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Safety of Proton Pump Inhibitors in Pediatric Population: A Systematic Review

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Abstract

Objective. Commonly recommended drugs for adults and children include proton pump inhibitors (PPIs), proven effective for treating peptic diseases like stomach ulcers, GERD, and Helicobacter pylori infections in children over 1-year-old. Yet, prolonged PPI use carries higher risks of adverse reactions, prompting this study's analysis. *Methods.* We have performed a systematic review of 30 articles, which include a total of 762 505 pediatric patients. *Results.* Adverse effects were encountered in 6.98% of the population. The 5 most common adverse effects were respiratory tract complications, gastrointestinal complications, urinary tract infections, asthma, and ENT infections. *Conclusion.* Hence, PPIs should be prescribed only when necessary, and physicians should prioritize patient education when considering their use.

Keywords

proton pump inhibitors, pediatric population, GI infections, secondary infections, adverse effects

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Introduction

Proton pump inhibitors (PPI) are the most efficacious drugs for suppressing gastric acid secretion in the stomach's parietal cells by inhibiting the H+/K+ ATPase.[1,2] They have been proven useful in treating peptic disorders in children, such as gastric ulcers, gastroesophageal reflux disease (GERD), and Helicobacter pylori infections.[3] As of 2015, Rabeprazole, Lansoprazole, Pantoprazole, Omeprazole, Dexlansoprazole, and Esomeprazole are the PPIs that have obtained FDA approval.[2]

Concerns have been expressed by gastroenterologists and FDA regulators about prolonged suppression of the proton pump in the pediatric age group due to the extended use of PPIs.[3] Tolia and Boyer reported the results of 32 to 47 months of PPI medication in 133 pediatric patients, with ages ranging from 0.1 to 17.6 years. Most patients received 2 daily doses of PPIs. During follow-up, hyperplasia of the parietal cells was noted in 0% to 16% of patients. Seventy-three percent of the children had increased levels of the hormone gastrin. Despite certain biochemical, histologic, and endoscopic alterations, long-term PPI medication seems to be effective, safe and well-tolerated in children.[4]

Histamine H2 receptor antagonists (H2RAs) and PPIs are both commonly used to treat GERD, peptic ulcer disease, and dyspepsia. Although both PPIs and H2RAs act on parietal cells via a different mechanism of

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Table 1. Keywords Used for Searching Data Sources.

Treatment terms	"Proton pump inhibitors" OR "Pantoprazole" OR "Lansoprazole" OR "Rabeprazole" OR "Omeprazole" OR "Dexlansoprazole" OR "Esomeprazole"
Population terms	"Paediatric population" OR "Children" OR "Child" OR "Kids"
Others	"Adverse effects" OR "Side effects" OR "Safety" OR "Complications"

action, PPI acid suppression is more potent.[4,5] PPIs (except rabeprazole) exhibit nonlinear pharmacokinetics in contrast to H2RAs, which follow linear pharmacokinetics in pediatric patients.[4]

Long-term PPI use has been associated with an increased risk of community-acquired pneumonia, gastroenteritis, and Clostridium infection and causes headache, diarrhea, nausea, and rash in pediatric patients[6,7] while H2RAs may lead to adverse effects like diarrhea, constipation, headache, and fatigue.[7]

A 16-year (2000-2015) Danish register-based study, where the annual use of PPI in children (0 -17 years old) increased by 8-fold[8] and a study conducted in the United States reported a 7.5-fold rise in PPI use in infants.[9] Thus, over the past 3 decades, there has been a noticeable increase in the prescription of PPIs for children. Research indicates that PPIs are occasionally used for unsuitable causes and are overprescribed. A study conducted by Alosaily et al reported that the use of Omeprazole was deemed appropriate in only 38.6% of the population and there was an overuse of PPIs in the institution.[10] Proton pump inhibitors are regularly prescribed, sold over the counter, and frequently taken for longer periods than may be necessary from a therapeutic standpoint.

