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When does proton pump inhibitor treatment become long term? A scoping review

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ABSTRACT

Objective Proton pump inhibitor (PPI) use has risen substantially, primarily driven by ongoing use over months to years. However, there is no consensus on how to define long-term PPI use. Our objectives were to review and compare definitions of long-term PPI use in existing literature and describe the rationale for each definition. Moreover, we aimed to suggest generally applicable definitions for research and clinical use.

Design The databases PubMed and Cochrane Library were searched for publications concerning long-term use of PPIs and ClinicalTrials.gov was searched for registered studies. Two reviewers independently screened the titles, abstracts, and full texts in two series and subsequently extracted data.

Results A total of 742 studies were identified, and 59 met the eligibility criteria. In addition, two ongoing studies were identified. The definition of long-term PPI use varied from >2 weeks to >7 years. The most common definition was ≥1 year or ≥6 months. A total of 12/61 (20%) of the studies rationalised their definition.

Conclusion The definitions of long-term PPI treatment varied substantially between studies and were seldom rationalised.

In a clinical context, use of PPI for more than 8 weeks could be a reasonable definition of long-term use in patients with reflux symptoms and more than 4 weeks in patients with dyspepsia or peptic ulcer. For research purposes, 6 months could be a possible definition in pharmacoepidemiological studies, whereas studies of adverse effects may require a tailored definition depending on the necessary exposure time. We recommend to always rationalise the choice of definition.

INTRODUCTION

Proton pump inhibitors (PPIs) are commonly used drugs worldwide. In Denmark, PPI prescriptions are redeemed by more than 10% of the population each year.[1] Incident and prevalent PPI use are rising, the latter driven primarily by ongoing use over months to years.[2 3] This has raised questions about whether continuous PPI therapy is actually needed in many patients. Around 40% of PPI users may be treated without an ongoing registered indication[4] and concerns have been raised about possible adverse effects, specifically related to use of PPIs over months to years.[5] Only 4–8 weeks of treatment with PPIs can cause rebound acid hypersecretion and acid-related symptoms in previously asymptomatic individuals,[6 7] potentially contributing to continued use of PPIs.

Trends in PPI use have been intensely investigated in recent years, with studies consistently referring to long-term PPI use. However, there is no consensus on how to define long-term PPI use[8] and the definitions of long-term use vary between studies. Substantial discrepancies in definitions of long-term use make it difficult to draw firm overall conclusions about the prevalence and impact of extended continuous PPI therapy and about discontinuation of long-term PPI therapy.

An appropriate uniform definition of long-term use of PPIs is relevant in a clinical context. Position statements or guidelines have provided comprehensive and rational clinical advice concerning long-term use but have not provided a clear definition of what long-term use is.[9 10] This makes it challenging in clinical practice to determine whether and when a patient is considered a long-term user and to decide when deprescribing can be discussed.

Therefore, the objectives of this study are to review and compare definitions of long-term PPI use which have been used in the literature and explore the rationale for each definition. Furthermore, we aim to suggest a generally applicable definition of long-term use of PPIs for research and clinical use.

MATERIALS AND METHODS

To fulfil our aim of mapping the literature with a clear definition of long-term PPI use and clarifying the definition of long term,

we chose a scoping review methodology.[11] Guided by the Preferred Reporting Items for Systematic Reviews and Meta-Analyses Checklist for scoping reviews,[12] we searched the databases PubMed and Cochrane Library for publications concerning long-term use of PPIs. The final PubMed and Cochrane searches were conducted in January 2019. The literature searches were assisted by a research librarian with expertise in medical literature databases. The search was conducted using the search terms "long-term AND proton pump inhibitor" using the title/abstract option in the search builder.

We also searched ClinicalTrials.gov in February 2019 for registered ongoing studies using the above-mentioned search terms.

STUDY SELECTION

Two reviewers (PFH and SR) manually screened the titles, abstracts, and full texts independently in two series. In the screening of titles and abstracts, studies were excluded by the following criteria: (1) articles published before 2003, (2) articles not written in English or a Scandinavian language, (3) case reports, (4) animal studies, (5) use of PPI for less than 2 weeks.

During the assessment of full texts, we further excluded studies without a timeframe for long-term use. Only studies with a concrete definition of long-term use were included, hence studies using definitions perceived as indirect or vague, leaving the interpretation to the authors, were excluded. Any uncertainties and disagreements throughout the study selection process were discussed and resolved by consensus among PFH and SR.

