# DRUG-INDUCED INJURY OF THE GASTROINTESTINAL TRACT

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**KEYWORDS**

• Drug-induced injury • Gastrointestinal tract • Nonsteroidal antiinflammatory drugs
• Chemotherapeutic agents

## ABSTRACT

The effects of drugs on the gastrointestinal (GI) tract are diverse and depend on numerous factors. Diagnosis is centered on histologic findings, with mostly nonspecific patterns of injury that must be interpreted in the correct clinical context. Nonsteroidal antiinflammatory drugs are a common cause of drug-induced GI injury, with effects primarily in the gastric mucosa but also throughout the GI tract. Another common class of drugs causing a variety of pathologic findings in the gut is chemotherapeutic agents. This article discusses the differential diagnosis of the various patterns of injury, including ischemic damage, and the histologic findings specific for certain drugs.

## OVERVIEW

It is probable that gastrointestinal (GI) chemical injury often remains undiagnosed, because pathologists rarely have sufficient clinical information to make the diagnosis. Some of the nonspecific inflammation seen throughout the gut presumably results from chemical or drug exposure. However, some agents produce characteristic histopathologic changes, making it possible for the pathologist to suggest at least the possibility of drug-induced injury. Overall, it is estimated that from 2% to 8% of patients receiving drugs experience an adverse GI reaction, with GI bleeding accounting for the largest burden of adverse drug-related hospital admissions. Up to one-third of drug injuries affect more than a single GI site.

Chemicals injure the GI tract in numerous ways. Drug injuries result from the drugs themselves, their metabolites, or from by-products of food-drug (chemical) interactions. Host factors, specific meal composition and volume, and the drug or chemical type determine the nature of the interactions. Patients become exposed to chemical injury via several mechanisms including accidental ingestion, overdose as the result of suicidal intent, therapies for numerous diseases, their use as preventive agents, their use in diagnostic tests, consumption of foods that contain chemicals, and consumption of supplements or substances found at health food stores.

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### ESOPHAGUS

Esophagitis caused by drug injury occurs in approximately 3.9 people per 100,000 population per year, and can be caused by many different drugs, especially antibiotics.[1] Elderly patients are at increased risk because of decreased saliva production, altered esophageal motility, being on more drugs because of comorbid conditions, and spending more time in a reclining position.[2] Lower esophageal sphincter (LES) pressure may be decreased by some drugs, leading to reflux esophagitis, which can exacerbate damage caused by acidic drugs, as well as aspirin, iron, and tetracyclines.[2] Hiatal hernias, strictures, rings, webs, and esophageal compression from an enlarged heart, thyroid, or lymph nodes can prolong the amount of time that pills are in contact with the esophageal mucosa, thereby increasing the risk of injury.

### STOMACH

Gastric erosions, ulcers, and hemorrhage can be caused by a variety of drugs, but the most common class of drugs implicated in gastric injury are nonsteroidal antiinflammatory drugs (NSAIDs). There is evidence that direct mucosal contact is not necessary for a drug to cause gastric injury, because intravenously administered agents can cause similar injuries to those administered orally. Patients on corticosteroids have an increased risk of gastric ulceration and upper GI bleeding with concomitant use of NSAIDs.[3,4]

### SMALL INTESTINE

The effects of drugs on the small intestine may result from direct mucosal toxicity, alteration of motility, induction of ischemia, interference with micelle formation, alteration of the state of dietary ions or other drugs, and inhibition of mucosal enzymes.[5] Malabsorption is a common final pathway of small intestinal injury by a variety of drugs.

### LARGE INTESTINE

Colitis caused by drug injury is likely underdiagnosed, and its true incidence is not known. The most common presentation is diarrhea, which can occur immediately or after the patient has been taking the drug for a long time, and accounts for 7% of all drug adverse events.[6] Drug injury to the colon can occur in a variety of ways, including ischemic, pseudo-obstructive, infectious, allergic, cytotoxic, or inflammatory mechanisms. Most drug-induced damage in the colon causes nonspecific histologic changes that are often indistinguishable from infectious colitis, ischemia, or idiopathic inflammatory bowel disease (IBD). Suppositories can cause nonspecific proctitis and rectal ulcers.[7]

## NSAIDS

### OVERVIEW

NSAIDs are widely prescribed[8] and commonly used in forms that are available over the counter. NSAIDs are commonly prescribed to treat joint diseases and to prevent cardiovascular and cerebrovascular thrombotic events. Patients taking NSAIDs have a threefold greater risk for the development of serious adverse GI events[3] and an increased risk of hospitalization for ulcer disease.[9,10] Aside from the commonly known complication of developing gastric and duodenal ulcers, which occurs in up to 25% of patients taking NSAIDs,[11] other significant gastroduodenal complications from NSAID use include GI bleeding, nonspecific small intestinal ulcers,[12] obstruction, perforation, and death.

Risk factors for complications from NSAID-related peptic ulcer disease include age greater than 60 years, history of previous ulcers, concurrent use of anticoagulants or corticosteroids, presence of systemic disorders, infection with *Helicobacter pylori*, and tobacco and alcohol use.[3,13–18] The type of NSAID also plays a role in the severity of GI injury.[19] Risk of NSAID-induced GI injury is also increased in the first month of use[9] and with increasing dose of the drug.[9,19–21] Sixty-five percent of patients on long-term NSAID therapy develop an enteropathy with bleeding, protein loss, and bile-acid malabsorption.[22,23]

### CLINICAL PRESENTATION

About 50% of patients taking NSAIDs experience GI symptoms, including dyspepsia, heartburn, nausea, appetite loss, abdominal pain, or diarrhea.[24,25] However, symptoms do not necessarily predict the presence of endoscopically apparent GI damage.[26] Clinically silent small bowel damage occurs in about two-thirds of all patients on NSAIDs,[27] and about 50% of patients with NSAID-related peptic ulcer disease do not present clinically until complications occur.[11] Bleeding, which can occur anywhere along the GI tract, is a serious complication seen after long-term NSAID use.[3] NSAIDs can also cause ileal dysfunction,