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REVIEW

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Effects of proton pump inhibitor (PPI) use on migraine – a critical review

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Abstract

Background Proton pump inhibitor (PPI) drugs are widely used and are among the most significant achievements of modern pharmacology. Their primary purpose is treating and preventing gastric acid-related disorders. Migraine and PPI intake are prevalent, and many people are affected by both. In the last few years, a potential link between PPI intake and the development of headaches—especially migraine–has come to increased attention. In this review, we critically examine the scientific data concerning the co-occurrence of these two entities.

Findings There seems to be a possible link between the use of PPIs and the occurrence of headache, especially migraine, suggesting a pathophysiological connection on several levels. Moreover, PPI use is only partially without side effects, even if these may not occur immediately. Whether the relation is causative or merely co-existential is currently not yet clear. The influence of genetics, environment, gut microbiome, medication intake and evolution of headache is multidirectional.

Conclusion A relation between the prevalence of migraine and the use of PPIs on a population and personal level seems likely. Although PPIs have many advantages, they should be prescribed with caution, especially in patients who suffer from headaches and migraine. In this narrative review, we aim to critically evaluate existing data and offer a potential approach to accurately identify any connections and interactions, leading to a better understanding of how these conditions may influence each other.

Keywords Migraine, Headache, PPI, Gut dysbiosis, Cytochrome P450

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Introduction

Migraine affects about 12% to 15% of the general population. Consequently, more than a billion people worldwide suffer from some form of migraine [1]. It is a common leading cause of disability, especially among young women [2]. The main characteristic is recurring uni- or bilateral periorbital or frontal headache episodes, accompanied by other neurological symptoms such as photo- and phonophobia [3–6]. In addition, migraine is regularly accompanied by gastrointestinal symptoms like vomiting and nausea, often leading to further medication use. Additionally, the use of non-steroidal anti-inflammatory drugs (NSAIDs) as acute migraine medication can persuade a migraine patient to the permanent intake of proton pump inhibitors (PPIs).

As Calcitonin-Gene Related Peptide (CGRP) plays a pivotal role in migraine pathogenesis, various migraine treatments are aimed at inhibiting the actions of this peptide. Interestingly, CGRP isoforms also seem to play a role in the gastrointestinal system, including inhibiting of gastric acid secretion. This may be an essential clue in the relationship between some gastric diseases and migraine [7]. The release of CGRP is triggered by capsaicin binding to the transient receptor potential vanilloid (TRPV1) channel and, for instance, has protective effects on the gastric mucosa and affects gastrointestinal passage [8].

This review aims to critically evaluate the recent or prior usage of proton pump inhibitors (PPIs) and their multidirectional link to headache disorders, especially migraine, also paying attention to genetic, environmental, and other factors. Our purpose is to critically evaluate the evidence for an association between PPI use and migraine and other headache disorders, explore potential mechanisms, and provide recommendations to healthcare providers and patients.

Proton pump inhibitors (PPIs)

PPIs were established in the late 1980's and are widely used – especially in the Western world – as suppressors of gastric acid secretion [9]. Meanwhile, PPIs are considered one of the biggest successes of modern pharmacology and are often offered over the counter as they are considered highly effective and safe. PPIs are prescribed in almost all therapy regimens of acid-related gastrointestinal disorders like gastro-oesophageal reflux disease (GERD), oesophagitis, and chronic gastritis [10]. Reduction of gastric acid secretion is necessary in pathological hypersecretory conditions such as Zollinger-Ellison syndrome, oesophagitis, and functional dyspepsia [11–14]. PPIs are also widely used as additional pharmacotherapy, for example, to avoid chronic gastritis type C in conditions that make a more extended intake of NSAIDs necessary, as it is everyday use in clinical practice. The most widely spread PPIs are omeprazole, esomeprazole, pantoprazole, and lansoprazole [9].

Mode of action, metabolisation, and side effects of PPIs

The olfactory perception or ingestion of food or alcohol activates neural pathways via vagal stimulation, which leads to gastric proton pumps releasing hydrochloric acid in the stomach to prepare food ingestion [11, 12, 15]. PPIs are absorbed in the stomach and diffuse into the gastric parietal cells. The plasma half-life of most PPIs is short, with a duration of approximately 30 min to 2 h. Furthermore, a single PPI dose can inhibit about two-thirds of proton pumps. However, a significant reduction of acid secretion occurs only after a few days of therapy [14, 16, 17].

The activated form of all PPIs binds to the hydrogen/potassium adenosine triphosphatase proton pump (H^+/K^+-ATPase), which normally pumps H^+ ions (with a positive charge) into the gastric lumen, thus forming the acidic environment found inside the stomach under physiological circumstances. By binding covalently to the H^+/$K.^+$-ATPase, the activated forms of the PPIs inactivate it, decreasing gastric acidity by up to over 90% [9]. This irreversible inhibition is only overcome by synthesising new hydrogen/potassium adenosine triphosphatase proton pumps, which may take approximately 54 h to regenerate fully [18].

PPIs are predominantly metabolised via the cytochrome P450 (CYP) system of the liver, especially CYP2C19 (omeprazole, pantoprazole) and CYP3A4 (lansoprazole, esomeprazole) or both (rabeprazole) [17, 19]. Most PPI doses are excreted by the kidneys, with the remainder excreted in bile [13, 14].