Figure 1 illustrates the study selection.

DATA EXTRACTION

Data were extracted independently by two reviewers (PFH and SR) with respect to year, country, setting, study

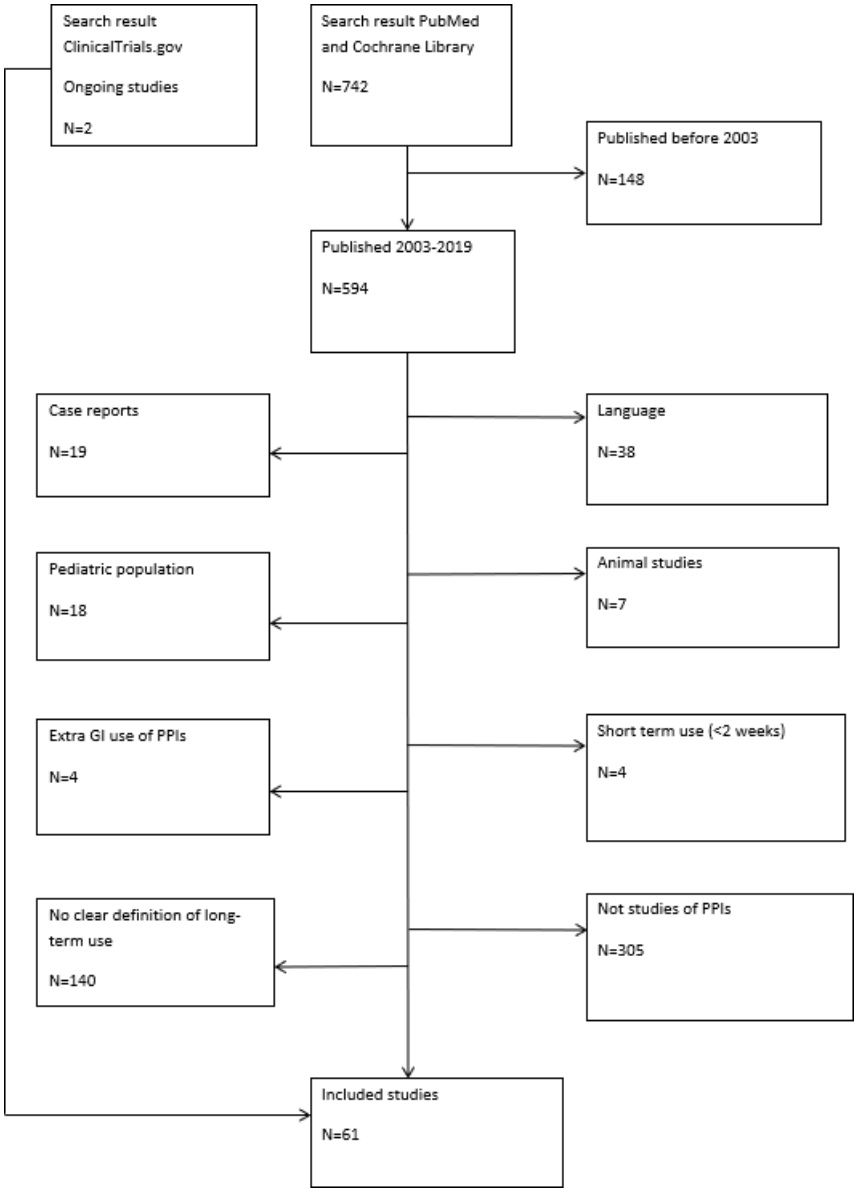

Figure 1 Flowchart of the study selection process. GI, gastrointestinal; PPIs, proton pump inhibitors.

design, aim, definition of long-term use and rationale for choice of definition. Any discrepancies, disagreements or uncertainties were discussed between SR and PFH and agreement was established.

RESULTS

The literature search identified a total of 742 studies in PubMed and Cochrane Library, of which 59 met the final eligibility criteria. By searching ClinicalTrials.gov we identified two ongoing studies, resulting in a total of 61 studies.

The selected studies concerned various aspects of long-term PPI use: adverse effects (n=35), treatment effects (n=13), pharmacoepidemiological studies (n=5) and discontinuation or dosage reduction (n=8). Table 1 summarises the characteristics of the included studies, which contained 28 different definitions of long-term use.

