It's enough to give you HEARTBURN

Wonder drugs they may be, but PPIs are overprescribed and pose some health risks

By Nathan Seppa

In the arms race against heartburn, one class of drug outperforms the competition by going straight to the source. The proton pump inhibitors, PPIs for short, block acid manufacture at the subcellular level. In contrast, acid reflux drugs such as Tums and Maalox neutralize the acid. Others, like Zantac and Tagamet, slow down its production by blocking the histamine 2-receptor. PPIs do require a day or two to start suppressing the symptoms of acid reflux. But once PPIs kick in, they put out the fire with stunning efficiency.

"No question about it. They are far more effective than anything we had before," says Randolph Regal, a clinical pharmacist at the University of Michigan in Ann Arbor.

When PPIs first hit the market in the 1980s, the acid-blocking pills — sold as Nexium, Prilosec and Aciphex, among other brand names — looked like wonder drugs. Since then, U.S. sales of PPIs have grown to roughly $14 billion a year.

But PPIs now risk becoming a victim of their own success. Several reports indicate these drugs are overprescribed, often in hospitals and to older patients. And other studies suggest that long-term use of the best-ever drugs for dousing heartburn carries its own risks. PPIs have accumulated a rap sheet linking them to a heightened risk of broken bones, bacterial infections and a few rare conditions. Other research suggests that weaning oneself off unnecessarily prescribed PPIs can be difficult and can cause, of all things, heartburn. These potential drawbacks are forcing regulators to rethink labeling on the drugs and leading doctors to reevaluate prescribing PPIs for some patients.

Although long-term use of PPIs can carry risks, none compares to the consequences of untreated reflux disease. The stomach acid that digests food and keeps bacteria at bay is highly corrosive. While the durable stomach usually withstands acid's violence, the esophagus, which runs from the mouth to stomach, is supremely vulnerable. When a leaky valve allows acid to splash up from the stomach, the result is acid reflux. Left untreated, it can cause esophageal scarring and even cancer.

The new findings suggest doctors and patients must better ascertain who really needs PPIs, says David Metz, a gastroenterologist at the University of Pennsylvania School of Medicine in Philadelphia. "The aim is to use therapeutics to make people better, with a risk-benefit ratio that's appropriate. We don't want to overtreat people who don't need PPIs or undertreat people who do."

Bad to the bone

Topping the list of PPI drawbacks is the specter of bone fractures. Metz and colleagues reported in the *Journal of the American Medical Association* in 2006 that people who had been taking a PPI for more than a year had a 30 to 60 percent increased risk of hip fracture over those not taking acid blockers. A higher dose of PPIs boosted the risk to more than double. A Danish study, published the same year in *Calcified Tissue International*, also found that PPIs increased the risk of a broken hip by about half.

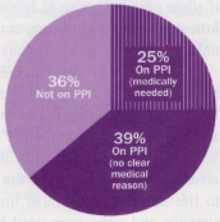
The U.S. Food and Drug Administration earlier this year slapped a fracture warning label on PPIs, both prescribed and over-the-counter, citing these and four other studies that showed an increase of fractures in people using the drugs.

While scientists are still sorting out how PPIs might affect bone, some theorize that acid is needed to dissolve calcium compounds, making calcium available in the blood and thus to the bone.

Another risk linked to PPIs is bacterial infection. Hospitalized patients getting a daily PPI are more likely to contract a *Clostridium difficile* bacterial infection than are people not taking any acid blockers, Harvard Medical School pulmonologist Michael Howell and colleagues reported in the May 10 *Archives of Internal Medicine*. Those getting the drugs more than once a day faced double

Unnecessary risk Among other concerns, PPIs have been linked to infection with the bacterium *Clostridium difficile*. In one hospital, a team identified 138 patients with *C. difficile*. Of these, 88 were on a PPI, though only 34 had a clear medical reason for taking the reflux drug.

PPI use in *C. difficile*–infected patients



SOURCE: M.N. CHOUDHRY ET AL/QJM 2008

FROM TOP: T. DUBE, PILLS: ROSIESMIUM/ISTOCKPHOTO; T. DUBE

to triple the risk that nonusers did.

Most cases of *C. difficile*, which can cause severe diarrhea, erupt in hospitals. PPIs lower stomach acidity, allowing *C. difficile* in the gut to survive when it wouldn't otherwise, Howell says. The microbes travel downstream, where they release toxins that cause the diarrhea.

Other microbes may survive as well, possibly causing pneumonia if they get splashed up into the esophagus and breathed into the lungs. A separate study by Howell's team showed a link between hospital-acquired pneumonia and PPI use, with the drugs raising the odds of infection by 10 to 40 percent.