Although PPIs are considered relatively safe in comparison with other drug classes, unexpected adverse events have been discovered recently in longtime and population-based surveys. For example, a slightly higher risk of gastrointestinal infection (predominantly with Campylobacter jejuni and Salmonella), lower bone density with consecutive bone fractures, and pneumonia could be observed, especially among long-term users (i.e., more than 3 months of PPI use). Nausea, rash, nephritis, and hepatitis seem to occur more commonly among PPI users. There are also reports of reduced or impaired resorption of vitamin B12, iron, iodine, or magnesium, causing various adverse events like iron deficiency and neurological and thyroid gland problems. A link to a more frequent occurrence of cardiovascular events has been discussed but has yet to be fully proven [11, 14, 20–22].

Drug-drug interactions in PPI treatment

Firstly, suppressing gastric acid secretion may influence the bioavailability of some medications. All PPIs decrease ketoconazole- and itraconazole levels in the blood and may increase digoxin absorption. As mentioned above, PPIs impact the drug metabolism via CYP2C19 and CYP3A4. Thus, the elimination or degradation of drugs such as contraceptives, fluvoxamine, phenytoin, carbamazepine, diazepam, and warfarin may be decreased while using PPIs (i.e., while using omeprazole). There is a relevant potential drug-drug interaction with clopidogrel, which is metabolised via CYP2C19 into the active form, potentially leading to unexpected side effects [11, 14]. Some of the drugs that are used for migraine treatment, including triptans and CGRP receptor antagonists [23–25], are also known to be metabolised via CYP, potentially leading to interactions, predominantly when metabolised via CYP3A4. Amitriptyline, a tricyclic antidepressant that is often used as prophylactic medication in chronic migraine, is also metabolised via CYP2C19, giving rise to potent adverse events [23].

Methods

We conducted a literature search in PubMed and Cochrane on the 7th of December 2024, using the keywords "migraine + proton pump inhibitors" (MeSH terms: 'migraine disorders' and 'proton pump inhibitors') to assess the recent literature on this topic. Twenty-seven studies were identified and critically analysed, with six studies meeting the research criteria (Fig. 1). We excluded manuscripts that were conducted on other indications of PPIs like Helicobacter pylori eradication, infantile colic, influence of PPI use on oncological diseases or animal studies. As the remaining six papers were very heterogeneous, a systematic review was not appropriate, leading to the decision of a narrative review.

Due to this limited outcome, we expanded the keyword search to related fields like "PPI and gastrointestinal microbiome" and "CGRP and PPI use," evaluated and discussed independently in separate chapters. Interestingly, some keywords lead to no further hits, like "PPI use in migraine", etc., which did not show any results, highlighting that much additional research seems necessary.

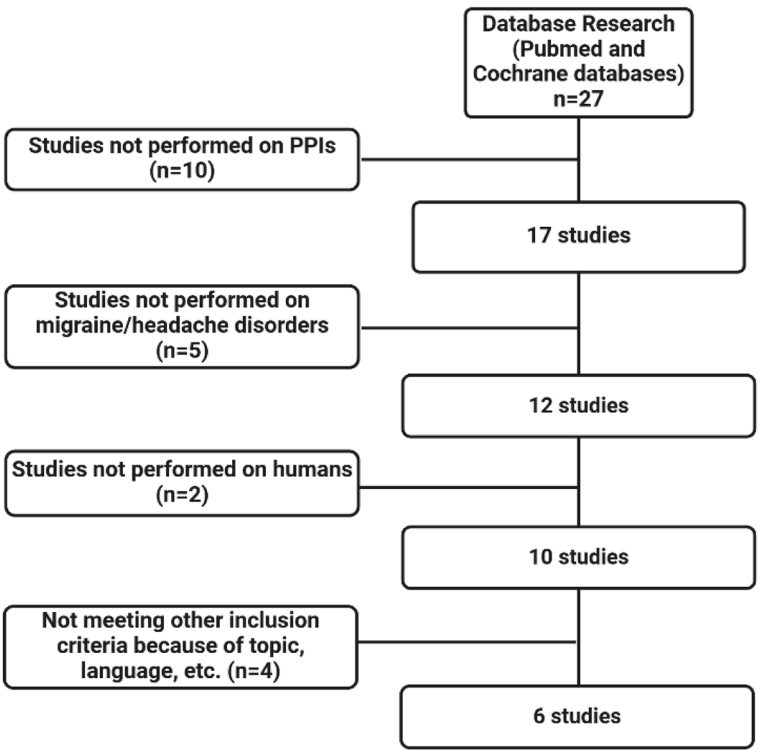

Fig. 1 Work-flow. Flow chart depicting how studies were selected for this review. Used MeSH terms were "migraine disorders" and "proton pump inhibitors". Criteria for exclusion were: studies not performed on PPIs, studies not performed on migraine or other headache diseases, studies that were not conducted on humans or studies that were excluded due to different reasons, like studies that were performed on pain sensitivity in headache patients, or that were not written in English language

Results

The link between migraine and PPI use

Findings in epidemiological and biobank data

In clinical trials on PPIs, adverse events quoted as "headache" or "migraine" were among the most common adverse events (1.3–8.8%) [25–28]. In a study on patients using lansoprazole [29] or omeprazole, headache was the fifth most commonly reported adverse effect [30]. As the potential link between migraine and PPI use was discussed, population-based and biodata bank surveys were conducted. We present the results of these studies in this chapter (Table 1).

