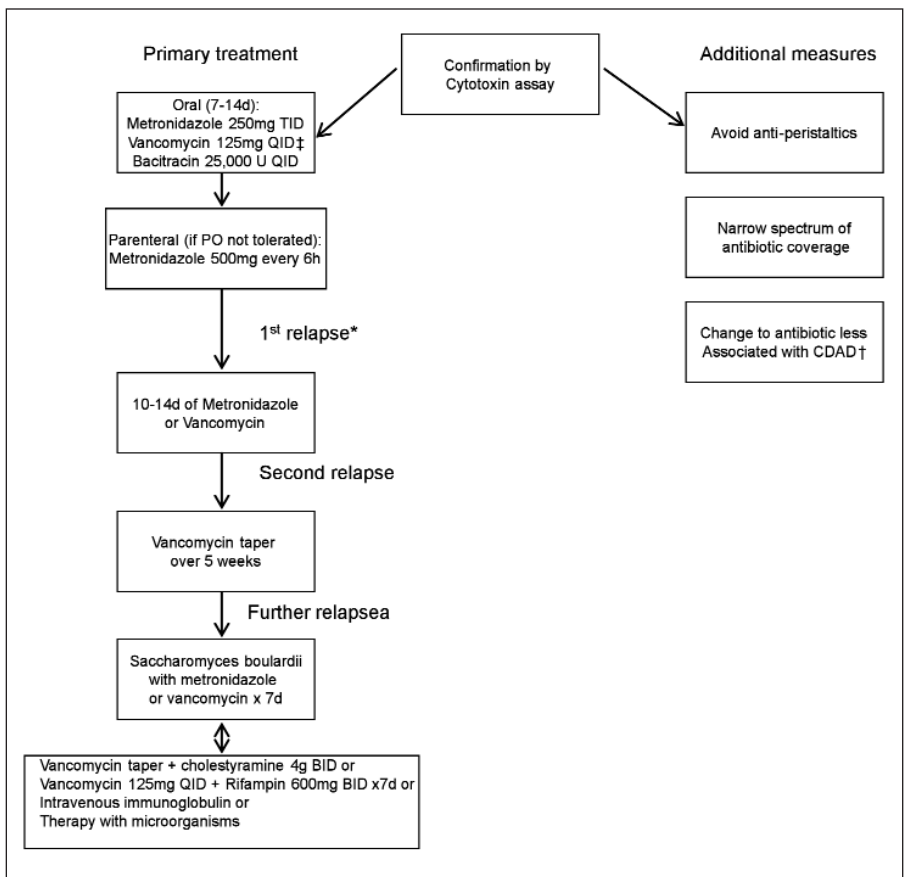


Figure 3. Management of Pseudo-membranous Colitis (3). ‡Reserve use for pregnant patients, age <10, severe life threatening colitis or metronidazole allergy. †Aminoglycosides, sulfonamides, macrolides, vancomycin, fluoroquinolones, tetracycline. *20% of patients will have relapse. Recommendations are to avoid antibiotics for 2 months after an episode of pseudomembranous colitis. ± vancomycin/metronidazole prophylaxis with antibiotics.

TREATMENT

Several recommendations for the treatment of chronic constipation have been anecdotal without randomized trials to support their use. Chin, et al randomized 157 residents of a long-term care facility that were age 64–94 years old to receive resistance training, functional skills training, both or “edu-

cational” control. Through a questionnaire on bowel movement frequency and defecation problems, they found that the percentage of patients in the study with constipation was 22%, low for this age group. However, none of the exercise programs had an effect on the percentage of subjects with constipation or laxative use (12). A large study of 1,000 employees in a Veterans Administration Health Care system used a questionnaire to identify those with chronic constipation and found no difference in exercise frequency between those who complained of constipation versus those who did not (13). There is insufficient evidence that increased fluid intake improves chronic constipation (13). At this time increased fluid intake and exercise can be recommended as overall health preserving measures, but may not be specific treatments for constipation.

