Therapeutics Initiative
Better prescribing. Better health.

THERAPEUTICS LETTER 160
January-February 2026

Understanding your acid reflux medication

PLAIN LANGUAGE SUMMARY

What was the goal of this research?

We wanted to see if "single-molecule" medicines (the ones with "dex" or "es" in their names, like dexlansoprazole or esomeprazole) actually work better than the original, more affordable versions (lansoprazole or omeprazole).

What did the researchers do?

We looked at high-quality clinical research studies that compared esomeprazole and omeprazole to find out if patients felt better faster when they used the more expensive medicines.

What did they find?

Four out of the five studies showed no difference between the drugs, and one study even slightly favoured the older drug. The single study that seemed to favour the newer drug seemed to be designed to favour it.

What about dexlansoprazole versus lansoprazole?

The evidence here was even weaker. Most of the studies were paid for by the drug companies themselves and seemed to be designed to favour the more expensive medicines. The studies compared a high-dose form of the new drug against a low-dose form of the old one. Despite this "uneven playing field", there is still no strong evidence that the newer drug helps patients more than the older drug.

What is the "right-handed" vs. "left-handed" molecule?

Many medicines are made of a mix of two mirror-image molecules (think of them like a right and left hand).

- Original drugs: Contain a 50/50 mix of both "hands."
- New drugs: Contain only one "hand" (e.g., just the right- or just the left-handed molecule).

By selling only one "hand," companies can get a new patent (right to sell the drug) and charge higher prices. However, this often results in patients taking 3 times the necessary dose of the active ingredient without any added health benefit.

Is it safe to take these drugs long-term?

We advise caution. More evidence is needed to know if it is safe for people to take high doses of these drugs for many years. Because long-term safety is still uncertain, the recommendation is to avoid high doses over long periods unless absolutely necessary.

What is the financial impact of using these newer drugs?

In British Columbia these newer drugs cost more than triple compared with the original ones. Switching from these newer medicines back to the original ones could save patients over 21 million dollars every year in British Columbia, with additional significant savings possible by switching to pantoprazole.

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Surge in doses of proton pump inhibitors: a sleight of handedness?

ABSTRACT

Background: While pharmacological properties of R- and S-enantiomers (mirror-image drugs) can differ, a 2021 systematic review of trials comparing single enantiomers to their mixtures showed that claims of clinical superiority are typically not supported by evidence.

Aims: This *Therapeutics Letter* assesses current evidence comparing clinical effects of dexlansoprazole with lansoprazole, and esomeprazole with omeprazole, and summarizes efficacy and safety findings of previous *Therapeutics Letters* on PPIs.

Methods: We conducted a systematic review of head-to-head randomized controlled trials of proton pump inhibitors (PPIs) comparing dexlansoprazole with lansoprazole, and esomeprazole with omeprazole, for treating gastroesophageal reflux disease (GERD) or erosive esophagitis (EE) in adults. Study quality was assessed using the Cochrane Risk-of-Bias-2 tool.

Results: Of 5 trials that compared esomeprazole and omeprazole at equivalent doses for treating GERD or EE, 3 showed no significant difference and 1 favoured omeprazole. The only study favouring esomeprazole was biased because it compared non-equivalent doses. Of 4 trials that compared dexlansoprazole with lansoprazole for GERD or EE, 3 were industry-funded. All trials appeared to be biased, since they compared high-dose (30 or 60 mg) double-release to low-dose (15 or 30 mg) single-release of the R-enantiomer (right-handed molecule). Prescribing of single-enantiomers in British Columbia resulted in patients taking 3 times higher doses of acid-suppression molecules, and paying higher prices.

Recommendations: PPIs should not be prescribed at high doses over many years until better long-term evidence of safety is available. Prescribing omeprazole or lansoprazole rather than single-enantiomers would potentially save over 21 million dollars per year in British Columbia, with additional significant savings possible by switching to pantoprazole.