One of the first real-world studies on headache and PPIs was conducted in 2002 in the Netherlands by Claessens et al. [31]. This study investigated the incidence and characteristics of headaches among 10,008 lansoprazole users in a large observational prospective, nested case–control study during the first 4 years of use of the PPI. It was found that 2.5% of the lansoprazole users got headaches, and the incidence was 7.2 per 1000 person-years, comparable to previous data [31]. Additionally, the study also detected that female patients, subjects with a history of analgesic use, and those reporting other adverse events were at higher risk of developing headaches. It was also found that discontinuing PPI therapy led to the cessation or reduction of the headache in 80.0% (20 out of 25 patients), interpreted as a possible hint that headaches may be a potential side effect of PPI use. One-third of patients had headaches classified as migraines. However, the response rate to this questionnaire-based survey was relatively low (44.6%), so the results may not be reproducible in the general population [31].

A study conducted in 2015 by Liang et al. [17] on the population of Taiwan highlighted the possible link between PPI use and headache. This study noticed an increased risk of acute headache after PPI intake. The adjusted odds ratio (OR; relative to the baseline period [before the start of PPI use]) was calculated for three different periods after the intake of PPI on days 7, 14, and 28 after the exposure. Within the first week after PPI intake, an OR of 1.41 ($p=0.002$, 95% CI 1.14–1.74) was found for developing a severe headache event. For 14 days, an odds ratio of 1.36 ($p<0.001$, 95% CI 1.16–1.59) could be observed. The findings on the 28 days were similar (OR 1.20, $p=0.002$, 95% CI 1.07–1.35). This relationship was powerful among participants of the female sex (OR 1.76; 95% CI 1.31–2.38; $p<0.001$) and after the use of lansoprazole (OR 1.73; 95% CI 1.21–2.47; $p=0.002$) and esomeprazole (OR 1.78; 95% CI 1.10–3.12; $p=0.046$) [17].

In 2019, Makunts et al. [22] evaluated data from the United States Food and Drug Administration to emphasise the link between PPI use and adverse events in the nervous system. The authors further addressed the Taiwanese study of Liang et al. [17]. Both studies came to similar results with one exception: Makunts et al. [22] reported similar migraine frequencies among PPI and H_2 receptor antagonists (H2RA) users, whereas Liang et al. [17] found higher numbers in patients taking PPIs. Nevertheless, there was a significant increase in the reporting of migraine episodes among the PPI monotherapy group (OR 2.19, 95% CI [1.29, 3.72]) [22].

Pisanu et al. conducted a cross-sectional and longitudinal analysis of migraine prevalence after PPI treatment in a population in the United Kingdom [19]. The authors observed an association between migraine chronification, CYP2C19 metaboliser status, and biological sex. The novel observation was the link to CYP metaboliser status, which will be discussed in the next chapter.

There is a more recent study on the population of South Korea, published by Kang et al. [32] in 2022, showing that people who reported PPI intake in the past had a 2.56 (adjusted odds ratio, 95% CI 2.36–2.79) times higher risk of developing migraine episodes compared to people without PPI intake. In those with current PPI use, an adjusted odds ratio of 4.66 (95% CI 4.29–5.06) was observed. Furthermore, a correlation with the duration of PPI use was discussed. There was an influence on the likelihood of migraine episodes depending on the duration of PPI intake (OR 2.49 (2.29–2.72) for less than 30 days of PPI intake, 4.41 (4.05–4.79) for 30 to 365 days and 4.14 (3.77–4.54) for more than 365 days) [32].

One of the most recently conducted studies on this topic was published in 2024 by Slavin et al. [33]. Data from the 1999–2004 National Health and Nutrition Examination Survey were used. A clear association between the use of any acid-suppression therapy and the occurrence of migraine or other severe headaches was found. Additionally, a significant trend towards a high association between PPI use and headache could be observed: The risk of developing a severe headache event was 70% higher in those who took some PPI [33]. Other types of acid-suppression therapy were also linked to the development of headache: The risk was 40% higher in people taking H2RAs and 30% higher in those who had taken generic antacids. The study further assessed for potential mitigation by dietary factors affected by acid-suppression therapy and found an interaction between H2RA use and magnesium intake ($p=0.024$). This study confirmed previous findings of a link between migraine and PPIs and suggested that other acid-reducing drugs may also have an impact on migraine [33].

To summarise, all of the cited studies showed a relation between headache or even migraine reports and the intake of PPIs [17, 19, 22, 31–33]. Population-based studies showed a significant association between PPI use and increased prevalence of migraine. The risk of migraine

Table 1 Findings on a potential link between migraine and the use of PPIs in epidemiological and biobank data

	Year of publication	Population origin	Sex	Total study population	Primary outcome	Headache classification	Statistic models	results
Claessens et al	2002	Netherlands	No data	10,008	Prevalence of migraine/ headache	Migraine 24,4% Tension-type headache 63,6% Not classified 12,2%	Prospective observational, nested control study	Increased prevalence of headache among lansoprazole users, identification of co-factors, cessation of headache after PPI stop
Liang et al	2015	Taiwan	187,720 (59.7%) female	314,210	Odds ratio for headache risk for a specific period (7,14 and 28 days) of time after PPI intake	Migraine 24,713 Tension-type 17,130 Unclassified 279,129	Population-based case-crossover study	PPI use is associated with an increased risk of acute headache; risk differs between gender and PPI in use
Makunts et al	2019	Multinational, f.e. USA, UK	No data	42,537	Frequency for side effects in the FDA Adverse Event Reporting System	Migraine 168	Odds ratio for side effects	Significant association between PPI monotherapy and neurological adverse events
Pisanu et al	2021	UK	77.4% female in migraine group, 53.4% in control group	Cross-sectional analysis: 468,280 Longitudinal analysis: 145,007	Migraine prevalence after PPI treatment	Cross-sectional analysis ($n = 468,280$) migraine $n = 16,390$ Longitudinal analysis: Migraine $n = 13,767$	Association between treatment with PPIs & migraine prevalence through cross-sectional analysis & longitudinal analysis	Higher prevalence of Migraine in PPI-users, risk factors for adverse events: male sex, CYP 2C19 poor metabolizers
Kang et al	2022	South Korea	18,686	140,795 (incl control group)	Incidence of Migraine compared to the control group	Migraine 28,159	Nested case–control study	Possible links between prior PPI use and incidence of migraine
Slavin et al	2024	US	5,932	11,818	Migraine/ severe headache prevalence over the past 3 months	No data	Cross-sectional analysis	Positive association between migraine or severe headache and use of acid-suppressing medications