The threshold for defining long-term PPI use varied from >2 weeks to >7 years of PPI use. The most common definition was ≥1 year (10 studies) or ≥6 months (10 studies). Nine studies defined long-term use as ≥8 weeks. A total of 10 studies used number of prescriptions, number of tablets or defined daily dose (DDD) in their definition. However, there was substantial variability in DDD/unit of time to define long-term use. Four studies used repeat prescriptions to define long-term use.

A total of 12 out of 61 studies (20 %) stated a specific explanation for their choice of long-term definition. Most studies rationalised their choice by referring to previous studies, guidelines or policy papers.

The definition of long-term use also varied within publications by the same author. In a study by Lundell *et al* from 2009,[13] long-term treatment was defined as >8 weeks when examining treatment failure in the follow-up of treatment effect. Six years later, Lundell *et al* defined long-term use as >3 years when studying the effects of long-term PPI use on serum gastrin levels and gastric histology.[14]

DISCUSSION

Main findings

In our review we were able to identify 61 studies on different aspects related to long-term use of PPIs. The definitions of long-term use varied substantially between studies and consensus in the literature on how to define long-term use of PPIs is lacking. One in five studies stated an explanation for their choice of definition.

Comparison with previous literature

To our knowledge this is the first study systematically assessing the different definitions used in studies of long-term use of PPIs. In a review from 2005, Raghunath *et al*[8] mention that there is no consensus on how to define long-term use and state the definitions used in some previous studies without attempting to establish a consensus-based definition. Additionally, a substantial amount of studies have emerged since 2005 and a new evaluation was required.

Implications

The substantial variability in definitions of long-term use makes it challenging to compare studies in this area. For example, it is difficult to compare the range, burden and magnitude of extended continuous PPI therapy when definitions of 'long-term' use vary widely. More uniform definitions could improve these aspects and allow for more reliable conclusions to be drawn across available studies.

In a clinical context, several guidelines on PPI prescribing exist, but definitions of long-term use are often lacking. An appropriate time to discuss ongoing use may be after an initial course of PPI is finished (eg, at 2–4 weeks for uninvestigated dyspepsia) to avoid ongoing use without indication. For several studies of patients with non-erosive reflux disease/gastro-oesophageal reflux disease identified in this review, long-term use was defined as using >4 or >8 weeks.[15–17] This may reflect the fact that efficacy trials demonstrate healing of oesophagitis with 4–8 weeks of PPI, which is also reflected in guideline recommendations.[18]

Once the recommended initial evidence-based course is completed and patients continue PPI treatment after 2–4/8 weeks (depending on whether the indication was dyspepsia, peptic ulcer or reflux), they could be considered long-term users. At this point, some patients may no longer require continuous PPI (from an efficacy/indication standpoint) and the indication for ongoing therapy could be discussed. However, it is unclear whether this currently happens widely in practice. Therefore, we suggest discussing appropriate PPI therapy with the patient after 2–4 weeks if the indication is uninvestigated dyspepsia and after 4–8 weeks if the indication is reflux symptoms where long-term treatment often is necessary.

From a research perspective, the optimal definition of long-term use may depend on the aim of the study. Long-term use most likely needs to be defined differently if the aim is to study side effects occurring after years of continuous use versus studying pharmacoepidemiological aspects of PPI use such as drug utilisation or characteristics of patients using PPIs or of doctors prescribing PPIs. As an example, the inconsistency in the definitions used by Lundell *et al* is probably due to a deliberate selection of definitions expedient to the given research aim.

The most appropriate definition may also depend on whether the aim is to study aspects of only continuous daily use of PPI or the aim is to include intermittent use of PPIs as well. It has been demonstrated that many patients use PPI sporadically and only a minority are taking PPIs continuously.[19] When choosing a definition of long-term use, it is important to keep in mind that restricting the definition to continuous daily use might exclude the many PPI users from the study population.