First line therapy is to gradually increase dietary fiber or add fiber supplements with a goal of 20–30 grams of fiber daily, which can be achieved by increas-

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instilling thickened barium into the rectum then obtaining radiographs while the patient defecates. This test is used to measure the anorectal angle and perineal descent, detect structural abnormalities such as a rectocele, and determine if complete evacuation of the rectum was achieved. Colonic transit testing is performed by obtaining an abdominal x-ray 120 hours after the patient has ingested radiopaque markers. Retention of 20% of the markers is suggestive of prolonged transit. Anorectal manometry measures the pressure of the anal sphincter at rest and the maximal voluntary contraction of the external sphincter, the anorectal inhibitory reflex (relaxation of the internal anal sphincter during balloon distention), rectal sensation, and ability of the anal sphincters to relax during straining. Patients with defecatory disorders can have inappropriate contraction of the anal sphincter at rest and while bearing down. The results of these tests can be limited, and a single test modality should not be used as the sole method of diagnosis.

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ing the daily amount by five grams a day. Patients should be alerted that bloating can occur with fiber supplementation, but it will become less severe with time. This regimen should be adhered to for several weeks as relief will not be immediate. If symptoms do not improve, an osmotic laxative can be added. Saline laxatives such as milk of magnesia are inexpensive and should be titrated to the point that stools are soft and not loose. Magnesium containing laxatives should be avoided in patients with chronic kidney disease. If relief is not achieved, then one can change to another osmotic laxative such as polyethylene glycol or lactulose. Tramonte, et al performed a systemic review of 36 randomized trials and found that fiber and laxatives modestly improved bowel movement frequency in adults with chronic constipation, but there was inadequate evidence to establish whether fiber was superior to laxative or that one laxative class is superior to another (14). However, Attar, et al studied 115 patients with chronic constipation and found that polyethylene glycol in small daily doses (13–26 g/day) was more effective and better tolerated than lactulose. There were no serious toxicities from PEG after one-to-three months treatment (15). Therapy should be titrated down to the least expensive/most effective maintenance dose. “Rescue” medications include suppositories, enemas and stimulant laxatives. These medications should only be used as needed. Currently there is insufficient evidence to support the use of probiotics, and prokinetics such as erythromycin or cisapride in chronic constipation (13). If these measures prove inadequate then further testing should be initiated to rule out slow transit constipation or pelvic floor dysfunction. Diagnosis of these conditions can greatly change therapy.

Pelvic floor dysfunction can conceivably occur after several years of chronic constipation and the resultant straining to defecate. Biofeedback has been used primarily for pelvic floor dysfunction and the goal is to retrain the pelvic muscles to relax appropriately during defecation. The success depends on patient motivation as well as frequency and intensity of the program, which often is multi-disciplinary with dietitians, behavioral psychologists and biofeedback therapists, but success rates are better than 75%.

Surgical treatment of chronic constipation has had disappointing results mostly because the patient popu-

lation that will benefit from surgery needs to be selected carefully. A total colectomy with ileorectal anastomosis is performed for patients with slow transit constipation that have failed a prolonged trial of laxatives, fiber and prokinetic agents. Patient satisfaction after colectomy can range from 39% to 100% (16).

TREATMENT OF CONSTIPATION IN THE SETTING OF CHRONIC OPIOID USE

Opioid induced constipation is seen in about 40%–50% of patients with metastatic malignancy who are on pain medications (17). Opioids have peripheral and central action on intestinal motility. Opiate effects via the CNS are mediated through μ and σ receptors. In the digestive tract μ and κ receptors can be found in the myenteric plexus, while σ receptors can be found in the submucous plexus and on circular smooth muscle cells of the intestine that are responsible for segmental non-propulsive gut motility. The longitudinal muscle layer that is responsible for propulsive movements does not have opioid receptors. Stimulation of these receptors increases gut motility and leads to increased colonic transit time. Opioids can also inhibit intestinal secretion stimulated by prostaglandins, carbachol, vasoactive intestinal polypeptide (VIP), cAMP, cholera and *E. Coli* toxin. This is mediated by σ receptors on in the submucosal plexus. As a result there is an overall increase in fluid and electrolyte absorption from the small and large intestine. It has been suggested that this can cause constipation, but it is more likely that absorption proceeds normally and desiccation of bowel contents is due to increased bowel transit time (17).