PPI use is accompanied by various adverse effects, as stated by numerous studies. In 1 such study by Cohen et al short-term side effects associated with PPI use were headache, nausea, and gastrointestinal symptoms[11] and PPI use was also found to be associated with C difficile infection, allergies like asthma, and autoimmune disease.[12-14]

Other adverse effects related to prolonged use of PPIs in adults and children are gastrointestinal diseases, infections, and hypomagnesemia[15,16] but bone growth concerns and allergic symptoms are more common among children.[13]

In a systematic review by van der Pol et al., headache was the most commonly reported treatment-related adverse effect of PPI use in children with GERD. Other adverse effects were diarrhea, abdominal pain, pharyngitis, and systemic infections.[17] However, there was not enough evidence to prove whether PPI in the pediatric population is safe or not. This review aims to assess the benefits and potential risks of PPIs for each patient individually and to encourage physicians to keep an eye out for side effects when administering a long-term PPI treatment.

Methods

The Systematic review was carried out according to the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) guidelines. The review was registered on PROSPERO (ID: CRD42023464370).

Data Sources and Search Strategy

A comprehensive search was conducted in PubMed, Scopus, and Web of Science databases without publication period restriction on September 3rd, 2023. The keywords used are summarized in Table 1. The search process was completed separately by 2 researchers. The studies' significance level was further screened by appropriately evaluating the publications' titles, abstracts, and full text. A total of 30 articles were included and reviewed.

Eligibility Criteria

The studies were included or excluded as per the defined inclusion and exclusion criteria. The inclusion criteria followed were:

(1) The study was a randomized control trial, cohort studies, case-control studies, or other original research articles
(2) The study population constituted children between the age group of 0 and 18 years
(3) The study consists of the demographic details of the patients
(4) The study reports short- or long-term side effects associated with PPI use in children

The following exclusion criteria were considered:

(1) Non-original studies, including conference abstracts, review articles, protocols, case reports, animal studies, and editorials.
(2) Articles in a language other than English.
(3) Studies in which more than 1 intervention is given to the same individual
(4) Unavailability of full texts.

Study Selection

Revman software was used to organize the search results and remove duplicates. Eight authors independently screened 313 non-duplicated records and the conflicts were resolved after a discussion with DA, SSM, and AS.

Data Extraction

Required data were extracted by 8 authors of the research team as follows: first author name, year of the study, place of study, number of participants, mean age, gender, the disease being treated, drug used, route of administration, treatment duration, adverse effects, and immune cell changes. The results of the included articles are discussed in Table 2. The first author investigated the extracted data and settled any disagreements among the other authors.

Quality Assessment

Newland Ottawa Scale (NOS) for cohort and case-control studies was implemented to critically appraise the included studies.[48] The jaded scale was used for randomized control trials (RCT). The Risk of bias was assessed by 8 authors independently. The risk of bias analysis is made available in the Supplemental Material.

Statistical Analysis

All data were extracted onto a predesigned Excel sheet and represented in percentages, mean, and standard deviation for appropriate variables.

Results

Patient Characteristics

A total of 30 studies (18 clinical trials, 12 cohort studies) were included in the final analysis. All the included studies are hospital-based. Data from the included studies are presented in Table 2. The selection process of articles is shown in the PRISMA diagram (Figure 1).

A total of 762 505 patients were included in the review. Among the 30 studies, the number of males and females were 390 321 (51.2%) and 372 000 (48.8%), respectively. The mean age was 7.39 years (SD 4.69).

The drugs used in the studies were esomeprazole (n = 7, 20.5%), rabeprazole (n = 4, 11.7%), dexlamoprazole (n = 2, 5.8%), lansoprazole (n = 8, 23.5%), pantoprazole (n = 7, 20.5%), and omeprazole (n = 6, 17.6%). The most common route of administration was oral (n = 29), with one study using intravenous route of administration. The duration of administration of PPIs ranged from 4 days to 3 years. An increase in the duration of drug usage was associated with an increase in the occurrence of adverse effects.

Adverse Effects

A comprehensive analysis of 30 global studies has shown that children exposed to Proton Pump Inhibitors (PPIs) face an increased risk of adverse reactions. With 762 505 cases, a total of 53 309 side effects were reported, accounting for 6.99% of the total. Adverse effects reported in children <2 years of age accounted for 0.58% of the total side effects (n = 311).[26,37,39,40,43,44] PPI usage has been associated with an elevated likelihood of secondary infections, hematological complications, and a spectrum of other adverse effects, encompassing bone fractures, psychiatric disorders, and asthma. Among these side effects, secondary infections were the most common.

