



Results of Topic Selection Process & Next Steps

The nominator is interested in the harms of proton pump inhibitors when taken for long periods of time.

We identified three reviews covering the scope of nomination's question, therefore, a new review would be duplicative of an existing product. No further activity on this topic will be undertaken by the Effective Health Care (EHC) Program.

Topic Brief

Topic Name: Harms of Proton Pump Inhibitors, #742

Nomination Date: 8/7/2017

Topic Brief Date: 10/11/2017

Author: Christine Chang

Conflict of Interest: None of the investigators have any affiliations or financial involvement that conflicts with the material presented in this report.

Summary:

- Appropriateness and importance: The topic is both appropriate and important.
- Duplication: A new review on this topic would be duplicative of an existing product. We identified two systematic reviews. One was a review of reviews inclusive of adverse events for PPIs and two focused on specific harms (B12 deficiency and dementia).

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Introduction

Proton pump inhibitors (PPI) are a class of medications that decrease the production of acid in the stomach. Over-the-counter PPI include lansoprazole, esomeprazole, omeprazole magnesium, and omeprazole with sodium bicarbonate. They are intended to treat frequent heartburn. These drugs are to be used for a 14 day course of treatment, up to 3 times per year [1]. Prescription PPIs are used to treat conditions like gastroesophageal reflux disease (GERD), stomach and small intestine ulcers, and inflammation of the esophagus [1].

PPIs are commonly used, and use has increased over time. A three-fold increase in the use of PPI was seen in ambulatory care visits between 2002 and 2009 [2]. More than 15 million patients prescribed PPIs in 2013, with likely higher use because of the PPI formulations available over the counter without a prescription [3]. PPIs are among the highest-selling classes of drugs in the U.S., with \$9.5 billion in sales in 2012.

Reported long-term adverse effects of PPI include risk of fracture, hypomagnesemia, iron deficiency, vitamin B12 deficiency, enteric infection, pneumonia, acid rebound, and acute renal injury [4]. The FDA has issued several drug safety communications about PPI:

- 2010: possible increased risk of fractures of the hip, wrist, and spine associated with PPI use at high doses and/or greater than one year [5].
- 2011: low magnesium levels associated with long-term use of PPI if taken long-term, typically longer than a year [6].
- 2012: association of PPI with clostridium difficile diarrhea [7].

Clinical guidance about the long-term use of PPI from several sources including professional societies [8-10] and the Choosing Wisely campaign [3, 11] recommend careful consideration of appropriate use of PPI, and use at the lowest dose and shortest duration in consideration of the condition being treated. Furthermore they all recommend that PPI use be re-evaluated regularly and patients counselled about potential long-term effects.

The nomination question is:

Key Question 1. What are the harms of long-term use of over-the-counter proton pump inhibitors?

In Table 1, we define the inclusion criteria through the population, interventions, comparators, and outcomes (PICO).

Table 1. Key Question and PICOTS

Key Questions	What are the harms of over the counter proton pump inhibitors (PPI) when taken long-term?
Population	Adults taking over the counter PPI for longer than recommended in drug labeling
Interventions	Over the counter PPI
Comparators	Placebo, no treatment, or other acid-blocking therapy
Outcomes	Vitamin B12 level, Vitamin D level, fracture, depression, dementia

Methods

To assess topic nomination Harms of Proton Pump Inhibitors, for priority for a systematic review or other AHRQ EHC report, we used a hierarchical process using established criteria. Each assessment determined the need for further evaluation. Details are provided in Appendix A.

1. Determine the *appropriateness* of the nominated topic for inclusion in the EHC program.

2. Establish the overall *importance* of a potential topic as representing a health or healthcare issue in the United States.
3. Determine the *desirability of new evidence review* by examining whether a new systematic review or other AHRQ product would be duplicative.
4. Assess the *potential impact* a new systematic review or other AHRQ product.
5. Assess whether the *current state of the evidence* allows for a systematic review or other AHRQ product (feasibility).
6. Determine the *potential value* of a new systematic review or other AHRQ product.

Appropriateness and Importance

We qualitatively assessed the nomination for appropriateness and importance.

Desirability of New Review/Duplication

We searched for high-quality, completed or in-process evidence reviews from the last three years related to the nomination question. Sources searched included AHRQ Effective Health Care Program website, VA Evidence Synthesis Program website, PubMed, Cochrane Collaboration, Canadian Agency for Drugs and Technologies in Health, and PROSPERO register of systematic reviews.