Table 1 Overview of the included studies

Definition based on time (n=51)

Studies of side effects related to long-term PPI use (n=29)

Author, year	Country	Setting	Study design	Aim	Definition of long-term use	Rationale
Haastrup *et al*, 2018[5]	Denmark	N/A	Review	Overview of side effects of long-term PPI use	>2 weeks	Earlier studies showing no important side effects if used ≤2 weeks
Revaiah *et al*, 2018[20]	India	Secondary sector	Single-centre, cross-sectional	Risk of small bacterial overgrowth in PPI users	>3 months	No
Torvinen-Kiiskinen *et al*, 2018[21]	Finland	Primary sector	Case–control	Risk of hip fractures among community-dwelling residents with Alzheimer's	≥1 year	No
Biyik *et al*, 2017[22]	Turkey	Outpatient gastroenterology clinic	Cohort study	Risk of hypomagnesaemia in PPI users	≥6 months	No
Takahari *et al*, 2017[23]	Japan	Secondary sector	Cross-sectional	Frequency of gastric cobblestone-like lesions in PPI users undergoing endoscopy	≥6 months	No
Lochhead *et al*, 2017[24]	USA	Nurses' health study	Cross-sectional	Association between PPI use and cognitive function	≥2 years	No
Kearns *et al*, 2017[25]	UK	Primary sector	Case–control	Association between PPI use and pancreatic cancer	>2 years	Avoiding reverse causation
Targownik *et al*, 2017[26]	Canada	General population	Cross-sectional	Association between PPI use and bone structure	≥5 years	No
Bahtiri *et al*, 2017[27]	Turkey	General population	Cohort	Risk of hypomagnesaemia	12 months	No
Huang *et al*, 2016[28]	Taiwan	General population	Cohort	Association between PPI use and risk of spontaneous bacterial peritonitis in patients with decompensated liver cirrhosis	>180 days	No
Takeda *et al*, 2015[29]	Japan	Outpatients	Cross-sectional	Prevalence of hypomagnesaemia	>1 year	No
Lundell *et al*, 2015[14]	N/A	Systematic review	Systematic review	Effects of PPI on serum gastrin levels and gastric histology	>48 months	FDA requesting 3-year safety data from manufacturers
Song *et al*, 2014[30]	Cochrane review	N/A	Systematic review	Risk of gastric pre-malignant lesions in PPI users	≥6 months	No
Lewis *et al*, 2014[31]	Australia	General population	Cohort	PPIs and risk of falls and fractures in elderly women	≥1 year	No
Helgadóttir, 2014[32]	Iceland	Secondary sector	Cross-sectional	Serum gastrin levels in PPI users	≥2 years	No
Bektas *et al*, 2012[33]	Turkey	Secondary sector	Cross-sectional	ECL hyperplasia in PPI users	≥6 months	No

Continued

Table 1 Continued

Definition based on time (n=51)						
Studies of side effects related to long-term PPI use (n=29)						
Author, year	**Country**	**Setting**	**Study design**	**Aim**	**Definition of long-term use**	**Rationale**
Pregun *et al*, 2011[34]	Hungary	Secondary sector	Cohort	Effect of PPI on serum chromogranin-A and gastrin levels	>6 months	No
Sarzynski *et al*, 2011[35]	USA	Primary sector	Retrospective cohort	Association between PPI use and iron-deficiency anaemia	>1 year	No
Fujimoto and Hongo, 2011[36]	Japan	Multicentre	Cohort	Efficacy and safety of 104 weeks treatment with rabeprazole	104 weeks	No
Lombardo *et al*, 2010[37]	Italy	Secondary sector	Cohort	Incidence of small intestinal bacterial overgrowth among PPI users	>2 months	No
Yoshikawa *et al*, 2009[38]	Japan	Secondary sector	Case–control	Body mass index changes during PPI therapy in patients with GORD	>10 months	No
Ally *et al*, 2009[39]	USA	Outpatient clinic	Retrospective	Risk of fundic gastric polyps in PPI users	>48 months	No
Van Soest *et al*, 2008[40]	The Netherlands	General practice	Case–control	Risk of colorectal cancer among PPI users	>365 days within 5 years	No
Hashimoto *et al*, 2007[41]	Japan	Secondary sector	Clinical trial	PPI-induced tolerance to histamine-2-receptor antagonists	>4 weeks	No
Yang *et al*, 2007[42]	UK	General practice	Case–control	Risk of colorectal cancer among PPI users	≥5 years cumulative use	The definition is argued to be able to demonstrate an accelerative effect on the transformation from adenomas to carcinomas
Robertson *et al*, 2007[43]	Denmark	Population based	Case–control	Risk of colorectal cancer among PPI users	>7 years	The definition is argued to be able to demonstrate an accelerative effect on the transformation from adenomas to carcinomas
Jalving *et al*, 2006[44]	The Netherlands	Secondary sector	Cross-sectional	Risk of fundic gastric polyps in PPI users	≥1 years	No
Hritz *et al*, 2005[45]	Hungary	Secondary sector	Clinical trial	Effect of PPI on gastric cell proliferation	6 months	No
ClinicalTrials.gov	Austria	Secondary sector	Clinical trial	Intestinal microbiota in PPI users	≥6 months	No