Keywords: Dexlansoprazole; Drug Costs; Esomeprazole; Esophagitis; Gastroesophageal Disease; Lansoprazole; Omeprazole; Proton Pump Inhibitors; Stereoisomerism; Systematic Review.

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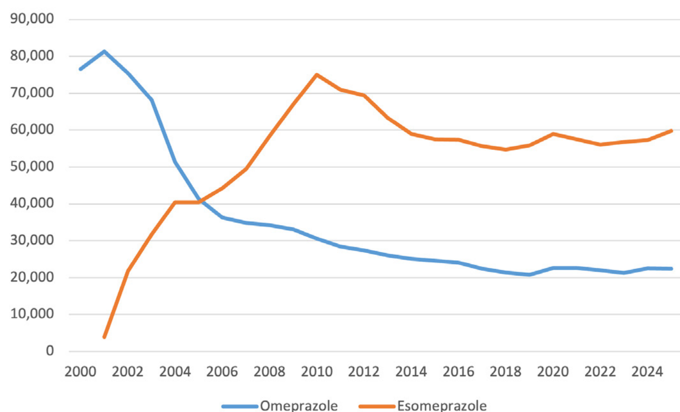
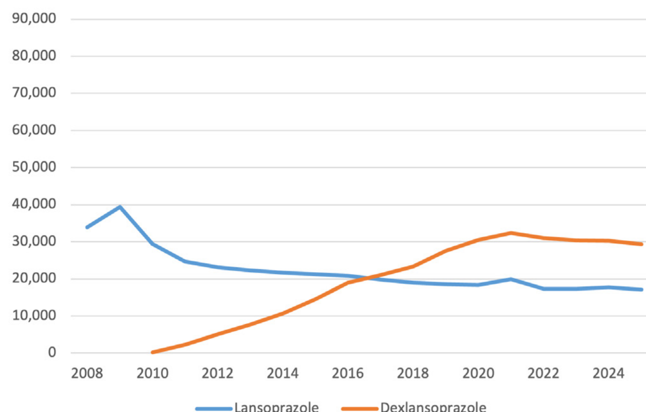
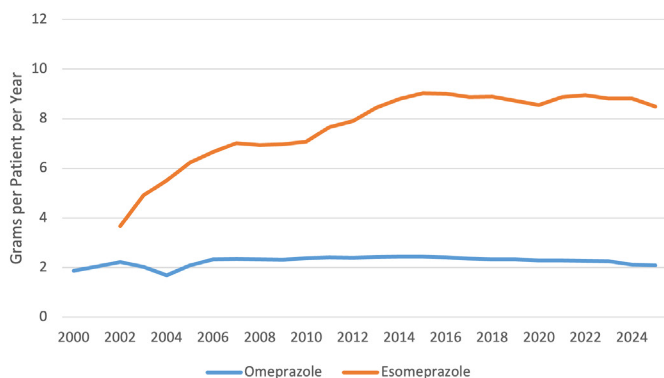
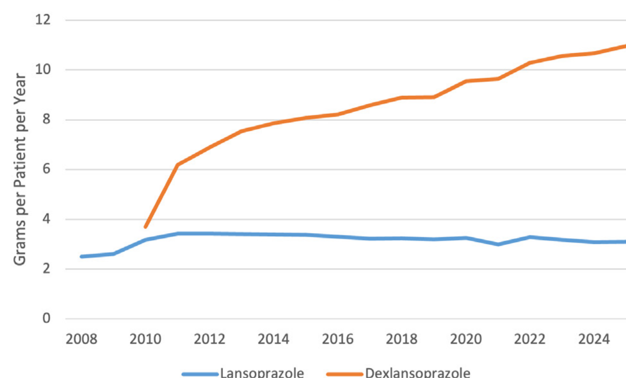
Surge in doses of proton pump inhibitors: a sleight of handedness?

