Proton Pump Inhibitors (PPIs) and C. difficile

The U.S. Food and Drug Administration (FDA) is informing the public that the use of stomach acid drugs known as proton pump inhibitors (PPIs) may be associated with an increased risk of *Clostridium difficile*–associated diarrhea (CDAD). A diagnosis of CDAD should be considered for patients taking PPIs who develop diarrhea that does not improve.

Patients should immediately contact their health care professional and seek care if they take PPIs and develop diarrhea that does not improve.

*Clostridium difficile* (*C. difficile*) is a bacterium that can cause diarrhea that does not improve. Symptoms include watery stool, abdominal pain, and fever, and patients may go on to develop more serious intestinal conditions. The disease can also be spread in the hospital. Factors that may predispose an individual to developing CDAD include advanced age, certain chronic medical conditions, and taking broad spectrum antibiotics. Treatment for CDAD includes the replacement of fluids and electrolytes and the use of special antibiotics.

The FDA is working with manufacturers to include information about the increased risk of CDAD with use of PPIs in the drug labels.

FDA is also reviewing the risk of CDAD in users of histamine H₂ receptor blockers. H₂ receptor blockers are used to treat conditions such as gastroesophageal reflux disease (GERD), stomach and small intestine ulcers, and heartburn. H₂ receptor blockers are marketed under various brand and generic drug names as prescription and OTC products.

Additional Information for Patients and OTC Consumers

- Seek immediate care if you use PPIs and develop diarrhea that does not improve. This may be a sign of *Clostridium difficile*–associated diarrhea (CDAD).
- Your health care professional may order laboratory tests to check if you have CDAD.
- Do not stop taking your prescription PPI drug without talking to your health care professional.
- Discuss any questions or concerns about your PPI drug with your health care professional.
- If you take an OTC PPI drug, follow the directions on the package carefully.

Additional Information for Health Care Professionals

- A diagnosis of CDAD should be considered for PPI users with diarrhea that does not improve.
- Advise patients to seek immediate care from a health care professional if they experience watery stool that does not go away, abdominal pain, and fever while taking PPIs.
- Patients should use the lowest dose and shortest duration of PPI therapy appropriate to the condition being treated.

Data Summary

FDA has reviewed reports from the FDA’s Adverse Event Reporting System (AERS) and the medical literature for cases of *Clostridium difficile*–associated diarrhea (CDAD) in patients undergoing treatment with PPIs. Many of the adverse event reports involved patients who were elderly, had chronic and/or concomitant underlying medical conditions, or were taking broad spectrum antibiotics that could have predisposed them to developing CDAD. Although these factors could have increased their risk of CDAD, the role of PPI use cannot be definitively ruled out in these reviewed reports. Patients who have one or more of these risk factors may have serious outcomes from CDAD with concomitant PPI use.

FDA also reviewed a total of 28 observational studies described in 26 publications. Twenty-
three of the studies showed a higher risk of *C. difficile* infection or disease, including CDAD, associated with PPI exposure compared to no PPI exposure.\(^2\)\(^{27}\) Although the strength of the association varied widely from study to study, most studies found that the risk of *C. difficile* infection or disease, including CDAD, ranged from 1.4 to 2.75 times higher among patients with PPI exposure compared to those without PPI exposure. In the five studies that provided information on clinical outcomes, colectomies, and rarely deaths, were reported in some patients.\(^4\)\(^{6}\)\(^{11}\)\(^{12}\)\(^{21}\)

The published studies varied in their ability to assess the association between *C. difficile* infection or CDAD and prior PPI use. There were limited data on the relationship between the risk of *C. difficile* infection or CDAD and PPI dose and duration of use. There also was little information on the use of OTC PPIs in community settings in these studies. Nevertheless, the weight of evidence suggests a positive association between the use of PPIs and *C. difficile* infection and disease, including CDAD.


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**References**


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