Diarrhea was the most predominant GI side effect, impacting 67 patients[18,19,22-26,28,31,34,38,39,42-44] (0.12% of total effects), followed by vomiting in 59 cases[18,22,24-26,32,34,38,40,41,43] (0.11% of total effects), abdominal pain in 50 instances[18,19,21,24,25,32,34,38] (0.09% of total effects), and less frequently, nausea in 11 cases[18,22,28,31,34,38] (0.02% of total effects), and GERD (Gastroesophageal Reflux Disease) in 15 cases[26,39] (0.03% of total effects). Other rare GI effects include hypergastrinemia, flatulence, regurgitation, and ileus.

Additionally, cutaneous side effects were observed in 53 patients. This category included skin rash in 12 cases[22,23,26,29,40,43] (0.02% of total effects), urticaria in 2 cases[19,23] (0.004% of total effects), eczema in 19 cases[26,39,40] (0.03% of total effects), and dermatitis in 20 cases[18,26,37,39] (0.037% of total effects).

Secondary Infections

Regarding secondary infections, among the 53 190 reported side effects, a substantial 84.6% (n = 44 997) were attributed to secondary infections, including bacterial, viral, and fungal infections.

Respiratory tract complications include[18-21,23,25,26,30,34,36,37,39,40,43,44] (n = 10 583, 19.8%) URTI (Upper respiratory tract infections), LRTI (Lower respiratory tract infections), nasopharyngitis, bronchitis, rhinitis, pneumonia, and rhinorrhea. ENT infections (n = 3707, 6.95%), CNS infections (n = 200, 0.37%), skin infections (n = 361, 0.68%), and musculoskeletal infections (n = 203, 0.38%) were also reported.[30]

Table 2. Table Representing the Data Extracted From the Articles.

