MC: Welcome to The Med Thread, your monthly dose of all things drugs.

CB: I'm Cathy,

MC: and I'm Mike and today we talk proton pump inhibitors, or PPIs for short. We'll discuss the history of these drugs, why a lot of patients consider them to be miracle drugs, why we use so much of them, and why there is a campaign to stop their inappropriate use today.

CB: And we're lucky to have a special in-studio guest with us today. A friend and colleague from the Canadian Deprescribing Network, with a much cooler accent than me, Justin Turner is here.
*(Dr. Justin Turner is a pharmacist, researcher and advocate for better medication use. He is based in Montreal, Quebec, but works across the country representing the Canadian Deprescribing Network. Information about his research can be found here: https://www.researchgate.net/profile/Justin_Turner)*

## History and Pharmacology

*(Pharmacology from Katzung, 2018, additional history from Brooks, 1985, Castell, 1985)*

MC: Acid-related disorders like esophagitis, peptic ulcer disease, and gastroesophageal reflux disease or GERD have been around for a long time, and there were various agents used to treat these conditions. However, it wasn't until the discovery of the proton pump in the parietal cells of the stomach that scientists now knew the final step in acid secretion.

CB: Scientists targeted this particular pump and discovered that when it was inhibited, acid secretion was halted, and there was a new treatment for acid-related symptoms. The first PPI on the market was omeprazole, which was introduced in 1989, and as early as 1991, they were hailed as miracle drugs! These agents have been used as the drug of choice for many of the acid-related disorders ever since. But why were they so great back then?
*(Benjamin, 1991)*

MC: Three closely related things stand out in this story.

First, often omeprazole or new acid suppressing drugs were compared to cimetidine, an acid blocking drug with lots of interactions, side-effects, so really not the most pleasant to take. So, having a drug with fewer side effects was already very positive.

Second, you could imagine, as a patient and as a physician, to know that you didn't need to do surgery or constantly drink thick, bad tasting stomach coating solutions. Some of the worst ones were sucralfate and bismuth but also those chalky anti-acids. There was only so much flavour you could put in to mask the taste.

Lastly, and perhaps the most important, was the fact that we could now treat conditions that were essentially poorly managed by pharmacotherapy before.

CB: By 2006, they were still marketed as miracles, but we'll talk about why that's changing, later on. Before PPIs we had histamine-2-receptor antagonists, like Zantac or Pepcid, synthetic prostaglandins, anticholinergic drugs, and antacids like Tums and Rolaids, but these didn't stand up to the PPIs.

*(Koop, 2006)*

If we compare the H2RAs to PPIs, PPIs were found to keep the pH of the stomach above 4 for 15-21 hours a day, where the H2RAs held that pH for only 8 hours.

MC: Generally, stomach pH is at about 2, like vinegar, so bringing it above 4 is a huge increase.

CB: This translated into improved patient outcomes; they found the new PPIs to be superior in suppressing acid secretion and the related symptoms. After omeprazole came lansoprazole, and now we have six different PPIs on the market, and although they are a little structurally different, they are generally similar in their pharmacological properties.

Let's take a closer look at how they work.

MC: Starting from the top, these drugs are actually sensitive to stomach acid themselves, so they are packaged in a variety of delivery systems for protection, things like enteric-coated tablets, gelatin capsules, and coated granules. They have to get through the stomach to the small intestine where they are absorbed. Then they come back to the other side of the stomach wall and enter the cells, where they bind to activated pumps.

CB: The pump stops working and no acid is secreted until the body can make more pumps. But, following a meal, our bodies don't activate all its pumps, only about 2/3 of them. That means there are some that can still produce acid after a single dose of PPI if we eat another meal later in the day.

MC: You may think the drug is still in the body, but no, it's actually metabolized and excreted very quickly, in about 5 hours.

CB: That's why we recommend taking PPIs before a meal. We want them to be there, ready to act when we eat, which would have stimulated acid secretion. Keep in mind too, that it takes almost a day for your body to make new pumps. So, as you continue to take the drugs on a daily basis, more and more of the pumps are disabled. We often see patients have a better response on day 2 or 3 than they do after just a single dose, and this is why!

## Use in Canada

CB: Alright, let's welcome our guest! Justin Turner, hi!

JT: Good day! Thank you for having me.

CB: Thanks for being here.

MC: Alright, we've got a lot of questions for you today, but let's first talk therapeutic use. When are we going to use these PPIs?

JT: PPIs are really good for getting rid of the acid in the stomach as you said, so that would be things like reflux or gastroesophageal reflux disease. It can be used with peptic ulcers and a few other conditions where we might want to use them long term like Barrett's esophagitis or to protect our stomach from the side effect of other medicines, like anti-inflammatories.