remained high also after discontinuation of PPI use in some studies [17, 19, 33], pleading against a causal relationship between these two entities. In contrast, there was a severe decline or cessation in reported headache/migraine events in others [22, 31], suggesting that there may be a causal relationship. Additionally, there is a correlation between the cumulative duration of PPI use and the likelihood of developing migraine episodes [32].

PPI metabolism in relation to CYP2C19 metaboliser status and genetic background

The genetic background plays a crucial role in various phenotypic presentations of individuals and serves as a potential determinant of disease development. In addition, genetic factors are significant contributors to the metabolisation of exogenous environmental factors such as nutrition and medication [34]. A drug's pharmacokinetics depend on an individual genetic background and enzyme state. Interactions with co-medication or nutrition are additional cofactors influencing the drug's pharmacokinetics and thus its primary effect. In particular, CYP2C19 shows a large genetic variability in terms of genotypes and thus drug efficacy and adverse events after medication use, possibly indirectly including worsening of migraine [19, 35].

The pharmacogenomic effect of CYP2C19 polymorphisms is variable, some of which have been associated with decreased or no function (e.g., CYP2C19*2 and CYP2C19*3) or increased function (CYP2C19*17) In the case of CYP2C19 rapid metaboliser status, PPIs are metabolised too fast with the potential of treatment failure related to lower drug concentrations. In contrast, slow metaboliser status is associated with higher drug exposure that increases the likelihood of a positive therapeutic response, but at the same time imposes these individuals at a higher risk for PPI toxicity [36].

CYP2C19 polymorphisms show regional and ethnic differences: Approximately 2% of Caucasians, 4% of African Americans, and 14% of Chinese people are reported to be CYP2C19 poor metabolisers, with up to 45% of all individuals identified as intermediate metabolisers [37]. Indeed, the exposure of individuals with Asian genetic background to omeprazole, which is metabolised by CYP2C19, is approximately four times higher than in Caucasians [37]. The relation between CYP2C19 status and drug metabolisation is depicted in Fig. 2.

The association between migraine prevalence, PPI use, and cytochrome P450 -phenotypes was investigated by Pisanu et al. [19] using cross-sectional analysis. This study provided novel findings: In particular, PPI use and migraine prevalence were associated at baseline (OR 1.25, $p < 0.0001$) in this study. In individuals that showed CYP2C19 rapid metabolisation a lower percentage of migraine was reported; however, these observations were exclusively made in patients exposed to PPIs. In general, PPI users showed higher incidences of migraine with and without aura in the follow-up (OR 1.43, $p < 0.0001$ and OR 1.24, $p = 0.002$). Moreover, PPI treatment and CYP2C19 poor metaboliser status showed an unexpectedly higher incidence of chronic migraine, but this relation was only found in males with an odds ratio OR of 3.81 ($p = 0.008$) [19]. The pathophysiological considerations are depicted in Fig. 3. As migraine is a disease with a female predominance, such novel gender-specific

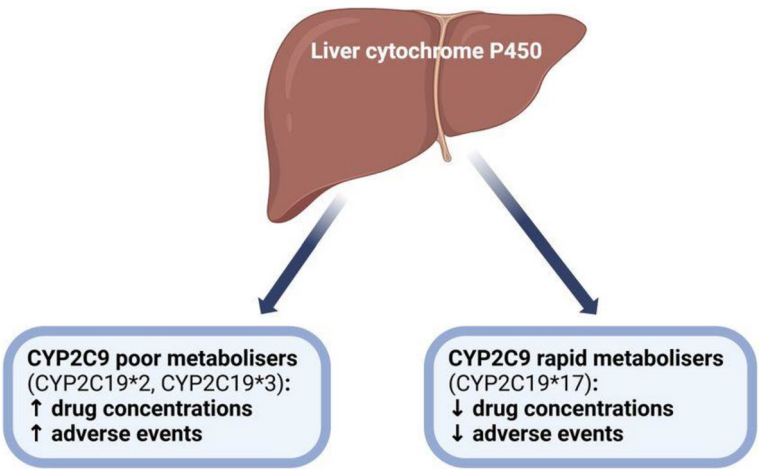

Fig. 2 CYP2C19 status of the liver and its influence on drug metabolisation. The cytochrome P450 system of the liver is essential for the metabolisation of drugs in the body. CYP2C19 poor metabolisers show higher drug concentrations and adverse events. In contrast, in rapid/fast metabolising individuals, drug concentrations tend to be lower, leading to fewer adverse events, but therapy failure is also much more common