Compilation of Findings

We constructed a table outlining the selection criteria (Appendix A).

Results

Appropriateness and Importance

This is an appropriate and important topic. PPIs are among the highest-selling classes of drugs in the U.S., with \$9.5 billion in sales in 2012. More than 15 million patients prescribed PPIs in 2013, with likely higher use because of the PPI formulations available over the counter without a prescription. Concerns have been raised about the overuse of PPI due to adverse effects long-term.

Desirability of New Review/Duplication

A new evidence review would duplicate an existing product (Table 2). We identified three systematic reviews. One was a review of reviews inclusive of adverse events for PPIs; and two focused on specific harms (B12 deficiency and dementia or cognitive impairment).

Table 2. Key question and relevant evidence reviews

Key Question	Duplication (Completed or In-Process Evidence Reviews)
Harms of long-term over the counter proton pump inhibitor	Total number of completed systematic reviews – 3 [12-14] <ul style="list-style-type: none"> • Abramowitz et al (2017). Adverse Event Reporting for Proton Pump Inhibitor Therapy: An Overview of Systematic Reviews. • Batchelor et al (2017). Dementia, cognitive impairment and proton pump inhibitor therapy: A systematic review • Jung et al (2015). Association between vitamin B12 deficiency and long-term use of acid-lowering agents: a systematic review and meta-analysis.

Summary

- Appropriateness and Importance: The topic is both appropriate and important.
- Duplication: A new review would duplicate existing reviews.

References

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13. Jung SB, N.V., Kapur A, Eslick GD, *Association between vitamin B12 deficiency and long-term use of acid-lowering agents: a systematic review and meta-analysis*. *Intern Med J*, 2015. **45**(4): p. 409-416.
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Appendix A. Selection Criteria Summary

Selection Criteria	Supporting Data
1. Appropriateness	
1a. Does the nomination represent a health care drug, intervention, device, technology, or health care system/setting available (or soon to be available) in the U.S.?	Yes, this topic represents a health care drug and intervention available in the U.S.
1b. Is the nomination a request for a systematic review?	No. The nominator is concerned about the lack of communication about harms, and research about the importance of Vitamins B12 and D.
1c. Is the focus on effectiveness or comparative effectiveness?	The focus is on harms of a medication class
1d. Is the nomination focus supported by a logic model or biologic plausibility? Is it consistent or coherent with what is known about the topic?	Yes, it is biologically plausible. Yes, it is consistent with what is known about the topic.
2. Importance	
2a. Represents a significant disease burden; large proportion of the population	A three-fold increase in the use of proton pump inhibitors (PPI) was seen in ambulatory care visits between 2002 and 2009.
2b. Is of high public interest; affects health care decision making, outcomes, or costs for a large proportion of the US population or for a vulnerable population	Yes, this topic affects health care decisions for a large population.
2c. Represents important uncertainty for decision makers	Some harms are known, but patients may not be aware of all harms.
2d. Incorporates issues around both clinical benefits and potential clinical harms	This nomination is focused on harms only.
2e. Represents high costs due to common use, high unit costs, or high associated costs to consumers, to patients, to health care systems, or to payers	PPIs are among the highest-selling classes of drugs in the U.S., with \$9.5 billion in sales in 2012.
3. Desirability of a New Evidence Review/Duplication	
3. Would not be redundant (i.e., the proposed topic is not already covered by available or soon-to-be available high-quality systematic review by AHRQ or others)	<p>A new review would be duplicate available resources.</p> <ul style="list-style-type: none"> • Abramowitz J, Thakkar P, Isa A, Truong A, Park C, Rosenfeld RM2. Adverse Event Reporting for Proton Pump Inhibitor Therapy: An Overview of Systematic Reviews. <i>Otolaryngol Head Neck Surg.</i> 2016 Oct;155(4):547-54. doi: 10.1177/0194599816648298. Epub 2016 May 17. • Jung SB, Nagaraja V, Kapur A, Eslick GD. Association between vitamin B12 deficiency and long-term use of acid-lowering agents: a systematic review and meta-analysis. <i>Intern Med J.</i> 2015 Apr;45(4):409-16. doi: 10.1111/imj.12697. • Batchelor R, G.J., Kemp W, Hopper I, Liew D, <i>Dementia, cognitive impairment and proton pump inhibitor therapy: A systematic review.</i> <i>J Gastroenterol Hepatol</i>, 2017. 32(8): p. 1426-1435.

Abbreviations: AHRQ = Agency for Healthcare Research and Quality; PPI = proton pump inhibitor