

## Supplementary Material

# Inappropriate Use of Proton Pump Inhibitor Among Elderly Patients in British Columbia: What are the Long-term Adverse Events?

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### 217 Recent Systematic Reviews of Specific Harms Associated With Proton Pump Inhibitors

#### Anemia

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#### Bone Fractures / Falls

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## CANCERS

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#### **Chronic Liver Disease/ Liver Cirrhosis/ Hepatic Encephalopathy**

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#### **Death**

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**Drug Drug Interactions**

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**Dental implant failure**

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**Hospitalization**

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**INFECTIONS****Bacterial peritonitis**

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**Clostridium Difficile**

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#### **Community-acquired Enteric Infection**

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#### **Community acquired pneumonia**

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#### **Gut Dysbiosis**

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#### **Small intestinal bacterial overgrowth**

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### Microscopic colitis

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### Coronavirus Disease

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## METHODS

### Search Strategy

The information specialist searched the following databases from 2013 until the end of June 2022 without restrictions to publication status or language: Ovid MEDLINE, Ovid Embase, and Epistemonikos. The Cochrane Central Register of Controlled Trials (CENTRAL) was searched without date limits. We present below the full MEDLINE search strategy from which the additional database strategies were derived:

Database: Ovid MEDLINE(R) ALL <1946 to June 29, 2022>

Search Date: 30 June 2022

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- 1 exp Proton Pump Inhibitors/ (20651)
  - 2 exp 2-Pyridinylmethylsulfanylbenzimidazoles/ (11708)
  - 3 (proton adj2 pump adj2 antagon\*).tw,kf. (333)
  - 4 (proton adj2 pump adj2 block\*).tw,kf. (232)
  - 5 (proton adj2 pump adj2 inhibitor\*).tw,kf. (16683)
  - 6 (PPI or PPIs).tw,kf. (26512)
  - 7 (hydrogen potassium adj3 antagon\*).tw,kf. (2)
  - 8 (hydrogen potassium adj3 block\*).tw,kf. (1)
  - 9 (hydrogen potassium adj3 inhibit\*).tw,kf. (15)
  - 10 Dexlansoprazole/ (78)
  - 11 (dexlansoprazole or dexilant or kapidex).tw,kf. (136)
  - 12 Esomeprazole Sodium/ (1177)
  - 13 (esomeprazole or alenia or escz or esofag or esomeprazol or esoprax or esotrex or inexistium or nexiam or nexlum or

- perprazole or sompraz).tw,kf. (1789)
- 14 (ilaprazole or noltec).mp. (80)
- 15 Lansoprazole/ (2176)
- 16 (lansoprazole or agopton or bamalite or banilux or betalans or compraz or dakar or daxar or dostab or duomate or il-satec or inhipraz or inhibitol or keval or lancid or lacopen or langaton or lanpra or lanpraz or lanprol or lanproton or lansazol or lansobene or lansol or lansone or lansop or lansopep or lansoprazol or lansox or lansozole or lanster or lanston or lanvell or lanximed or lanzo or lanzol-30 or lanzopral or lanzoprazole or lanzor or lanzul or lapraz or laproton or lasgan or levant or limpidex or loprал or lupizole or monolitum or ogast or ogasto or ogastoro or ogastro or opiren or pamper or praton or prevacid or prezal or prolanz or prosogan or pysolan or promeco or pro ulco or sopralan or suprecid or takepron or tanzolan or ulpax or zoton).tw,kf. (5473)
- 17 Omeprazole/ (8913)
- 18 (omeprazole or aleprozil or antra or arapride or audazol or baromezole or desec or dointol or domer or dudencer or duogas or emeproton or epirazol or ezipol or gasec or gastec or gastop or gastrimut or gastrolac or gastroloc or glaveral or hovizol or hyposec or inhibitron or inhipump or logastric or lomac or lopraz or losamel or losec or losecosan or ludea or madiprazole or maxor or medoprazole or medral or meicerал or mepral or mepzol or mezzopram or miol or miracid or mopral or mopralpro or nexium or nocid or ocid or ogal or olex or olexin or omedar or omelon or omep uno or omepral or omeprazen or omeprazol or omeprazon or omepril or omeraz or omesec or omestad or omez or omezin or omezol or omezo-lan omezole or omezzol or omisec or omizac or omolin or ompranyt or omprazole or onexal or oprax or ozoken or parizac or penrazole or pepticum or peptidin or peptilcer or peptizole or pra-sec or prazidec or prazole or prilosec or probitor or pro-ceptin or protocol or ramezol or rapinex or reglacid or risek or romep or roweprazol or secrepina or severon or stomacer or stomec or stozole or suifac ulcerol or ulcozol or ulnor or ulsek or ulsen or ulzol or vulcasid or wonmp or xoprin or zatrol or zefxon or zegerid or zenpro or zimor or zoltum).tw,kf. (9365)
- 19 Pantoprazole/ (1415)
- 20 (pantoprazole or anagastra or branzol or controloc or eupantol or inipom or inipomp or pantecta or pantodac or pan-todar or pantoloc or pantop or pantozol or pepticus or protium or protonix or rifun or somac or ulcepraz or ulcotenal or zen-tro or ziprol or zurcal or zurcale or zurcazol).tw,kf. (2245)
- 21 Rabeprazole/ (1027)
- 22 (rabeprazole or aciphex or dexrabeprazole or pariet or pariprazole or rabec or rabeloc).tw,kf. (1293)
- 23 or/1-22 (53370)
- 24 (ae or co or de).fs. (6637288)
- 25 (safe or safety or side effect or side effects or unsafe).ti,kf. (238114)
- 26 (safe or safety or side effect or side effects or unsafe).ab. /freq=2 (320082)
- 27 ((adverse or fatal or harm\* or serious or toxic or undesirable) adj3 (effect\* or event\* or outcome\* or patient\* or reac-tion\*)).ab,kf. (660046)
- 28 (adrs or complication or complicationoxious or teratogen\* or tolerable or tolerability or toxicity or treatment emer-gent).ti,kf. (186384)
- 29 (adrs or complication or complications or noxious or teratogen\* or tolerable or tolerability or toxicity or treatment emergent).ab. /freq=2 (492078)
- 30 (cessat\* or discontinu\* or reduce or reduced or reduces or reducing or reduct\* or stop\* or taper\* or withdraw\*).tw,kf. (4250194)
- 31 (death or deaths or fatal or fatalities or fatality or warning).ti. (182962)
- 32 exp product surveillance, postmarketing/ (17584)
- 33 exp adverse drug reaction reporting systems/ (8512)
- 34 exp clinical trials, phase iv/ (363)
- 35 exp \*drug hypersensitivity/ (36981)
- 36 exp \*drug toxicity/ (90543)
- 37 exp "drug-related side effects and adverse reactions"/ (127663)
- 38 substance-related disorders/ (102665)