Continued

Table 1 Continued

Author, year	Country	Setting	Study design	Aim	Definition of long-term use	Rationale
Definition based on time (n=51)						
Studies of side effects related to long-term PPI use (n=29)						
Studies of treatment effects of long-term PPI use (n=13)						
Kiso *et al*, 2017[46]	Japan	Outpatient clinic	Cross-sectional	Endoscopic findings in patients undergoing gastric screening	>8 weeks	No
Funaki *et al*, 2017[47]	Japan	Outpatient clinic	Cross-sectional	Efficacy of PPI in patients with NERD with and without irritable bowel syndrome	>6 months	ROME III criteria for functional disorders (duration >6 months)
Hatlebakk *et al*, 2016[48]	Europe (several countries)	Secondary sector	RCT	Comparing anti-reflux surgery with PPI treatment in patients with chronic GERD	5 years	No
Yoon *et al*, 2014[49]	South Korea	HP-positive patients	RCT	Eradication rates with different durations of pretreatment with PPI	≥56 days	No
Poh *et al*, 2011[17]	USA	Outpatient clinic	RCT	Comparing stimulus response functions to acid in users and non-users of PPI undergoing acute stress	8 weeks	No
Labenz *et al*, 2009[50]	Sweden	Secondary sector	RCT	Predictors of symptom resolution in patients with GERD during maintenance PPI therapy	>6 months	Maintenance phase after healed oesophagitis
Sugano *et al*, 2013[51]	Japan	Outpatient clinic	Clinical trial	Gastroprotective effect of omeprazole	1 year	No
Fujimoto and Hongo, 2010[52]	Japan	Secondary sector	Cohort	Relapse of GERD during long-term PPI therapy	104 weeks	No
Kandil *et al*, 2010[15]	Egypt	Outpatient clinic	Cohort	Effect of exogenous melatonin in patients with GERD	4 and 8 weeks	No
Mason *et al*, 2008[53]	UK	General practice	RCT	Effect of HP eradication in long-term users of PPI	A repeat prescription for PPI begun at least 12 months ago	Previous article by Hungin *et al*[54]
Raghunath *et al*, 2009[55]	UK	Primary care	Cross-sectional	Symptoms in patients on long-term PPI therapy	A repeat prescription for PPI begun at least 12 months ago	Previous article by Hungin *et al*[54]
Usai *et al*, 2008[16]	Italy	Secondary sector	Cohort	Recurrence of reflux symptoms in patients with coeliac disease with NERD	>8 weeks	No

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Table 1 Continued

Author, year	Country	Setting	Study design	Aim	Definition of long-term use	Rationale
Definition based on time (n=51)						
Studies of side effects related to long-term PPI use (n=29)						
Frazzoni *et al*, 2007[56]	Italy	Secondary sector	Cohort	Efficacy of long-term PPI on intraoesophageal acid suppression	2 years of continuous use	No
Studies of deprescribing long-term PPI (n=6)						
Pezeshkian and Conway, 2018[57]	USA	N/A	Review	Guidance on deprescribing PPI in older adults	>12 weeks	Approved duration of treatment
Boghossian *et al*, 2017[58]	Cochrane review	N/A	Systematic review	Effects of deprescribing PPI in adults	≥28 days	No
Walsh *et al*, 2016[59]	Canada	General practice	Cross-sectional	Deprescribing	≥8 weeks	Guideline recommending reassessment of PPIs after 8 weeks
Van der Velden *et al*, 2013[60]	The Netherlands	Primary care	RCT	Deprescribing	≥1 year	No
Bjornsson *et al*, 2006[61]	Sweden	Secondary sector	Clinical trial	Discontinuation	>8 weeks	No
Krol *et al*, 2004[62]	The Netherlands	General practice	RCT	Discontinuation	≥12 weeks	No
Pharmacoepidemiological studies of long-term PPI use (n=3)						
Othman *et al*, 2016[63]	UK	General population	Cohort	Prevalence and pattern of PPI prescribing	≥1 year continuous use	No
Lødrup *et al*, 2014[64]	Denmark	General population	Survey	Use of PPIs	≥120 days the past year	No
Haroon *et al*, 2013[65]	Ireland	Secondary sector	Survey	Reasons for treatment	2 years	No
Definition based on quantity of PPI (n=10)						
Studies of side effects related to long-term PPI use (n=6)						
Imfeld *et al*, 2018[66]	UK	General population	Case–control	Risk of dementia	≥100 prescriptions	No
Shao *et al*, 2018[67]	Taiwan	General population	Case–control	Risk of hepatocellular carcinoma	>28 DDDs	No