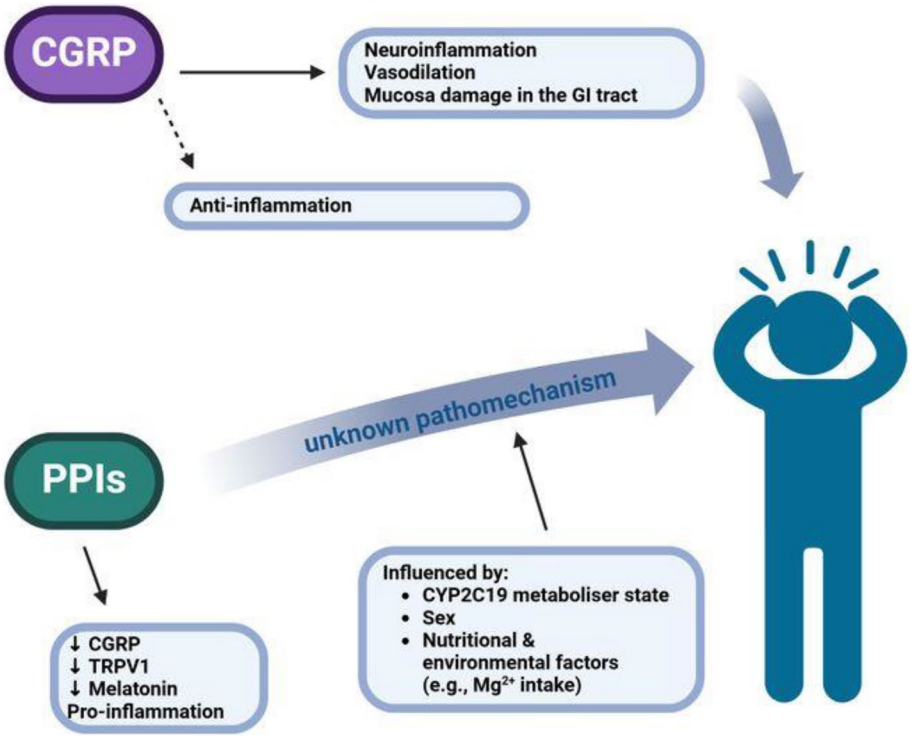

Fig. 3 Possible influence of PPIs on CGRP and migraine/headache evolution. CGRP has multiple biological effects, like neuroinflammation, vasodilatation, and antiinflammation. It plays a crucial role in the evolution of headaches. PPI ingestion can lower the levels of CGRP, TRPV1, and Melatonin in the body and have a pro-inflammatory effect. Via a still unknown pathophysiological pathway – or even more than one – PPI use can lead to migraine or severe headache events. This is further influenced by CYP 2C19 metaboliser status, sex, and nutritional and environmental factors like magnesium intake

findings should give rise to further investigations. Personalised medicine, including pharmacogenetic testing, can increase the therapeutic safety and efficiency of PPIs, minimising adverse effects and, consequently, improving therapeutic adherence.

The genetic factors predisposing to migraine are diverse [38], and even today, only some of the involved factors are known or fully understood.. One of the first studies conducted in this field was done by Dahlöf et al., who showed in 1992 that CYP-dependent hydroxylation did not play a crucial role in migraine attacks [39]. Besides, Sutherland et al. in 2017 hypothesised that different functional polymorphisms of various enzymes that are involved in the synthesis and metabolism of estrogen, such as CYP and catechol-O-methyltransferase (COMT), may have an impact on the origin of menstrual migraine. No functional polymorphisms associated with menstrual migraine could be found in this survey [40]. Considering the above, it is still unsure whether CYP polymorphisms per se, apart from their effect on drug metabolism, affect migraine.

The research field of PPI and neurological diseases is not restricted to headache disorders [20, 23]. In 2017, Wang et al. [20] pointed out that PPI use was associated with a higher risk of hospitalisation because of ischaemic stroke (hazard ratio HR 1.36 (95% CI 1.14–1.620, $P=0.001$). This study yielded higher incidences of stroke-related hospitalisation in younger patients (≤ 60 years), while other essential risk factors, including diabetes mellitus and atrial hypertension, were less relevant than PPI use [20]. These data confirm the assumption that headaches may be related to the gastrointestinal system [41].

Impact of the PPI use on the gastrointestinal system, microbiome, and migraine

A bidirectional relationship between the gastrointestinal and central nervous systems is called the "gut-brain axis" [42]. After a long period of abandonment, this area has attracted increasing attention in recent years. A variety of gastrointestinal disorders, like helicobacter pylori infection, which is associated with gastritis type B, irritable bowel syndrome (IBS), and celiac disease (CD),

have been reported to coexist often with migraine [43]. Although the precise pathophysiological correlation remains fully elucidated, several immunological and inflammatory mechanisms and nutritional factors are thought to underly these comorbidities. Various inflammatory mediators like IL-6, TNF-α, etc., neuropeptides, stress hormones, and the profile of the gut microbiome were shown to be involved in the development of migraine attacks. Nutritional substances are also likely to play a role in these interactions [44]. Since the use of PPIs can have various effects on the gastrointestinal tract and its functions, they may also play a role in the pathophysiological processes that contribute to the development of migraine. Regular use of PPIs was shown to increase the risk of IBS [45, 46] and to be associated with poor clinical course [45, 47]. It has been postulated that these clinical correlations may be related to the intestinal microbiome's deterioration, also called 'dysbiosis,' resulting from the disruption of the gastric acid barrier due to PPI use [45]. Consequently, reduced microbial diversity was associated with increased gastrointestinal inflammation and infections [48–50]. A new concept called 'PPI-induced dysbiosis' arose from these recent studies and was reported to be associated with metabolic syndrome and systemic low-grade inflammation [51]. Obesity constitutes one of the hallmark components of the metabolic syndrome, and it is highly associated with an increase in migraine episodes [52].

Gut dysbiosis [53] caused by PPIs is also closely related to multiple adverse effects, including vitamin and mineral deficiency [54, 55]. PPIs may cause hypomagnesemia [56], and decreased levels of this nutrient are also thought to play a role in the pathophysiology of migraine [57], as stated above [33]. These mechanisms are depicted in Fig. 4.