Key messages: If you add the prefix "es" to "omeprazole" or "dex" to "lansoprazole", **you almost double the effective dose** of proton pump inhibiting (PPI) molecules that a patient takes. Furthermore, the most commonly prescribed PPI dose in British Columbia (BC) doubled when the "es" and "dex" versions of PPIs appeared. Thus, almost 100,000 patients in BC ingest **3 times more acid suppression molecules** than similar patients did before the "new" PPIs became available (Figures 1 to 4). **This costs over 21 million dollars more per year for no additional clinical benefit** (Table).









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This *Therapeutics Letter* builds on a Therapeutics Initiative evaluation of *single-enantiomer* drugs – reformulations of existing drugs with only the right-handed or left-handed molecule.[1]

Such reformulations were accepted by patent offices as inventions ("new" drugs), which allowed pharmaceutical companies to lengthen patent protection and increase prices. In each case, the dose increase was accompanied by a big price increase. BC PharmaNet data suggest that British Columbians are potentially spending 21 million dollars more per year on these "new" PPIs compared to the "old" ones, with no evidence of added benefit and a potentially increased risk of harm.

Racemic mixtures vs. single enantiomers

Many drugs are 50/50 mixtures of two mirror-image molecules, called enantiomers. They are classified as right-handed (R) or left-handed (S) by the direction they twist polarized light.

Some pharmacological properties of right-handed and left-handed molecules can differ if one of them fits more snugly when it attaches to a protein.[2,3] Like when your right hand fits more snugly than your left hand into your right glove.

Some manufacturers isolate and market a single enantiomer under a different brand name, often claiming greater efficacy, faster onset, or fewer adverse effects. However, purported clinical superiority is not typically supported by evidence.[4] For example, *Therapeutics Letter* 159 examined citalopram and escitalopram, and found it to be an example of enantiomer substitution without clear clinical benefit.[5]

Omeprazole is a 50/50 mixture of the R- and S-enantiomers, whereas **es**omeprazole consists solely of the S-enantiomer (**es** for S, *sinister*, Latin for *left*.) Similarly, lansoprazole is a 50/50 mixture of R- and S-enantiomers, while **dex**lansoprazole consists only of the R-enantiomer (**dex** for *dexter*, Latin for *right*.)

Market entry and marketing messages

Omeprazole (brand name Losec in Canada, Prilosec in the US) was introduced in Canada in 1989, staking its place as the first PPI approved by Health Canada. As patent protection for omeprazole neared expiry, the S-enantiomer formulation, esomeprazole (brand name Nexium), was introduced in 2001. In 2016, Nexium became available in Canada without prescription ("over the counter"); current prices are about $1 per tablet.

Lansoprazole (brand name Prevacid) entered Canadian markets in 1995. As patent protection neared expiry, the R-enantiomer formulation, dexlansoprazole (brand name Dexilant), was introduced in 2010. Later, Prevacid became available in Canada without prescription ("over the counter"); current prices are about $1 per tablet.

Marketing messages for single-enantiomer PPIs have emphasized improved acid suppression, commonly measured using intragastric pH metrics, a surrogate outcome.[6,7] However, the US Food and Drug Administration (FDA) concluded in 2000: "**It is recommended not to allow the sponsor to claim that** [**esomeprazole**] **has any clinical advantage over** [**omeprazole**]" because the trials compared **unequal** doses strongly favoring the patented product.[8]

Likewise, *Therapeutics Letter* 45 in 2002 found no proven advantage of S-omeprazole over omeprazole.[9] The following paragraph from that *Letter* still holds 24 years later:

> "The duration of acid suppression is determined by irreversible inhibition of the proton pump, rather than by the parent drug's elimination half-life. Because S-omeprazole is less susceptible to small intestinal and hepatic metabolism than the R-form, at equal doses, esomeprazole achieves 70 to 90% higher steady-state serum concentrations than racemic omeprazole. **Therefore lower doses of esomeprazole can be used to produce equivalent acid suppression to omeprazole.**"

Here we update results of randomized controlled trials (RCTs) comparing omeprazole with **es**omeprazole, and comparing lansoprazole with **dex**lansoprazole. Plus, we summarize messages from previous *Therapeutics Letters* on PPIs, and recent meta-analyses of RCTs concerning potential adverse outcomes.