The pharmacology of opioid effect on intestinal motility has been the basis for examining opioid antagonists as treatment for constipation. Naloxone has been studied the most extensively, but all of the studies have been small and have not had a controlled design or precisely defined inclusion or outcome criteria. The results have been mixed, but all suggest that naloxone has a narrow therapeutic window between reversing constipation and loss of analgesia. Currently, use of naloxone to reverse opioid induced constipation is an unlabeled indication. Based on these few studies of narcotic dependent patients the recommendation is to start doses as low as 0.8 mg twice a day with a max-

imum of five mg a day watching for toxicity and loss of analgesia (17). Thomas, et al in a retrospective chart review of 23 patients who received enteral naloxone or IV neostigmine in the treatment of constipation found that success rates in the naloxone group were lower than expected. It was also associated with vital sign abnormalities (mostly blood pressure lability), withdrawal symptoms and abdominal pain. It was their recommendation that naloxone be administered in an ICU environment to facilitate close monitoring of vital signs and rapid response to adverse effects (18).

Nalmefene and Naltrexone are central and peripherally acting opioid antagonists similar to naloxone, but they have a longer half life. Nalmefene is four times as potent as naloxone in its antagonizing effects on the receptor. Its use as an oral agent has been limited by the propensity to reverse analgesia or to induce withdrawal. It can also cause elevation in transaminase levels with doses of 300 mg/day, which is reversible with cessation of the drug. A new medication that is not commercially available is methylnaltrexone, which is a quaternary opioid antagonist that has greater polarity and therefore has less ability to cross the blood-brain barrier. It has the potential to be an effective treatment for opioid induced constipation yet preserve central analgesic effects.

Recommendations for treatment for constipation in patients on chronic narcotics differs from treatment of functional constipation in that more emphasis is placed on stool softeners and laxatives as opposed to fiber supplementation. This is because the primary mechanism of opioid induced constipation is slowed stool transit due to decreased propulsive contractions in the intestine. A prospective trial of 57 patients on methadone randomized to lactulose, polyethylene glycol and placebo showed no significant difference between the two treatment arms, but both were superior to placebo ($p < 0.01$) (19). Opioid rotation was also recommended, which can be achieved either from changing the route of administration of the same opioid or using an alternative opioid. Because cross tolerance of opioids is incomplete, changing to a lower equianalgesic dosage of a different opioid may allow for continued analgesia and a lower potential for adverse effects (20). The authors stress the importance of having a bowel regimen in place prior to initiating chronic opioid therapy in order to prevent constipation.

DEFINITION AND MECHANISMS OF MEDICATION INDUCED DIARRHEA

No definition of diarrhea is universal, but diarrhea is generally defined by an increased frequency of bowel movements (>3 in 24 hours), and/or decreased stool consistency, and/or increased stool weight (>200 g in 24 hours) (3). Diarrhea is a common side effect of many classes of medications. It accounts for 7% of all adverse drug effects and over 700 drugs have been implicated in causing diarrhea (3). Medications most frequently involved are antibiotics, laxatives, antihypertensives, lactulose or sorbitol containing products, antineoplastics, antiretroviral drugs, magnesium containing compounds, antiarrhythmics, nonsteroidal anti-inflammatory drugs, colchicine, antacids and acid-reducing agents, prostaglandin analogs, as well as many supplements (3,21).

Diarrhea occurs when infectious agents, toxins, and other noxious materials are present in the gut causing disruption of normal fluid secretion and motility and stimulating the gut to expel the contents. This response is protective for acute irritations of the gut but becomes an issue when chronically present and no longer serving a physiologic role. There are several mechanisms responsible for drug induced diarrhea and often two or more can be present simultaneously (3) (Table 2). These include: osmotic diarrhea due to ingestion of poorly absorbed and osmotically active solutes such as sorbitol, lactulose, and magnesium salts; secretory diarrhea due to increased small intestinal ion secretion or inhibition of ion absorption leading to excess of water and electrolytes in the intestinal lumen as seen with stimulant laxatives; exudative diarrhea from disruption of intestinal mucosa through inflammation often seen with antineoplastics; malabsorption of fats or carbohydrates causing steatorrhea; and increased intestinal motility seen with cisapride and erythromycin. Lymphocytic or collagenous colitis due to NSAIDs has also been described (3,22). The mechanism of antibiotic associated diarrhea is due to disruption of normal intestinal flora, which leads to either proliferation of pathogenic microorganisms or impairment of the metabolic functions of the microflora (3). Except with pseudomembranous coli-