CB: I remember learning about heartburn and reflux and that we should try to use a number of non-pharmacological options first, or at least in conjunction with medications. Has anything changed about this thinking?

JT: That's a great question and I always believe we should use the non-drug options first. So losing weight, avoiding caffeine in some people that can upset it, or alcohol, stopping smoking. And there's some evidence behind raising the head of the bed so you're sleeping with a slight slope and gravity can help pull it down. So there's some really great lifestyle choices we can make.

And then it's a matter of whether we start with antacids and work our way up to PPIs or start with PPIs and work our way down. I vividly remember about 20 years ago, my mother in-law, after every meal, going to the fridge, grabbing a large bottle of Gaviscon and drinking about half of it with every shot. She then found PPIs and her life is much better, so when I'm offering a patient step-up treatment, she always come to mind. But by the same token, PPIs don't resolve symptoms instantly because they only block a small number of the pumps and it gets better day by day. So I think patient choice and frequency of symptoms really comes to mind when I think, do we step-up with the pharmacological treatments or do we step-down. But remembering her drinking half a bottle of Gaviscon everyday is something that comes to mind every time I think of PPIs.

MC: Over the past couple of years, the PPIs have become more widely available and they've been used more. The FDA approved over the counter PPIs as early as 2003, but more recently has published more information for consumers about warnings and risks about their use, so it's good, but it's only part of the issue.
*(FDA, OTC Heartburn Information for Consumers: https://www.fda.gov/drugs/resourcesforyou/consumers/ucm511944.htm)*

In Canada, small packages of PPIs, enough for 14 days, first started being available without a prescription in late 2014. The difference in Canada is that the products are still required to be kept behind the pharmacy counter. A conversation with the pharmacist is a requirement before it is sold. This helps a bit in decreasing misuse, but what we're really looking at today are the prescription products.
*(https://napra.ca/national-drug-schedules)*

CB: We've talked about usage and drug spending in our biologics episode, so here, we're looking at it again for prescription PPIs. The latest numbers from the Canadian Institute for Health Information show that in Newfoundland, it's second in usage behind those cholesterol drugs. 35% of people on provincial drug plans are using PPIs, costing almost $4.5 million in 2016.
*(CIHI National Health Expenditure: https://www.cihi.ca/en/national-health-expenditure-trends)*

So my question for you, Justin, is, you've been all over the country talking about this. How does this trend look nationwide?

JT: Well it's great to be in Newfoundland, we're the best. We've got the highest use of PPIs here, by a long way. And interestingly in Canada, if you start over in BC, the use is about 8%, and as you head across, the further west *[east]* you go the average is sort of in the high teens, low 20s, then we come up here to high 20s, low 30s, so I'm not sure if the prevalence of reflux is higher here or we just like treating it, or rather, we forget to stop treating it.

CB: Yes, so there's a lot of things we pride ourselves on being the best on, but I'm not so proud of that, so we are doing some work to stop that.

MC: And you do mention that maybe it is that more people are suffering from these gastrointestinal issues. Do you that's true, do you think there's any research behind that?

JT: There's not a lot of research behind that. If you look, some of the studies have tried to assess what the prevalence of reflux is, and it's maybe 10% in other parts of the world, some of the US studies say, maybe as high as 40%, so truly difficult to survey a large number of people and say have you had reflux symptoms recently. So the prevalence seems to vary from country to country, but I'm not sure why from Canada it varies across, as far as medication use.

MC: Right, so that actually might be a good research project to do here, to see what our population is like here.

CB: Yes, I can say I certain see PPIs used a lot.

## Deprescribing 101

CB: In our first episode, we hinted at deprescribing while talking about sleep medications and it's great to have Justin here to tell us more about this concept because we have a program in Newfoundland right now trying to deprescribe PPIs. So Justin, how do you explain deprescribing? So what is deprescribing?

JT: Great question Cathy, deprescribing is a team process between the patient and the healthcare providers, where they review each patient and decide whether the benefits still outweigh the harms or maybe the benefits aren't there anymore or maybe the harms are getting worse. And at that point, reducing the dose and stopping them. So deprescribing really a fancy way for saying, stopping medicines.

CB: That's certainly a good way to explain it. And why are trying to deprescribe PPIs? Why is this an issue for us?