Less certain but also raising concern is whether PPIs interfere with B12 vitamin levels and with the activity of some drugs. Early reports suggested problems with PPI use and a particular anticlotting medication called clopidogrel, or Plavix, but more recent data have cast doubt on that link.

Too many 'scripts

Not everyone agrees that the risks are as worrisome as these studies suggest. David Johnson, a gastroenterologist at Eastern Virginia Medical School in Norfolk, says that some other studies haven't found any risk from PPI use, and that many studies fail to take into account the risk run by a patient who stops taking a PPI. "If you only look at one side, it's not a balanced assessment," Johnson says.

He also questions why people with pernicious anemia, who make very little stomach acid, aren't beset by *C. difficile* infections or pneumonia. "And their bones should just crumble," he says, if acid suppression is deleterious. "It just doesn't make sense."

The absolute risk of the medical problems linked to use of PPIs — the likelihood that a given individual will encounter one — is small. In the study by Metz and his colleagues, for example, it works out to four broken hips per 1,000 people using PPIs for more than a year. That's up from two per 1,000 nonusers, calculates Hye-Kyung Jung of Ewha Womans University in Seoul, South Korea.

"But we ended up giving PPIs to everybody," counters Howell, and that multiplies the population at risk. There were 119.4 million prescriptions for PPIs dispensed in 2009 in the United States, according to IMS Health, a Norwalk, Conn.–based research firm. And that doesn't include over-the-counter sales.

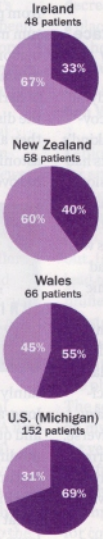
Hospital prescribing of acid neutralizers started in the 1970s when doctors realized that the practice could prevent the stress-induced bleeding ulcers that plague patients in intensive care units and are exacerbated by stomach acid. (Easing the symptoms of stomach ulcers is considered a valid medical use of PPIs today.)

A Canadian study in 1994 had shown that such stomach bleeding was rare in hospitalized patients who didn't have respiratory failure or a defect in the blood's clotting ability. But six years later, Yale University scientists reported that many patients at low risk of developing a stomach bleed were being placed on PPIs or other acid-blockers anyway.

Research done at the University of Michigan Hospital revealed that most acid-suppressing drug prescriptions doled out by the hospital's doctors were inappropriate — the patients didn't have acid reflux and weren't at risk of stomach bleeding. And a 2006 study from New Zealand found that four in 10 hospital patients were on PPIs inappropriately. What's more, people are often sent home from the hospital with a prescription for a PPI, and they fill it. "A lot of people just go on the medication they are prescribed and don't ask questions," says Regal.

On the rebound

Giving people PPIs when they don't need them may result in PPI rebound, Swedish scientists report. Pharmacist Anna Niklasson and colleagues at the University of Gothenburg randomly assigned 48 healthy volunteers without acid reflux to receive either a PPI or a placebo for 28 days. By standard scoring of stomach distress, both groups started with very little heartburn. One week after treatment ended, however, stomach distress rose dramatically in those who had been on PPIs but not in the others. And 11 of the 25 on PPIs complained of stomach problems afterward, compared with only two of 23 on a placebo.



Global overprescribing Four hospital-based studies highlight the common practice of prescribing PPIs to patients even when the patients don't need the heartburn drugs.

■ On PPIs with valid medical reason
■ On PPIs with no valid medical reason

SOURCES: SAAD *ET AL/INT. J. OF CLIN. PRACTICE* 2005; GRANT *ET AL/PHARMACY WORLD & SCIENCE* 2006; BATUWITAGE *ET AL/POSTGRAD. MED. J.* 2007; PHAM *ET AL/ANNALS OF PHARMACOTHERAPY* 2006

"The stomach tries to compensate for the decrease in acid secretion that PPI medication leads to," says Niklasson. "So when patients stop their PPIs, they have an up-regulated capacity." The effect seems to last only two weeks, but may explain why even people inappropriately prescribed PPIs could have trouble stopping them, she says.

Despite these reports, pharmaceutical firms continue to promote PPIs actively. Internist Mitchell Katz, director of public health for the city of San Francisco, says the drugs are being marketed to young adults. He cites a commercial on the Internet that shows young people going out on the town, discussing taking a PPI in *anticipation* of possible heartburn later. "I think PPIs have become more of a lifestyle drug. People don't really understand the risks," Katz says.

PPIs continue to be the best drug for acid reflux. "Many people will need to take them," says researcher Shelly Gray of the University of Washington in Seattle. "But some people take PPIs who could manage with changes in lifestyle or with a less potent heartburn medication." ■

Explore more

■ M. Katz. "Failing the acid test." *Archives of Internal Medicine*. May 10, 2010.

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