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Table 1
Mechanisms of drug induced constipation (35)

<i>Medication or Medication Class</i>	<i>Mechanism</i>
Opioids	Predominately through μ and σ receptors—decreased propulsive peristaltic waves, increased tone, enhanced nonpropulsive contractions, reduced anorectal inhibitory reflex due to increased anal sphincter tone
Anticholinergics: Anti-Parkinsonian drugs Anti-psychotics (chlorpromazine) Anti-histamine (diphenhydramine) Tricyclic antidepressants	Decreased Ach mediated stimulation of predominately M ₂ receptors in the GI tract decreasing motility and secretions. (muscarinic receptor blockade)
Calcium channel blockers Clonidine	Reduced motility and may promote intestinal electrolyte and water absorption Stimulates absorption and inhibits secretion of fluid and electrolytes and increasing intestinal transit time by interaction with receptors of enteric neurons and enterocytes
Iron	Possibly due to iron induced changes in intestinal bacterial flora
Sympathomimetics (ephedrine)	Smooth muscle relaxation via B ₂ receptors

tis, there are usually no endoscopic findings. Diarrhea can be further divided into acute, which appears within the first few days of treatment or chronic which lasts greater than three-to-four weeks and can occur long after the start of a medication (3). This latter presentation can lead to diagnostic uncertainty.

ANTIBIOTIC ASSOCIATED DIARRHEA

Antibiotic-associated diarrhea can be defined as the unexplained onset of diarrhea that occurs with the administration of any antibiotic (23). Diarrhea is commonly associated with use of antibiotics and can be related to a number of different mechanisms, depending on the antibiotic used (21). The majority of cases, which may be from 70%–80%, are categorized as a nonspecific, or simple antibiotic associated diarrhea (23). These episodes are usually mild and typically resolve with discontinuation of the associated antibiotic. This type of diarrhea typically results from a disturbance in the normal colonic flora, leading to impaired fermentation of carbohydrates and osmotic diarrhea and/or reduced production of short-chain fatty acids which by reducing colonic absorption of fluid causes secretory diarrhea (3). Reduced digestion of bile salts by normal colonic flora and the resultant increased colonic concentration can

stimulate secretion of fluid by the colon and cause a secretory diarrhea (21). Drugs that have high rates of causing simple antibiotic associated diarrhea typically have a larger impact on anaerobic bacteria in the normal fecal flora than antibiotics with lower incidence rates (24). The most studied antibiotics include clindamycin and oral ampicillin, which lead to diarrhea in 10%–25% and 5%–10% of patients, respectively (24). Rates of diarrhea with other antibiotics include 10%–25% with treatment with amoxicillin-clavulanate, 15%–20% with cefixime therapy, and 2%–5% with treatment with other cephalosporins, fluoroquinolones, azithromycin, clarithromycin, erythromycin, and tetracyclines (23). Some antibiotics associated with diarrhea are caused by mechanisms other than alteration of intestinal microflora. Erythromycin induced diarrhea is caused by increased motility through stimulation of motilin receptors. Neomycin in large doses can also lead to diarrhea associated with malabsorption (25).

Simple antibiotic associated diarrhea occurs in a dose-related fashion. This complication is more common in drugs given orally rather than parenterally, except with drugs excreted in the bile, such as clindamycin, ampicillin, cefoperazone, and nafcillin; this diarrhea generally resolves within days of discontinuing the offending antibiotic (24).