First author	Year of study	Study design	Place of study	Participants	Mean age [Range]	Gender	Condition being treated	Drug	Route of administration	Treatment duration	Adverse effects (no of events)
Tammara et al[18]	2011	Clinical trial	USA	59	N/A [1 month-6 years]	64.28%B, 35.71% G	GERD	Pantoprazole (59)	Oral	7 days (42) 28 days (17)	fever (6), diarrhea (8), gastroenteritis (3), rhinitis (3), GI infection (2), contact dermatitis (2), tooth disorder (2) vomiting (4), abdominal pain (2), nausea (2), increased cough (2), URTI (2).
Gutiérrez-Junquera et al[19]	2018	Prospective cohort study	Madrid	57	11 [5.5-12.8] years	73.7% B, 26.3% G	Eosinophilic esophagitis	Esomeprazole	N/A	12 months	diarrhea (3), abdominal pain (1), urticaria (1), headache (1)
Duncan et al[20]	2018	Retrospective cohort study	USA	293	8.8 months	58.38% B, 41.62% G	Oropharyngeal dysphagia	lansoprazole, pantoprazole, omeprazole (149)	NA	7.11 months	pneumonia, URTI, gastrointestinal infections, and sepsis
Gremse et al[21]	2019	Clinical trial	USA, Poland, Portugal, Mexico)	62	N/A [12-17 years]	100% B	Esophagitis	Dexlansoprazole (62)	Oral	36 weeks	headache (14), oropharyngeal pain (6), diarrhea (4), nasopharyngitis (7), abdominal pain (8), Pharyngitis (6), URTI (4), bronchitis (3), sinusitis (1), insomnia (3), erosive esophagitis (1)
Hassall et al[22]	2006	Cohort study	Canada	166	8 [0.75-11.5] years	N/A	GERD, esophageal atresia	Omeprazole, lansoprazole.	NA	3 years	nausea (2), diarrhea (1), skin rash (1), agitation (1), irritability (1), vomiting (1)
Gunasekaran et al[23]	2002	Clinical trail	USA	63	14.1 [12-17] years	50.8% B, 49.2% G	GERD	Lansoprazole (63)	Oral	5 days	peripheral edema (1), maculopapular rash (1) urticaria (1), sensitive teeth (4), diarrhea (4), dizziness (4)
Haddad et al[24]	2013	Clinical trial	United States, Belgium, Denmark, France, Italy, Poland, Israel, South Africa, India	127	5.7 [1-11] years	56% B, 44% G	GERD	Rabeprazole (127)	Oral	12 weeks	vomiting (18), (18), abdominal pain (15), diarrhea (14)
Haddad et al[25]	2014	Cohort study	United States, Belgium, Denmark, France, Italy, Poland, Israel, South Africa, India	64	6 [1-12] years	57.81% B, 42.19% G	GERD	Rabeprazole	N/A	36 weeks	URTI (8), vomiting (7), abdominal pain (5), diarrhea (4), pyrexia (3), cough (2)
Kierkus et al[26]	2006,2007	Clinical trail	USA, Europe, Australia	45	N/A [1-11 months]	53.3% B, 46.7% G	GERD	Pantoprazole	Oral	5 days	anemia (4), constipation (3), vomiting (3), hypoxia (3), cough (4), rhinitis (4), fever (3), URTI (3), otitis media (3), infection (2), diarrhea (2), GERD (2), pharyngitis (2), contact dermatitis (2), eczema (2), rash (2)
Kuhn et al[27]	2017	Retrospective cohort study	Pennsylvania, USA	526	9.9 years	28.1% G, 71.9% B	N/A	Proton pump inhibitors (30)	N/A	N/A	Eosinophilic esophagitis (30)
James et al[28]	2007	Clinical trial	USA	24	14.2 [12-16] years	45.83% B, 54.17% G	GERD	Rabeprazole	Oral	5-7 days	headache (4), nausea (2), asthma (1), fatigue (1), periorbital edema (1), diarrhea (1), dysmenorrhea (1), pharyngolaryngeal pain (1), proteinuria (1), polyuria (1).
Sandström et al[29]	2012	Clinical trial	USA	59	N/A [0-17 years]	50.8% B, 49.2%G	GERD	Esomeprazole (59)	IV	4 days	constipation (6), pyrexia (5), erythema (3), pruritus (3), rash (3), arthralgia (3), tachycardia (3)
Lassalle et al[30]	2023	Cohort study	France	1 262 424	N/A [1.8-6.2 years]	53.4% B, 46.6% G	N/A	Proton pump inhibitors (606 645)	N/A	N/A	GI infections (9412), ENT infections (3700), LRTI (10 446), UTI (2798), skin infections (360), musculoskeletal system infections (203), nervous system infections (200), bacterial pathogen (3177), viral pathogen (14 598), traumatic Injuries (Excluding Fractures) (1106)
Gilger et al[31]	2015	Clinical trial	Belgium, France, Italy, USA	109	N/A [1-11 years]	51.4% B, 48.6% G	GERD	Esomeprazole (108)	Oral	53.4 days	diarrhea (3), headache (2), somnolence (2), flatulence (1), nausea (1), cough (1), asthenia (1), viral infection (1), arthralgia (1).
Kukulka et al[32]	2011	Clinical trial	USA	36	14.6 [12-17] years	38.9% B, 61.1% G	GERD	Dexlansoprazole (36)	Oral	7 days	abdominal pain (4), vomiting (2), headache (1)
Fleishman et al[33]	2020	Retrospective cohort study	USA	32 001	4 years [6 months-15.5 years]	52.5% B, 47.5%G	N/A	Esomeprazole, lansoprazole, pantoprazole, omeprazole (431)	NA	2 years	Fracture (431)

(continued)

Table 2. (continued)