Search strategy and study quality

We searched MEDLINE, Embase, PubMed, Epistemonikos, and Cochrane CENTRAL for head-to-head RCTs comparing **esomeprazole with omeprazole**, and **dexlansoprazole with lansoprazole**, for gastroesophageal reflux disease (GERD) or erosive esophagitis (EE) in adults.

Study quality was assessed using the Cochrane Risk of Bias 2 (RoB-2) tool. Across both drug pairs, nearly all identified RCTs were rated as having **high risk of bias**, most commonly due to non-equipotent doses, selective outcome reporting and short follow-up. Trials of dexlansoprazole versus lansoprazole used non-equivalent dose comparisons favouring the patented product.

Esomeprazole vs. omeprazole: differences explained by bias and dose

We identified five RCTs that compared esomeprazole and omeprazole for the management of GERD or EE.[10-15] Of these, three trials demonstrated no significant difference between the two agents,[10-12] and one favoured omeprazole.[14]

One trial reported superior healing of EE with esomeprazole 40 mg and 20 mg over omeprazole 20 mg.[15] However, pharmacokinetic data indicate that 20 mg of esomeprazole should have been compared, not with 20 mg, but with at least 32 mg of omeprazole, because faster deactivation of right-handed molecules makes them less than half as efficacious as left-handed molecules.[16]

Dexlansoprazole vs. lansoprazole: biased trials

We found four head-to-head RCTs comparing dexlansoprazole with lansoprazole. Three of the four were industry funded.[17-19] All 4 trials compared unequal doses. Not only were the doses of dexlansoprazole doubled, the formulation involves two releases, one delayed.

The two largest studies, reported in one paper,[18] had identical designs (N=4092). They evaluated the efficacy of dexlansoprazole 60 mg and 90 mg compared to lansoprazole 30 mg over an 8-week treatment

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period for healing EE. Both studies demonstrated the non-inferiority of dexlansoprazole to lansoprazole. In a superiority analysis, dexlansoprazole 60 mg failed to show superiority over lansoprazole in both studies based on life-table analysis. Superiority was observed only in the crude-rate analysis of one study. Furthermore, a *post hoc* analysis of both studies found no statistically significant difference in the healing of severe EE (LA Grades C or D) between dexlansoprazole 60 mg and lansoprazole 30 mg.

Utilization and cost

In BC, 22,444 patients filled at least one prescription for omeprazole in 2025, compared with 59,737 for esomeprazole (Figure 1). If all esomeprazole users last year had used omeprazole 20 mg instead, potential savings could have been over 10 million dollars (Table). Similarly, 17,075 patients filled at least one prescription for lansoprazole in 2025, compared with 29,328 for dexlansoprazole (Figure 2). If all dexlansoprazole users last year had used lansoprazole 30 mg instead, potential savings could have been over 10 million dollars (Table). Further savings could be achieved by using 40 mg of pantoprazole every second day, which costs $0.23 per tablet—less than $0.12 per day, and is a full PharmaCare benefit.

Summary of previous *Therapeutics Letters*: ongoing concern about risks of long-term use

Long before discoveries of gut microbiome roles in the immune system and brain health, *Therapeutics Letter* 3 (1994)[20] cautioned that chronic hypochlorhydria from daily omeprazole might increase risk of various GI diseases. Patients most likely at risk of any complications are those with a genetic deficiency of CYP 2C19, the enzyme that metabolizes omeprazole. These individuals (about 5% of Caucasians and 20% of people with East Asian ancestry, who can only be identified in a research setting) are exposed to plasma concentrations of omeprazole which are over 10 times higher than other patients taking omeprazole.

As newer PPIs entered the market, *Therapeutics Letter* 13 (1996)[21] and 26 (1998)[22] reviewed RCTs and found no evidence that lansoprazole and pantoprazole were better than omeprazole. *Therapeutics Letter* 45 (2002)[9] found that esomeprazole offered no therapeutic advantage at equivalent doses of omeprazole.