Table 2
Mechanisms of drug induced diarrhea

<i>Medication or Medication Class</i>	<i>Mechanism</i>
Laxatives	Osmotic diarrhea (osmotically active solutes)
Stimulant laxatives	Secretory diarrhea (excess of fluids and electrolytes)
Erythromycin, cisapride	Motility diarrhea (shortened transit time)
Antimicrobials	Pseudomembranous colitis (bacterial proliferation)
Antineoplastics	Exudative diarrhea (protein losing enteropathy)
NSAIDS	Lymphocytic or collagenous colitis
α -glucosidase inhibitors	Maldigestion/malabsorption of carbohydrates (osmotic diarrhea)
Lipase inhibitors (Orlistat)	Maldigestion/malabsorption of fat (steatorrhea)

Approximately 20% of antibiotic associated diarrhea is caused by infection with *Clostridium difficile*. In contrast to simple antibiotic associated diarrhea, *Clostridium difficile* associated diarrhea (CDAD) is not dose related and symptoms can last weeks to months after the offending antibiotic has been discontinued, often until treatment for the infection is administered (24). The antibiotics most commonly associated with *Clostridium difficile* infection include clindamycin, ampicillin, amoxicillin, quinolones and the cephalosporins.

Clostridium difficile is a gram-positive bacillus and is a spore-former, allowing it to survive under harsh conditions and during antibiotic therapy. The development of infection caused by *Clostridium difficile* involves several steps. The first step involves a disturbance in the normal flora of the colon, often caused by antibiotic therapy, but also seen with immunosuppressants and anti-neoplastic drugs. The second step is colonization of the individual by the organism. This occurs by the fecal-oral route, during which the spores are able to survive the harsh conditions of the stomach and subsequently germinate in the colon. The majority of patients only develop asymptomatic colonization and do not demonstrate symptoms of CDAD. In those patients who do develop symptoms, the time of onset can range from the first day of antibiotic therapy to six weeks after antibiotics have been stopped (26). Other factors which play a role in the development of CDAD include the host susceptibility to infection, the virulence of the infecting strain, and the type of antibiotic used and timing of exposure

(25). Reduced levels of anti-toxin A antibody have been linked to increased probability of symptoms in infected patients. Clinically significant strains of *Clostridium difficile* that cause diarrhea demonstrate production of two distinct exotoxins. Toxin A has been shown to bind to specific receptors in the brush border of the intestinal epithelium, while the site of binding of toxin B has not yet been described. Toxin induced release of inflammatory mediators and cytokines leads to chemotaxis of inflammatory cells and increased fluid secretion by the epithelium. Histologic changes seen in the colonic epithelium include patchy necrosis with production of an exudate composed of fibrin and neutrophils. More widespread necrosis and ulceration may result leading to pseudomembrane formation. This pseudomembrane is composed of necrotic cellular debris, fibrin, mucin, and leukocytes.

Infection with *Clostridium difficile* can present as a spectrum of diseases ranging from asymptomatic colonization or simple antibiotic associated diarrhea, to more severe manifestations of pseudomembranous colitis or fulminant colitis. As mentioned previously, asymptomatic carriers represent the majority of patients with *Clostridium difficile* infection; treatment is not recommended in this group. Patients can present with colitis and no evidence of pseudomembranes on endoscopic examination. These patients more commonly exhibit malaise, abdominal pain, nausea, anorexia, watery diarrhea, low-grade fever, and peripheral leukocytosis. Pseudomembranous colitis is a more severe illness as
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patients can present with more profuse diarrhea and occasionally occult bleeding or high fevers.

Fulminant colitis occurs in between 1%-3% of patients with *Clostridium difficile* infection. Patients may demonstrate severe abdominal pain and distention, high fever, and marked leukocytosis. Life-threatening complications seen in fulminant colitis include colonic perforation, toxic megacolon, and even death.

Multiple methods are available for the diagnosis of *Clostridium difficile* infection. The most sensitive and specific test is a tissue culture assay for toxin B. It has a sensitivity of 94%–100% and specificity of 97%–99%. The most widely used test for *Clostridium difficile* diagnosis is the enzyme-linked immunosorbent assay (ELISA) for toxins A and/or B. Latex agglutination assays are available, which detect the enzyme glutamate dehydrogenase. This enzyme is also produced by other bacteria, leading to the poor specificity of this test. Bacterial culture for *Clostridium difficile* is a highly sensitive test, but detects toxinogenic strains as well as non-toxin producing strains. Compared with other tests, culture can take up to two-to-five days to perform. Polymerase chain reaction can also be used, with sensitivity and specificity similar to those of ELISA testing (25).