JT: That's a good question. When we look at PPIs, you've got the benefit and the harm of the medicine. Now PPIs long-term we do know more and more that they're associated with long term harms. But often it really comes back to the benefits when we talk about PPIs. The benefits for PPIs are really short term, 4-8 weeks, and unfortunately what we're seeing is that people forget to stop them, because they work and the symptoms are controlled. But there's really no need to take a medicine that may cause side effects, may cause drug-drug interactions, cost patients a lot of money, when there's no need to take them.

MC: And I think that's a very interesting way of approaching medicines. We always think about using medicines to treat something, but we tend to forget about some of these side effects and historically, for the PPIs, there really weren't any.

There's this one book from 2006, that concerns about bacteria growing in the stomach, risk of cancer, inflammation and loss of a functional stomach have all been refuted and that the drugs have an excellent safety profile. Even drug interactions seem unimportant.
*(Koop, 2006)*

I think there's an assumption behind this thinking. It assumes that we know enough about drugs that are affected by changes in stomach acid levels and also about drug metabolizing enzyme interactions. So what's the story now about PPIs?

JT: I'll start at the end there, with drug metabolizing. There's been a few studies showing that some of the PPIs can interact with different medications, making them ineffective. It's a little bit controversial and I guess if we look at the side effects, it's very difficult to look at long term side effects in a short term clinical trial. So we really have to rely on epidemiological data which looks at the whole population over time to see who's been exposed to these medicines and who hasn't and then monitor those people to say, is there a higher risk of developing certain diseases. And now that PPIs have been out, as you say, since the late 80s, we've got enough data to say, hey, long term use of these may not be as safe as we once thought.

CB: And so sometimes deprescribing can be easy and sometimes it can be hard. When it comes to PPIs, what are some difficulties we see when we're trying to deprescribe PPIs?

JT: One of the interesting studies that I've found with PPI use, is this thing called withdrawal symptoms. Now, you might be used to taking Tylenol and when you stop it, nothing happens. Or you might see, with the opioid crisis, when people stop their opioids, suddenly they get bad side effects. Well PPIs fit in the middle. They're not that harmful but some interesting studies have found that if you give healthy people with no history of reflux at all PPIs, for 4 weeks, or one of the studies was 8 weeks, and then you suddenly stop them, about half the people develop reflux symptoms. So it goes a little bit back to the pharmacology, how we've said that you're blocking the proton pump and some of the other hormones like gastrin or histamine, which were mentioned before, build up. And when we suddenly unblock the proton pump, those hormones cause a rush in stomach acid which then cause us to get symptoms. So the difficult bit is that not all patient gets told, hey look, you've got a 1 in 2 chance that for the next few weeks you might get some symptoms, here's some really practical strategies of what to do when you stop it. So unfortunately if people stop them on their own without any advice, they often get return of symptoms.
*(Reimer, 2009 and Niklasson, 2010)*

CB: Yea, and I do hear that a lot, and I'm suggesting to deprescribe PPIs sometimes and my patients will say, 'oh I tried that before and I got the worst heartburn I've ever had'. So that does make sense and I think if they're prepared and they know that these symptoms may be coming and it's just the initial couple of days and the rebound, and there's other things you can take, like TUMS or whatever agent that you choose, can help with those symptoms. So certainly not going to last forever.

MC: It's interesting, you mention some of the studies of people who don't have reflux symptoms to begin with, so the over the counter product says that people shouldn't be using it for more than 2 weeks. So if someone were to use it for 2 weeks, could they still get some of these withdrawal symptoms?

JT: We're in an evidence-free zone there cause most of the studies looking at rebound aren't 2 or 4 weeks, but the pharmacology behind it says, quite possibly, if we block for that long, they're going to get a rebound of acid come back. Most of the time, when I sell it over the counter, I say,

'take it if you need it and when you don't need it, cut back on the dose,' so those 14 tablets hopefully last someone longer than 2 weeks to try and avoid that.

MC: That's a really good point. I think we often just tell people to take it and then we forget about the second part, about stopping it.

CB: When it comes to deprescribing PPIs, what are some general concepts that you use, when you're guiding a patient through this?

JT: Well deprescribing as we said at the beginning is really patient-centred, so I have a conversation with the patient. There's no head to head trials, but we do know that when the acid comes back for those 50% of people, some people just like taking an antacid and it helps and it's great, it's perfect. Others prefer an in-between drug like a H2 antagonist, which also helps to control the histamine surge that goes on to cause the rebound symptoms. And others using PPIs when needed or a prn basis, is just as effective to control the symptoms. I give the patient the option and it's really up to them on what they want to do.

CB: Excellent, and what kind of resources are out there that can help pharmacists or prescribers or whoever it may be, really help guide the patient through this. Any resources or any kind of places that you look?