Continued

Table 1 Continued

Author, year	Country	Setting	Study design	Aim	Definition of long-term use	Rationale
Definition based on time (n=51)						
Studies of side effects related to long-term PPI use (n=29)						
Sieczkowska *et al*, 2018[68]	Poland	Outpatient clinic and general practice	Cohort	Risk of small intestinal bacterial overgrowth	PPI for at least 75% of the time during the previous 3 months at a minimum dose of 20 mg per day	No
Chien *et al*, 2016[69]	Taiwan	General population	Case–control	Risk of periampullar cancer	>180 DDDs	No
Clooney *et al*, 2016[70]	Canada	General population	Cross-sectional	Gut microbiome in long-term PPI users	>180 tablets each year in a 5-year period	No
Den Elzen *et al*, 2008[71]	The Netherlands	General population	Cross-sectional	Risk of vitamin B_{12} deficiency	>810 DDDs in 3 years	No
Studies of deprescribing long-term PPI (n=2)						
Reimer and Bytzer, 2010[72]	Denmark	Primary care	Cross-sectional	Discontinuation in symptomatically treated patients	120 tablets of any PPI in the previous 12 months	No
Clinicaltrials.gov	USA	Primary care	Clinical trial	Evaluation of a deprescribing programme	90-day prescription within 120 days	No
Pharmacoepidemiological studies of long-term PPI use (n=2)						
Wallerstedt *et al*, 2017[4]	Sweden	General population	Cross-sectional	Prevalence of PPI use among residents ≥65 years	Filled prescriptions for PPI covering ≥75% of the year	No
Haastrup *et al*, 2016[2]	Denmark	General population	Cohort	Predictors of incident long-term use among first-time users	>60 DDDs within 6 months	Definition used in other studies

DDDs, defined daily doses; ECL, enterochromaffin-like; FDA, Food and Drug Administration; GERD, gastro-oesophageal reflux disease; HP, *Helicobacter pylori*; N/A, not available; NERD, non-erosive reflux disease; PPI, proton pump inhibitor; RCT, randomised controlled trial.

Therefore, it is not possible to have just one definition of long-term use that is appropriate for all research purposes and the definition used should fit the aim and context of the study. If the aim is to study drug utilisation or magnitude of long-term use, we suggest a long-term definition of 6 months as a possible definition. Most PPIs are supplied in packages of no more than 100 pills. Thus, taking PPIs daily for 6 months would require at least one renewal of the prescription. Patients initially redeeming 100 pills, but not using all of them, would not be classified as long-term users.

If the aim is to study side effects related to long-term use, the definition of long term might need to be shorter or longer than 6 months depending on the length of exposure time needed for the side effect to occur.

In conclusion, we observed substantial variability in definitions of long-term PPI treatment. The majority of definitions did not include a rationale for the choice of definition. The variety of definitions complicates the comparison of research results and raises challenges in clinical practice, such as identifying an appropriate timeframe for discussing deprescribing. We suggest that long-term use could be defined as more than 4–8 weeks of PPI use in a clinical context depending on the indication for PPI therapy. One definition does not fit all research purposes. Thus, we suggest more than 6 months of PPI use as a possible definition for long-term use in pharmacoepidemiological studies and for studies of adverse effects the definition should be tailored the exposure time needed for the side effect in question to occur. When studying long-term use of PPIs, we suggest always giving well-argued choices of definitions.

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