Furthermore, the gut constitutes one of the extrapineal sources of melatonin. Alterations in the intestinal microbiome may decrease the production of beneficial microbial metabolites like melatonin. Lower melatonin levels are linked to the modifications of glutamatergic transmission, which also plays a key role in the pathophysiology of migraine [58]. Although current studies reporting an increased risk of migraine in patients using PPIs did not report the exact mechanisms linking these two conditions, the above-mentioned clinical associations may contribute to the development of migraine in PPI users. Based on these data, it seems reasonable to suggest that the tailored approach for the management of migraine may necessitate the use of probiotics in PPI users with known migraine (Figs. 5 and 6).

The interplay between PPI use and CGRP

Previous studies suggested that CGRP plays a pivotal role in migraine pathogenesis. In addition, CGRP is also involved in the gastrointestinal system, where it has a protective effect on the gastric mucosa. This may be an

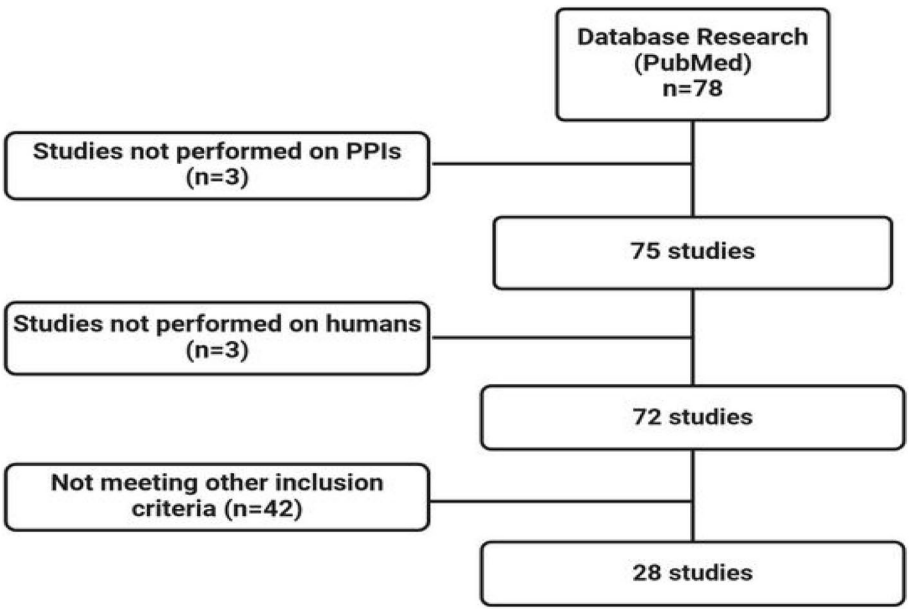

Fig. 4 Flowchart depicting how studies were selected for this review: PubMed research yielded 78 studies. We used the MeSH terms "PPI use" and "microbiome". Exclusion criteria were: Studies not performed on PPIs, studies not performed on humans and, studies that did not meet inclusion criteria, f.e. studies that were performed on the influence of PPI use on other than headache diseases ($n = 27$), or studies performed on the pharmacodynamics of PPIs etc.. A total of 28 studies were included, although not all were citied. The final research was done on the 8.th of December in 2024

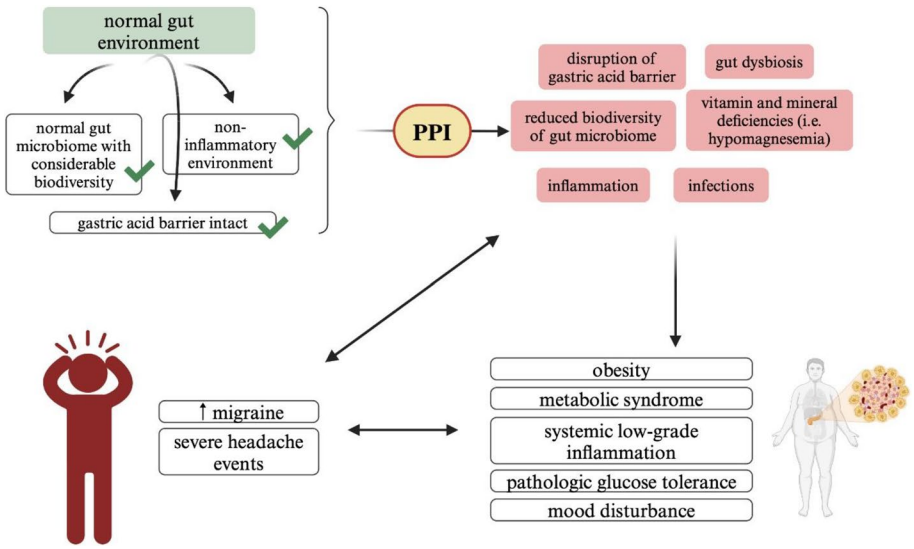

Fig. 5 Influence of PPIs on the gut microbiome. A normal gut environment consists of considerable biodiversity, an intact gastric acid barrier and a non-inflammatory environment. PPIs can lead to gut dysbiosis, reduced biodiversity, a proinflammatory climate, and disruption of the gastric acid barrier, leading to infections and vitamin and mineral deficiency. This can, for example, lead to migraine episodes. Other possible consequences can be obesity, metabolic syndrome, systemic low-grade inflammation, which is also more common in obese individuals, and mood disturbances. All of these are also very commonly associated with migraine and migraine episodes