JT: Yea, I'll do a shameless plug for https://www.deprescribingnetwork.ca which is a great resource for anything to do about deprescribing. On there we link through to Barb Farrell's group, she's a pharmacist and researcher in Ontario who's done some amazing work at deprescribing guidelines and I recommend those for absolutely anyone, healthcare provider, pharmacist, physician, because it really steps through which patients are suitable for deprescribing PPIs, because I must stress, not everyone is suitably for stopping PPIs. And steps through in a step-wise process how to go about doing that. Also on deprescribingnetwork.ca we've got some patient brochures that step through for patients what are the real benefits and harms, what are the alternatives that they can take instead, and how should I go about starting a conversation with my healthcare provider. So great resources on the website there.
*(Farrell, 2017)*

CB: Yes, and I'm glad you mention that, because I use those resources all the time and I've given out a fair number of those brochures, so certainly useful.

So next question, which I think is a bit of loaded question, but very important. How do we figure out who needs to continue their PPIs and who doesn't?

JT: That is a bit of a loaded question. If we look at the evidence and I'm going to keep going back to the evidence, things like Barrett's esophagitis and Zollinger Ellison syndrome, definitely need to be continued long term, no question about that whatsoever. If it's for reflux or if it's for peptic ulcer disease or H. Pylori infection that's being treated, then we can look at stepping down the dose. So the current guidelines and what Choosing Wisely Canada will say is, after a year, you should be looking at trying to reduce the dose. The systematic review that Barb Farrell's group has put together from the Bruyere Research Institute, they say, after 4 to 12 weeks is where the evidence sits and step the dose down. So I think the lowest dose possible is best and for a lot of people, if we can coach them through the withdrawal symptoms, the lowest dose is actually not taking it at all.

*(Choosing Wisely: Bye-Bye, PPI. https://choosingwiselycanada.org/perspective/ppi-toolkit) (Boghossian, 2017)*

CB: For sure, and as pharmacists, we can always ask our patients, 'why were you prescribed this in the first place?' We can go back and look for scopes and see if there is any kind of disease or pathology found and if not, we can certainly guide them and help to make that decision.

JT: That's a great point, and there's been research across the world looking at, do people know why they're on a PPI, and because I can tell you there's a million times I've gone out and asked, 'why are you taking this' and 'I don't know' is the response and I'm reassured by the evidence that approximately 50% of people in studies where they've got access to medical records, hospital records, scope records, we still have no idea why it's started. And the guidelines clearly state, if you don't know why it's there, then we should be reducing the dose and stopping it. But I think that's just good common sense and good clinical practice.

MC: You mention, Cathy and you both mentioned about scoping. Patients often ask, 'do I need a scope,' so what's the answer there?

JT: That's a really good question and the guidelines clearly state, when people should be scoped and particularly for example, high risk patients, so for males over the age of 50 who have some extra risk symptoms, whether they be overweight, they smoke, or they have a family history of Barrett's esophagitis, they're at increased risk of developing that too, so they should scoped at some point if their symptoms are uncontrolled or ongoing for a number of years. And in that case, the studies vary but somewhere between 5% of people who have an endoscopy at that stage will get diagnosed with Barrett's and they need to continue. But one of the questions I commonly get asked is, 'does a patient need a scope before we stop the PPI?' and the clear answer is no, that's a very low value treatment and that's not choosing wisely at all.

MC: Great, that's very good to know and definitely we can share that with our patients, that we're trying to get them off of PPIs.

## Here and now

MC: So we're talking about deprescribing and the deprescribing program here in Newfoundland, can you elaborate on what's being done here?

JT: Yea I can. It's really exciting to be in Newfoundland. Yesterday *[September 23, 2018]* we launched at the Pharmacy Association of Newfoundland *[and Labrador]* conference a really exciting initiative, that's a government sponsored initiative, to try and address the really high use of PPIs here. I travel as part of my job at the Canadian Deprescribing Network and work with many different provincial governments, looking at how we can scale up evidence-based research at a population level to try and help reduce harmful medications and reduce patient harm. And what's really exciting here is that the research for the last 20 years, where we've really only focused on healthcare providers, we haven't changed medicine use much, but when we bring patients into that conversation, we're able to change medicine use and make appropriate choices. So I'm really excited to say that the government here, for the next 3 years, is going to help, working with some of our stakeholders such as Choosing Wisely Newfoundland, who can reach the physicians. The pharmacy association who can educate pharmacists. We work with

some of the nursing bodies as well. But most importantly, it's going to involve a lot of patient education to get them to query and feel comfortable going in to their nurse, or their pharmacist or their doctor and say, 'hey, should I really be on this medicine, is this the right medicine for me right now?' Because we never start a medicine intending to do harm, but as things change, we may find that the balance of benefit and harm changes and reminding patients it's okay to ask that question is the whole point of this process.