Treatment of CDAD should begin with discontinuation of the offending antibiotic whenever possible and supportive measures such as fluid and electrolyte replacement is important to educate hospital personnel on strict handwashing with soap and water as well as proper disinfection of contaminated surfaces. Enteric isolation precautions for patients with infection should be performed. Antiperistaltic agents and opiates should be avoided in patients with CDAD.

Antimicrobial therapy is indicated for patients with moderate to severe disease or with significant coexisting conditions. However, in up to 25% of patients, diarrhea will resolve without antimicrobial therapy (25). First line therapies for CDAD include vancomycin 125 mg four times daily, metronidazole 250 mg three times daily, or bacitracin 25,000 units four times daily, all for courses of seven-to-14 days. Parenterally administered metronidazole 500 mg given every six hours can be used if oral agents are not tolerated.

There has also been some evidence to support the use of probiotics in the treatment of recurrent relapses of *Clostridium difficile* infection. *Saccharomyces*

bouardii at a dose of one gm daily during concurrent treatment with vancomycin or metronidazole has demonstrated effectiveness in the treatment of adults in a hospital setting (27).

DIARRHEA ASSOCIATED WITH PROTEASE INHIBITORS

Diarrhea is a common complication of HIV infection and it is estimated that 50%–60% of AIDS patients will have diarrhea during the course of their illness. Studies have shown that severe diarrhea is related to lower baseline CD4+ counts and higher viral loads when compared to patients with less severe or no diarrhea. Diarrhea has also been associated with the use of protease inhibitors commonly used in the treatment of HIV (28).

The mechanism causing diarrhea with the use of protease inhibitors remains unclear; episodes are mild to moderate and the incidence ranges from 12.3%–19.9% with saquinavir, 12.8%–21.6% with ritonavir, 0%–4.6% with indinavir, 14%–32% with nelfinavir, and 33%–56% with amprenavir (28).

Treatments for antiretroviral associated diarrhea range from over-the-counter agents to prescription medications. Sources of soluble fiber, such as oat bran or psyllium, act as bulk forming agents and increase the intestinal transit time. Oat bran has been shown to decrease the number of loose stools and improve symptoms in up to 84% of patients. Psyllium use has also been shown to lead to less frequent stools in 55% of patients as well as improved symptoms in 40% of patients. Loperamide acts by inhibiting propulsion in the small and large bowel and limiting secretion. Combinations of pancreatic enzymes have been studied and act by reducing the fat content of stool, leading to increased consistency and decreased frequency of stools. The use of the naturally occurring extract of the *Croton lechleri* plant, SP-303, has also been shown to be of benefit for these patients. The mechanism of action remains unclear, but it is thought to act by decreasing chloride ion secretion in the cells of the GI tract, leading to decreased stool weight and frequency.

CHEMOTHERAPY INDUCED DIARRHEA

Diarrhea is a common problem associated with advanced cancer and can have a significant impact to

the patient by contributing to dehydration and electrolyte imbalances, malnutrition, immunodeficiency, and pressure ulcer formation. In patients with cancer, diarrhea can be caused by a number of factors, including excessive doses of laxatives, predisposition to infection by *Clostridium difficile*, radiotherapy, enteral feeding, bowel obstruction, or presence of concurrent disease processes. Several chemotherapeutic agents have been implicated in causing diarrhea. The agents most commonly causing diarrhea include 5-fluorouracil, capecitabine, and irinotecan (CPT-11) (29).

Dysfunction of the GI tract in patients undergoing cancer chemotherapy is due to the cytotoxic effects of the agents leading to mucositis. This can cause pain and ulceration in the entire gastrointestinal tract and can lead to abdominal pain and bloating, constipation, diarrhea, and vomiting. Mucositis occurs in about 40% of patients who receive chemotherapy in standard doses and affects close to 100% of patients who receive high-dose chemotherapeutic agents or who have undergone stem cell or bone marrow transplantation (30).