- 39 abnormalities, drug-induced/ (14713)
- 40 exp brain diseases/ (1351684)
- 41 exp confusion/ (16343)
- 42 exp neurocognitive disorders/ (294526)
- 43 (alzheimer\* or amnesi\* or confus\* or deliri\* or dementia).mp. (374982)
- 44 (cognit\* adj2 (declin\* or impair\*)).mp. (114157)
- 45 exp fractures, bone/ (201172)
- 46 (bone\* adj2 (broken or fractur\*)).mp. (81936)
- 47 bone density/ (58811)
- 48 (bone densit\* or bone mineral content\* or bone mineral densit\*).mp. (91273)
- 49 (bone\* adj2 strength\*).mp. (7594)
- 50 magnesium deficiency/ (4408)
- 51 (magnesium adj2 deficien\*).mp. (5116)
- 52 (hypomagnesemia\* or hypomagnesaemia\*).mp. (4375)
- 53 exp vitamin b 12 deficiency/ (11701)
- 54 (vitamin adj (b12 or b 12) adj2 deficien\*).tw,kf. (4816)
- 55 anemia, iron deficiency/ (11247)
- 56 (anaemi\* or anemi\* or iron deficien\*).mp. (222634)
- 57 exp pneumonia/ (268764)
- 58 (lung inflammat\* or pneumonia\* or pneumonitides or pneumonitis or pulmonary inflammat\*).mp. (298999)
- 59 acid rebound.tw,kf. (52)
- 60 exp acute kidney injury/ (53328)
- 61 (acute kidney failure\* or acute kidney injur\* or acute kidney insufficienc\* or acute renal failure\* or acute renal injur\* or acute kidney insufficienc\*).mp. (76253)
- 62 exp neoplasms/ (3705208)
- 63 (carcinoid\* or cancer\* or malignan\* or neoplasm\* or polyp\* or precancer\* or premalignan\*).mp. (4203335)
- 64 exp enterobacteriaceae infections/ (108170)
- 65 ((cronobact\* or enteric or enterobacteri\*) adj2 infection\*).mp. (14443)
- 66 exp clostridium Infections/ (32001)
- 67 ((clostridium or c difficile) adj2 infection\*).mp. (14213)
- 68 diarrhea/ (51110)
- 69 (diarrhea\* or diarrhoea\*).mp. (135178)
- 70 (angina\* or cardiac or cardiovascular or coronary or heart or infarct\* or myocardi\* or preinfarct\*).mp. (2519554)
- 71 gastriti\*.mp. (32067)
- 72 metaplasia\*.mp. (22467)
- 73 dysplasi\*.mp. (89884)
- 74 or/24-73 (16049792)
- 75 systematic review/ (200284)
- 76 meta analysis.mp,pt. (247557)
- 77 ((systematic adj3 review\*) or (systematic adj2 overview\*)).tw,kf. (263925)
- 78 (embase or medline or pubmed or searched).ab. (340995)
- 79 or/75-78 (533776)
- 80 23 and 74 and 79 (1624)

81 animals/ not (humans/ and animals/) (4989046)

82 80 not 81 (1608)

83 82 and (2013\* or 2014\* or 2015\* or 2016\* or 2017\* or 2018\* or 2019\* or 2020\* or 2021\* or 2022\*).ed,dt. (1120)

#### **INCLUSION CRITERIA**

Systematic reviews (with or without meta-analysis) were included that met the following criteria: (Cochrane “PICOS” format):

P—adults aged 18 years or older.

I—PPI therapy for any indication for duration of more than 12 weeks.

C—Non-use or histamine type-2 receptor antagonist (H2RA) use.

O—any adverse events