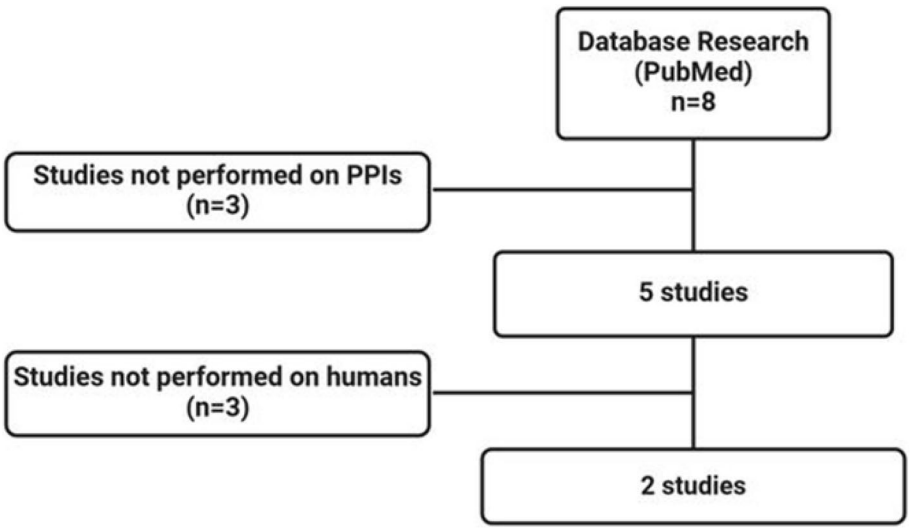

Fig. 6 Flowchart depicting how studies were selected for this review: PubMed research was performed using the MeSH terms "PPI use" and "CGRP". It yielded eight studies all in all. Exclusion criteria were studies not performed on PPIs and and studies not performed on humans. A total of 2 studies were included. The final research was done on the 8.th of December 2024

essential clue in the relation between some gastric diseases and migraine [7, 8]. This intriguing area of research, albeit still insufficiently explored, could open new avenues for exploring the interplay between migraine and PPI. As further detailed below, there is a direct correlation between PPI use and CGRP levels. PPI use seems to influence the level of circulating CGRP in various ways [59–61]. For instance in 2005, Mózsik et al. [59] performed a study on rats to show the influence of different medications (indomethacin and omeprazole) on CGRP levels and TRPV1 expression. Indomethacin was used to cause experimental gastric mucosa damage,

while omeprazole was supposed to protect it. Results showed that treating rats with omeprazole inhibited gastric secretion and—more importantly for our divagations—dose-dependently increased secretion of CGRP and expression of TRPV1, reversing the decrease caused by mucosal damage. In the same year, Katagiri et al. [60] performed a study on humans in which no influence on CGRP levels could be detected. During the COVID-19 pandemic, Ochoa-Callejero et al. [61] conducted a survey of patients suffering from COVID-19. They observed that serum CRGP levels were significantly lower in patients who received PPIs than in those who did not. As novel antimigraine-treatments like gepants and CGRP monoclonal antibodies aim to affect the actions of CGRP in various ways, PPI use may have unpredictable effects on the outcome of these treatments.

Discussion

There are indications that PPI intake can lead to an increase in headaches, especially migraine. However, we did not find robust, replicated evidence demonstrating that migraines are "developed" following PPI use. Although the much-increased risk of developing severe headaches after intake of PPIs might have a strong influence on the prescription of these drugs in individuals with headache syndromes, no clear evidence of a pathophysiological context could be found. There is a high prevalence of headache events in people using PPIs. However, there is still no evidence on whether the drugs per se cause the headache or whether this relation is not causal and is due to merely comorbidities. Some studies observed that discontinuing PPI use led to an end of headache episodes, suggesting a potential pathophysiological connection [31], whereas others did not confirm this observation [19]. Another possible explanation for these findings could be that people with a high intake of PPIs might be more prone to report headache events or even that, hypothetically, patients suffering from migraine or other headache syndromes tend to be more precautious and consequently more likely to report adverse events. In this review, we aim to critically evaluate existing data to offer a potential approach to accurately identify any possible connections and interactions. Thus, whether the potential link between PPI use and headache or migraine evolution is causative or merely coincidental remains part of ongoing discussion.

Limitations of findings in population-based studies

The studies discussed in this review are heterogeneous and cannot be easily compared. As mentioned before, in the last few years several studies have been conducted on this topic, leading to a considerable amount of information. However, these data should be treated with precaution and critically evaluated. For example, database studies show limited precision. Some of these—for example, Liang et al. [17]—just reported coded diagnoses. Consequently, the authors could not differentiate further unclassified "headache events" more precisely into "migraine" and other headache syndromes. As this is a problem in all studies evaluated, even small biases or uncertainties in description can significantly impact the result. Subsequently, the rather unprecise description of "severe headache events" used as a synonym for migraine—or not—makes evaluating this part of the survey quite challenging. This means that most reported headache cases associated with PPI use were nonspecific, thus also limiting the meaningfulness of this survey. Another limitation of database studies is that disease-related characteristics, like severity, duration, etc., were not reported in most of the cited studies. Also, no information is provided about within-person confounding, like clinical fluctuation, symptom severity, comorbidities, comedication, etc. This—among other factors—leads to the problem that unmeasured confounding influences could not be eliminated. As it was pointed out in the study itself, Liang et al. mentioned the probable impact of NSAID intake on gastrointestinal problems in people suffering from migraine, which could not be adequately evaluated through these limitations [17]. The headache occurrence was further based on physician visits, which leads to the fact that the headache incidence might be underestimated because patients who did not seek medical advice were not represented, thus leading to a potentially biased view of the reality of PPI-linked headache events. Over and beyond, most studies did not record whether the medical consultations were due to the worsening of a known headache disorder or completely new onset symptoms. Finally, most of the cited studies had no information about the dosage, duration, etc., of the drug exposure.