Some chemotherapeutic agents have different mechanisms of toxicity leading to diarrhea. 5-Fluorouracil causes cessation of mitosis in the intestinal crypt cells and leads to increasing numbers of immature secretory cells resulting in dysfunctional absorption and secretion of fluids and electrolytes. The diarrhea caused by toxicity with 5-fluorouracil can be either watery or bloody in nature. Inflammation due to 5-fluorouracil toxicity may range from mild colitis to severe necrotizing enterocolitis with pneumocystic colitis (29). Irinotecan can lead to diarrhea by two separate mechanisms. Diarrhea occurring immediately after the administration of the drug is caused by acute cholinergic properties of the medication and usually responds well to atropine. Diarrhea that occurs greater than 24 hours after drug administration is thought to be due to the direct effect of SN38 glucuronide, an irinotecan metabolite produced by intestinal bacteria, on the epithelium of the colon (29).

Treatment of diarrhea caused by chemotherapeutic agents varies with the severity of symptoms. Rehydration is a key to treatment, especially in patients with large volume diarrhea, as also correcting electrolytes imbalance, particularly hypokalemia. The most commonly used agents to prevent diarrhea are opioid

preparations. Loperamide is most frequently used because it has predominately local activity in the gut and poor systemic availability. For more severe cases of diarrhea, octreotide is a potential therapy. Octreotide is a somatostatin analog that acts on the gut epithelial cells by inhibiting local hormones such as serotonin, vasoactive intestinal peptide, gastrin, insulin, and glucagon. It also works by increasing the transit time in the intestine, promoting absorption, and decreasing the secretory activity of the gut and mesenteric blood flow (30). The starting dose of octreotide is 100–150 mg either subcutaneous (SC) or intravenous (IV) three times daily. The antidiarrheal effect of octreotide is dose-dependent, therefore the dose can be titrated to 500 µg SC/IV three times daily or used by continuous infusion of 25 to 50 µg/h.

MISCELLANEOUS

Multiple other commonly used medications can cause diarrhea and in most instances the mechanism of action is only partially understood. Theophylline and caffeine may cause an increase in intracellular cAMP and increase fluid secretion known as “Starbuck’s diarrhea” (31). Antiarrhythmics like quinidine can cause diarrhea, but if diarrhea is associated with tinnitus and hearing loss then immediate evaluation is necessary for cinchonism. Profound acid suppression with proton pump inhibitors and H₂ blockers can cause diarrhea. It is felt to be dose and age related, and may be secondary to the alteration of the bacterial content of the gut (32). Beta blockers can cause diarrhea, and rarely can be associated with mesenteric ischemia by decreasing cardiac output and decreasing splanchnic blood flow (33). NSAIDs may be associated with collagenous colitis (22). Diarrhea is a known side effect of colchicine and it is commonly used in refractory constipation (34). Treatment usually involves withdrawal of the medication, but in some instances it may slowly improve on its own. If the medication is deemed necessary anti-diarrheals such as Lomotil can be used in conjunction with the medication (35).

CONCLUSION

Medication induced constipation and diarrhea is a common problem that often goes undiagnosed due to vari-

ability of symptom onset in relation to medication use. Patients may not often associate the medications they take as potential offenders. Therefore, it is vital to obtain a detailed medication history of all medications taken in the past two months and thus likely avoid multiple diagnostic tests. One must recognize high-risk patient populations for medication induced diarrhea or constipation such as the elderly, nursing home or long-term care residents, patients with chronic pain, those with prolonged hospitalization or being treated with broad spectrum antibiotics. When symptoms do not improve with discontinuing the medication, the condition should be managed as outlined for chronic constipation. Treatment of diarrhea is largely dependent on the mechanism but the initial focus should focus on rehydration and electrolyte replacement. As always look for a cause. Ideally physicians should recognize potentially constipating or diarrhea inducing medications and initiate preventative strategies prior to symptom onset. ■

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