



THERAPEUTICS INITIATIVE

Evidence Based Drug Therapy

Trends in utilization of proton pump inhibitors in British Columbia

The first three Therapeutics Letters focused on complaints related to the upper gastrointestinal tract, a common presentation to the primary care physician.¹⁻³ These Letters reviewed evidence about H₂-blockers, eradication of *Helicobacter pylori*, and drugs used for gastroesophageal reflux. However, they also raised concerns about chronic acid suppression by daily dosing of omeprazole, the first proton pump inhibitor (PPI) on the Canadian market. By 1994 there was already concern that long-term proton pump inhibition could be problematic. Since then, the popularity of PPIs has increased to the point that they are amongst the most widely used drugs in the world. **Seven Therapeutics Letters cover PPIs, reporting comparative effectiveness, benefits and harms, as well as evidence for deprescribing.**⁴⁻¹⁰

This Letter examines PPI utilization trends in BC since the year 2000. As shown in Table 1, BC's population grew by 20.4% during this period, while the number of PPI users increased by 257%. Defined daily dose (DDD) is the assumed average maintenance dose of a drug used for its main indication in adults. For PPIs, DDD is equivalent to 20mg/day of omeprazole. **Annual per capita DDD of PPIs increased from 5.4 in 2000 to 22 in 2018.** This represents a large per-capita increase in dose and inhibition of acid secretion in BC since 2000 (Table 1). According to the Canadian Institutes of Health Information (CIHI) approximately 9.5% of seniors in BC use PPIs chronically.¹¹



CIHI defines “chronic drug use” as “at least 2 claims and 180 days’ supply for a given drug class.” It is unknown how many seniors in BC are taking PPIs for longer than 8 weeks.

BC citizens have spent \$1.74 billion on drug and dispensing costs for PPIs over the last 18 years, an average of \$96.7 million per year. These costs include BC Pharmacare, private drug insurance and out-of-pocket spending.¹²

Is this a concern elsewhere?

PPIs are the second most commonly prescribed drug class among seniors in Canada: the use increased from 26.7% in 2011 to 29.1% in 2016; prolonged therapy is predominant: 73.5% of seniors using PPIs (even excluding those using oral corticosteroids or chronic NSAIDs) took them for 8 weeks or more.¹¹ Growth in PPI consumption around the world over the last two decades has also generated global concern. Reports from Europe¹³ and Asia¹⁴ endeavouring to explain this trend raise questions about potentially inappropriate prescribing for non-approved indications.

Table 1: PPI trends in British Columbia

	2000	2018	Percentage increase
BC population	4.04 million	4.86 million	20%
Total PPI users	123,845	442,559	257%
Annual number of PPI prescriptions	442,000	2,391,000	440%
DDD of PPI per BC inhabitant	5.4	22.0	309%



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A Cochrane review reported that approximately 25% to 70% of people are prescribed a PPI inappropriately and that chronic PPI use without reassessment contributes to polypharmacy.¹⁵

What is the appropriate duration for PPIs?

Proton pump inhibitors (PPIs) treat several different conditions including dyspepsia, gastroesophageal reflux disease (GERD), and peptic ulcer disease (PUD). Randomized controlled trials (RCTs) for these conditions typically do not exceed 8-12 weeks of therapy. In seeking evidence on the comparative effectiveness of PPIs we reported that “studies were mostly short-term and excluded patients with any complications or co-morbidities so are mainly applicable to a relatively healthy population treated for short durations”.⁹

PPI product monographs in Canada recommend that initial treatment for GERD should be at least 4 weeks for PPIs to ensure healing, but also that after 4-8 weeks, therapy should be discontinued. Patients with recurring symptoms can be initiated on regular, intermittent or on-demand therapy. However, long-term PPI use should be reserved for people who need maintenance therapy: those taking oral corticosteroids or chronic NSAIDs and those with erosive esophagitis, Barrett’s esophagitis, or a pathological hypersecretory condition.

Our 2016 systematic review found evidence that at 4 to 8 weeks among patients with GERD 60% to 85% experienced relief of heartburn and endoscopic healing was seen in 66% to 82% patients with GERD or PUD.¹⁶

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What do we know about PPIs and their long-term adverse events?

Estimates of the frequency of adverse events associated with long-term use of PPIs are derived from retrospective observational studies, rather than RCTs. They include fractures, hypomagnesemia, iron deficiency, vitamin B₁₂ deficiency, enteric infection (including *C. difficile*), pneumonia, acid rebound, acute renal injury and neoplasia (gastric polyps, gastric cancer, carcinoids, and colon cancer).¹⁴

Despite considerable heterogeneity and inconsistency between observational studies, most studies support an association between long term PPI use and *C. difficile* infections in hospitalized patients¹⁷ as well as community and hospital acquired pneumonia¹⁸.

Causal associations are difficult to establish, yet many of the potential adverse effects of PPI therapy are underpinned by a reasonable explanatory biological hypothesis. The relationships of PPI dose or duration to harms remain unknown. High quality, prospective, well designed observational studies are needed to assess harm associated with dose and duration of therapy.

Conclusions

- PPI utilization in British Columbia has risen much faster than population growth.
- **For most indications, PPIs are only recommended for up to 8 weeks duration.**
- In many clinical settings, we do not know whether the benefits of long-term PPI use outweigh the harms.
- Patients on long-term PPI therapy should be reassessed.

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