Some of the cited studies – for example, Liang et al. [17] and Kang et al. [32]- were conducted on a rather homogeneous population (of primarily East Asian origin in the case of these two studies), and it remains uncertain whether the given results could be generalised to other populations [17, 32]. Population-based studies are essential for providing comprehensive insights into the potential relationship between PPI use and migraine. However, they show several limitations: Due to their observational nature, they cannot establish causality, particularly in the case of cross-sectional

studies. Also, variability in data quality from different sources can affect the reliability of the study's findings. Finally, information bias and missing data can further compromise the quality of the results. Ultimately, it must be noted that in all cited studies, only well-known medications to cause headache or migraine were examined. However, there may still be unidentified factors or drugs that can cause such symptoms [17].

A complete overview of all expected and suggested biases and limitations of the cited studies can be found in Table 2.

Conclusion

Although there seems to be an association between the treatment of PPIs and the evolution of headache disorders, especially migraine, details on the potential mechanisms are not known yet. While PPIs might potentially affect CGRP levels (although not consistently over different studies [59–61]), they might also indirectly affect headache and/or migraine by metabolic routes via the gut-brain axis [45, 48–51, 53–56]. Pharmacogenetics does not yet play a prominent role in everyday clinical practice, but seems of relevance in elucidating pathophysiological mechanisms, and may guide clinicians in their practice in future [19]. Methodological sound surveys need to be enrolled in this broad field in future, as a potential association between PPIs and headache and/or migraine might have significant clinical consequences. On a more direct approach, practitioners should consider including PPIs in a patient's drug history when dealing with headache patients and also advise patients with headache disorders to consider abandoning PPIs after weighing all individual advantages and disadvantages. This might

Table 2 Overview of limitations and biases of the cited studies

	Data on sex	Possible biases and limitations
Claessens et al	none	- no contact with a medical professional - low response rate – reproducibility in the general population? - participation was voluntarily and probably biased - only voluntarily reported diagnoses
Liang et al	available	- survey performed on known risk factor for headache events - precise diagnosis of headache disorder was not available - reported coded diagnoses – no in patient confound factors, no clinical data - only patients with contact with a medical professional were reported - possible deviations in the claims data - case-crossover design does not account for within-person confounding (f.e. acute indication of PPI use, fluctuations in disease severity) - could not delineate whether the clinic visits for headache were because of headache exacerbation or new onset headache based on the claim data
Makunts et al	none	- survey performed on known risk factor for headache events - adverse event reporting is voluntary, so frequencies etc. could not be referred to general population - occasionally missing demographic variables - lack of comprehensive medical record data - no in-patient confound factors - some concurrent medications and comorbidities may be also underreported, which in turn may affect the cohort composition and statistical analysis - over-the-counter medication and supplement use still remains a significant unknown variable as it relies on patient self-reporting - physiological mechanisms cannot be derived from this study due to its observational nature – no causality can be implied
Pisanu et al	available	- survey performed on known risk factors for headache events - over-the-counter medication and supplement use still remains a significant unknown variable as it relies on patient self-reporting
Kang et al	available	- survey performed on known risk factor for headache events - reported coded diagnoses – no in patient confound factors - only patients with contact with a medical professional were reported - no causality could be extracted from this study due to its retrospective nature - medication adherence could not be monitored - unmeasured confounding influences could not be eliminated (f.e. NSAID intake) - confounding effect of missing data (like f.e. genetic background, family history) was not considered - no evaluation between migraine and different kinds of PPI
Slavin et al	available	- survey performed on known risk factor for headache events - reported coded diagnoses – no in patient confound factors - only patients with contact with a medical professional were reported - cannot imply causality due to study design - no data on confounding factors

also include monitoring PPI use in headache patients, including PPI use in the patient´s anamnesis and consideration of pharmacogenetic testing like CYP2C19 metaboliser status in some cases. Consequently, the possible link between PPI use and headache occurrence should be part of the patient´s education. If PPI medication is necessary for a patient suffering from migraine or another chronic or recurring headache disorder, shorter periods between clinical visits or feedback via telephone or in a digital way should be kept in mind.

Abbreviations

PPI	Proton pump inhibitor
GERD	Gastro-oesophageal reflux disease
NSAID	Non-steroidal anti-inflammatory drug
BMI	Body mass index
CI	Confidence intervall
US	United States of America
HP	Helicobacter pylori
IBS	Irritable bowel disease
CD	Celiac disease
IL-6	Interleukin 6
TNF-α	Tumor necrosis factor α
CGRP	Calcitonin-gene-related protein
VIP	Vasoactive Intestinal Peptide
NPY	Neuropeptide Y
CYP	Cytochrome P450
COMT	Catechol-O-methyltransferase
TRPV1	Transient receptor potential vanilloid
GBD	Global Burden of Disease
UK	United Kingdom (of Great Britain)
H2RA	H2-receptor antagonists
e.g.	Exempli gratia/for example
i.e.	Id est

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All authors, on behalf of the European Headache Federation, contributed equally to the drafting and critical revisions of the manuscript. VTS took the lead in writing, drafting, and revising the manuscript. CL and AMvdB supervised the entire process and designed the review concept. All authors read and gave final approval and accepted responsibility for the manuscript.

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Declarations

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Competing interests
The authors declare no competing interests.

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