Therapeutics Letter 99 (2016)[23] reviewed 63 RCTs and found no evidence that any one PPI is superior to another for symptom control or healing of esophagitis in GERD or peptic ulcer disease. The trials were judged to be at high risk of selection, performance, detection, and reporting bias, and no long-term head-to-head studies designed to detect adverse effects had been conducted. Claims of therapeutic advantage were not supported by reliable evidence.

Therapeutics Letter 111 (2018)[24] provided guidance on deprescribing PPIs, as many patients in BC remained on PPIs far beyond recommended durations:

- **Consider deprescribing PPIs after 4 weeks of treatment when symptoms have resolved.**
- **Reduce PPI dose by half at 1-2-week intervals until the PPI is discontinued**; or
- **Increase dosing interval from daily to every 2-3 days.**
- **Switching to H2RA or oral antacids during the taper may also be helpful.**
- The *Canadian Association of Gastroenterology* (CAG) and *Choosing Wisely Canada* recommend: "**PPI therapy for gastrointestinal symptoms should not be maintained long term without an attempt to stop/reduce them at least once per year in most patients.**"[25]

Therapeutics Letter 118 (2019)[26] showed how PPI utilization in BC had risen faster than population growth, despite most indications requiring no more than 4 to 8 weeks of treatment.

Therapeutics Letter 126 (2020)[27] reviewed recent observational studies signaling possible serious harms, including increased mortality, and noted that even large randomized trials were mostly less than 1 year of follow-up, too short to detect long-term risks.

Update: recent meta-analyses of RCTs are somewhat reassuring

Major cardiovascular adverse events (MACE): A meta-analysis of 52 placebo-controlled RCTs (mostly omeprazole) found rates of MACE were lower in the treated group than the placebo controls, but in trials of ≥1 year duration a 1% increase in the MACE rate was almost statistically significant.[28] A meta-analysis of 4 RCTs of PPIs (mostly omeprazole), nested within trials of dual antiplatelet therapy in the elderly, found no difference in rates of ischemic outcomes.[29] A network meta-analysis of 6 trials of PPIs nested in trials of clopidogrel (3 of the RCTs being among the 4 in the preceding meta-analysis) showed no difference in MACE rates but 5 of the trials were ≤3 months long.[30]

C. difficile infection (CDI): A meta-analysis showed no impact: 8 RCTs of PPI vs. placebo showed a nonsignificant 20% increase in CDI; 4 RCTs of PPI vs. H2RAs showed a nonsignificant 28% decrease in CDI.[31]

Conclusion

Prescribing the "es" or "dex" versions of PPIs is unwarranted and wasteful. It exposes patients to greater risk of harm, especially when PPIs are prescribed at higher doses and for a year or more.

Table: Tablet size and cost of (es)omeprazole and (dex)lansoprazole in BC, and potential annual savings from evidence-based prescribing

Drug	Cost per tablet (from BC PharmaNet data)						Cost for 90 days*	Patients in 2025	Potential annual savings
Dose:	10 mg	15 mg	20 mg	30 mg	40 mg	60 mg			
Omeprazole	$1.02		$0.29				$33	22,444	$10,757,711
Esomeprazole			$0.97		$1.15		$121	59,737	
Lansoprazole		$1.06		$0.68			$78	17,075	$10,303,145
Dexlansoprazole				$2.53		$2.58	$277	29,328	

* *Weighted average price x 90 days x apparent rate of use (1.2 tablets per day according to PharmaNet data)*

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Data availability statement

Access to data provided by the BC Ministry of Health is subject to approval but can be requested for research projects through the Data Stewards or their designated service providers. The following data sets were used in this study: *PharmaNet* and *Client Roster.* All inferences, opinions, and conclusions drawn in this publication are those of the authors, and do not reflect the opinions or policies of the Data Stewards. The data was provisioned under ISA 16-036.

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