CADTH Evidence Driven.

Proton Pump Inhibitors (PPIs) and *Clostridium difficile* Infection (CDI)

What does the evidence say?

There is an association between PPI use and CDI. CADTH reviewed all the available evidence: 7 systematic reviews and 22 observational studies. The review was limited by some lower-quality studies.[1]

Do PPIs cause CDI?

We will probably never have enough evidence to know for sure. To be able to say conclusively that one thing causes another usually requires a randomized controlled trial (RCT) in which people are randomly assigned to different treatments. This means that the groups of people assigned to different treatments are very similar and any differences observed between the groups are likely due to the thing we are trying to study.

In the case of PPIs, we have observational trials, in which patients or their health care providers have chosen their treatments and the researcher simply observes and reports on what happens. There may be some other reason (called a "confounder" or "confounding factor") that people who choose to take PPIs are also more likely to develop CDI. For example, they may have more complex medical conditions or be more at risk for hospitalization.

It would be helpful to have RCTs to answer this question, but would you sign up to participate in a trial if you knew you might be randomly assigned to a treatment that might cause you harm? Such trials are unlikely to happen, so we need to consider results from high-quality observational studies.

What does Health Canada say?

In 2012, Health Canada issued an advisory about the possible association of PPI use and CDI.[2] PPI prescribing information must now include the precaution that a decrease in stomach acid may increase the risk of gastrointestinal infections such as *Salmonella*, *Campylobacter*, and *C. diff*.

This warning reminds health professionals that PPIs should be used at the lowest possible dose for the shortest possible duration.

Key Terms

Proton Pump Inhibitors — PPIs

Proton pump inhibitors (PPIs) are a class of medications used to treat common gastrointestinal (GI) conditions such as ulcers and gastroesophageal reflux disease (GERD). They work by blocking an enzyme in the wall of the stomach to reduce the production of acid. They include dexlansoprazole (Dexilant), esomeprazole (Nexium), lansoprazole (Prevacid), omeprazole (Losec), pantoprazole (Pantoloc), pantoprazole magnesium (Tecta), and rabeprazole (Pariet). PPIs are one of the most frequently prescribed medications in Canada and their use continues to increase.

Clostridium difficile Infection — CDI

***Clostridium difficile* (*C. difficile* or *C. diff*) is a gram-positive, spore-forming, anaerobic bacterium transmitted through spores or bacteria in stools or through spores in the environment. Risk factors include antibiotic use, immunosuppression, surgery, other health problems, and hospitalization. In fact, *C. diff* is the most frequent cause of infectious diarrhea in hospitals and long-term care facilities in Canada, with a reported overall incidence of 4.6 cases per 1,000 patient admissions in 2004 to 2005. Symptoms of *C. diff* infection include watery diarrhea, fever, loss of appetite, nausea, and abdominal pain; however, some people can have *C. diff* bacteria present in their bowels and not show any symptoms.**

How has this changed practice?

CADTH conducted focus groups with health care professionals across Canada. Clinicians in these groups were aware of some potential harms of PPI therapy, and some were aware of the association between PPIs and CDI specifically. Several pointed to the biological plausibility of developing CDI while on acid-lowering therapy, saying that "stomach acid is there for a reason." However, this awareness rarely prevented clinicians from prescribing PPIs. Clinicians generally consider PPIs to be relatively harmless compared with other medications. Reasons for continuing PPI therapy long term vary but often include patient preference or prescriber time constraints.[3]

What about probiotics?

It's unknown whether natural health products such as probiotics can help prevent CDI in people who use PPIs. There is some evidence that probiotics may reduce the risk of recurrent CDI in other people at risk (for example, those taking certain antibiotics),[4] but a CADTH review could find no evidence specific to people taking PPIs.[5]

When patient and clinician agree that stopping PPI therapy may be appropriate, how should they do it?

There's no evidence on the best way to stop PPI therapy. Stopping PPI therapy can lead to rebound acidity, so it makes sense to taper the dose gradually, but current practice guidelines don't provide enough detail on dose reduction schedules, and clinical studies are lacking.[6]

An evidence-based guideline for "deprescribing" PPIs is in development.[7]

Bottom Line

Studies have shown that PPIs are inappropriately prescribed in 50% or more of the patients who use them.[6] It can be difficult to reassess therapy in a busy clinic with many competing priorities, but it's important to weigh the risks and benefits, and discuss these with patients. A Health Canada advisory reminds health professionals that PPIs should always be used at the lowest possible dose for the shortest possible duration.[2]

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CADTH receives funding from Canada's federal, provincial, and territorial governments, with the exception of Quebec.

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August 2015

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