CB: Yes, I think an empowered patient is certainly a powerful thing so I'm really really happy you're here to help spread the word, and that it was launched yesterday with success.

So lastly, what do we want to communicate to our patients about risks of these drugs long term or simply risk vs. benefit?

JT: That's a great question. I know your first podcast was on sleeping pills and there when I talk about stopping sleeping pills, there are a lot of harms and potentially as we use the sleeping pills long term, the benefits wear off. In the case of PPIs, it's a lot harder to convey the harm side. We do know that long term use increases the risk of fractures, potentially community acquired pneumonia in older men, kidney disease, whether it's chronic or acute is on the rise and tends to follow the increased rise of PPIs. So epidemiologically, we're finding some data. It may or may not be really robust data, but it's there and it's signalling that they may not be as safe as we used to think they were. Clostridium difficile infections for example, they're on the rise and there's a definite association there between proton pump inhibitor use. But that's only half the scale of benefits and harms. And the harm side may not be that convincing compared to some other drug classes, but the benefit side, particularly for reflux and GERD, it isn't there at all. So after 4 weeks, I think, if there's no benefit, then the harms definitely outweigh the benefits and the scales still tip that way. So when I talk to patients to try and say, it's not so much about the harms, because risk of kidney disease is low, increasing that risk is still quite low. But it's about the benefits, if you're not getting a benefit from a medication there's no point taking it. Let's use our medicines and resources appropriately.
*(Schoenfeld, 2016, one example of a fairly large number of studies and mixed results)*

CB: And I think that's a very important message. We've certainly learned a lot today and I want to say a huge thank you to Justin for joining us and I'm glad we were able to nab you after the conference while you're still here in Newfoundland, so thank you for being here with us!

JT: It's my pleasure, it's great to be here.

MC: As always, you can find our references and notes on our webpage at www.mtsclinic.ca and if you have questions, comments or things you want to hear about, send us a message on Facebook via the School of Pharmacy or email medthread@mun.ca.

CB: And join us next month we will talk about contraception. That's it for today! Thanks for listening!

MC: Bye for now!

## References

Benjamin, Stanley B., and Martin J. Collen. *Pharmacology of Peptic Ulcer Disease*. Berlin ; New York: Springer-Verlag, 1991. Print. Handbook of Experimental Pharmacology ; v. 99.

Boghossian, Taline A., et al. "Deprescribing versus continuation of chronic proton pump inhibitor use in adults." *Cochrane Database of Systematic Reviews* 3 (2017).

Brooks, Frank P. *Peptic Ulcer Disease*. New York: Churchill Livingstone, 1985. Print. Contemporary Issues in Gastroenterology ; Vol. 3.

Castell, Donald O., Wallace C. Wu, and David J. Ott. *Gastro-esophageal Reflux Disease : Pathogenesis, Diagnosis, Therapy*. Mount Kisco, N.Y.: Futura, 1985. Print.

DiPiro, Joseph T. *Pharmacotherapy A Pathophysiologic Approach, 10e*. 10th ed. New York, N.Y.: McGraw-Hill Education LLC., 2017. McGraw-Hill's AccessPharmacy. Web.

Farrell, Barbara, et al. "Deprescribing proton pump inhibitors: Evidence-based clinical practice guideline." *Canadian Family Physician* 63.5 (2017): 354-364.

Katzung, Bertram G. *Basic & Clinical Pharmacology*. 14th ed., McGraw-Hill Education LLC., 2018. Web.

Koop, H. "Medical Therapy of Gastro-Oesophageal Reflux Disease." *Gastroesophageal Reflux Disease : Principles of Disease, Diagnosis, and Treatment.* Eds. Frank A. Granderath, Thomas Kamolz, and Rudolph Pointner. Wien ; New York: Wien ; New York : Springer, 2006. 103.

Niklasson, Anna, et al. "Dyspeptic symptom development after discontinuation of a proton pump inhibitor: a double-blind placebo-controlled trial." *The American journal of gastroenterology* 105.7 (2010): 1531.

Reimer, Christina, et al. "Proton-pump inhibitor therapy induces acid-related symptoms in healthy volunteers after withdrawal of therapy." *Gastroenterology* 137.1 (2009): 80-87.

Schoenfeld, Adam Jacob, and Deborah Grady. "Adverse effects associated with proton pump inhibitors." *JAMA internal medicine* 176.2 (2016): 172-174.