First author	Year of study	Study design	Place of study	Participants	Mean age [Range]	Gender	Condition being treated	Drug	Route of administration	Treatment duration	Adverse effects (no of events)
Zannikos et al[34]	2011	Clinical trial	US, Belgium	28	6.7 [1-11] years	57.1%B, 42.9%G	GERD	Rabeprazole (28)	oral	5 day	vomiting (3), abdominal pain (3), diarrhea (2), hypergastrinemia (3), nausea (1), pancreatitis (1), regurgitation (1), toothache (1), volvulus (1), viral gastritis (1), streptococcus pharyngitis (2), URTI (1), cough (3), asthma (1), pyrexia (2), chills (1)
Turco et al[35]	2005-2009	Case control study	Italy	68	N/A [1.1-17.8 years]	50.8% B, 49.2% G	Protracted diarrhea and abdominal pain	Proton pump inhibitors (19)	N/A	N/A	Clostridium difficle infection (19)
Righini Grunder et al[36]	2017	Cohort study	Montreal, Canada	73	4.78 years [3.64-7.97]	43.8% G, 56.2% B	Esophageal atresia	Proton pump inhibitors (73)	Oral	2 weeks (43), Ongoing (30)	Regurgitation (49), eosinophilic esophagitis (15), pneumonia (15), bolus impaction (10)
Ward et al[37]	2010	Clinical trial	USA	40	37.9 weeks	75% B, 25% G	GERD	Pantoprazole	Oral	≥5 days	constipation (2), anemia (2), hypoxia (2), rhinitis (2), and contact dermatitis (2).
Fiedorek et al[38]	2005	Clinical trail	United States	87	14.1 [12-17] years	39% B, 61% F	GERD	Lansoprazole (87)	Oral	8 weeks	headache (20) abdominal pain (12), dizziness (3), asthenia (2), diarrhea (2), vomiting (2), nausea (3), anorexia (1)
Orenstein et al[39]	2006-07	Clinical trial	Poland, United States	162	16 [4-49] weeks	76.9%B, 23.07% G	GERD	Lansoprazole (81)	Oral	N/A	URTI (29), dermatitis (16), Eczema (16), constipation (12), GERD (12), ear infections (including otitis media) (15), Fever (15), Diarrhea (10), Rhinorrhea (10), LRTI (11), Candidiasis (8), Viral infection (8), Vomiting (6), Ileus (1), Dehydration (1), Epididymal infection (1), Arachnoid cyst (1), Cellulitis (1), Febrile convulsion (1), Klebsiella infection (1)
Omari et al[40]	2007	Clinical trial	Australia	50	N/A [1-24 months]	62% B, 38% G	GERD	Esomeprazole (50)	Oral	1 week	irritability (3), nasopharyngitis (3), vomiting (2), eczema (1), UTI (1), constipation (1), nasal congestion (1), rash (1), regurgitation (1)
Tolia et al[41]	2002	Clinical trial	USA	66	7 [1-11] years	61% B, 39% G	GERD, erosive esophagitis	Lansoprazole	N/A	8-12 week	pharyngitis (15), gastroenteritis (8), headache (7), vomiting (7)
Tolia et al[42]	2004, 2005	Clinical trial	Belgium, France, Italy, and the United States	109	5.7 [1-11] years	51.3% B, 48.6% G	Erosive esophagitis	esomeprazole	oral	8 weeks	diarrhea (3), headache (2), somnolence (2)
Winter et al[43]	2010	Clinical trial	United States,Canada, Europe, South Africa	106	4.9 [1-11] months	65.38% B, 34.61% G	GERD	Pantoprazole (52)	Oral	4 weeks	URTI (7), rash (4), ↑CPK (3), otitis media (3), vomiting (3), diarrhea (2), cough (2), laryngitis 2
Winter et al[44]	2015	Clinical trial	United States, France, Germany, Poland	98	4.9 [1-11] months	76.9% B, 23.07% G	GERD	Esomeprazole (39)	Oral	2 weeks	URTI (6), pyrexia (5), rhinitis (4), diarrhea (4), nasopharyngitis (23)
Yanqin Li et al[45]	2020	Cohort study	China	42232	6.2 years [1 month-18 years]	39% B, 61% G	All hospitalized pediatric patients	Proton pump inhibitors (11496)	Oral	N/A	Hospital-acquired Acute Kidney Injury (HA-AKI) (962)
Wang et al[46]	2021	Cohort study	Sweden	80870	12.9 [1-17] years	37% B, 63% G	N/A	Omeprazole (65860), Esomeprazole (11305), Pantoprazole (821), Lansoprazole (3219), Rabeprazole (6)	N/A	3 years	Asthma (4428) [Omeprazole, 2854; Esomeprazole, 1250; Pantoprazole, 37; Lansoprazole, 305]
Wang et al[47]	2022	Cohort study	Sweden	29320	11.9 [7-17] years	40.3% B, 59.7% G	N/A	Omeprazole (25061), Esomeprazole (3328), Pantoprazole (209), Lansoprazole (865), Rabeprazole (0)	N/A	1.6 years	Depression (273), Anxiety (432) [Esomeprazole, 97; Omeprazole, 843]

Abbreviations: B, boys; G, girls; URTI, upper respiratory tract infection; LRTI, lower respiratory tract infection; UTI, urinary tract infection; CPK, creatinine phosphokinase.

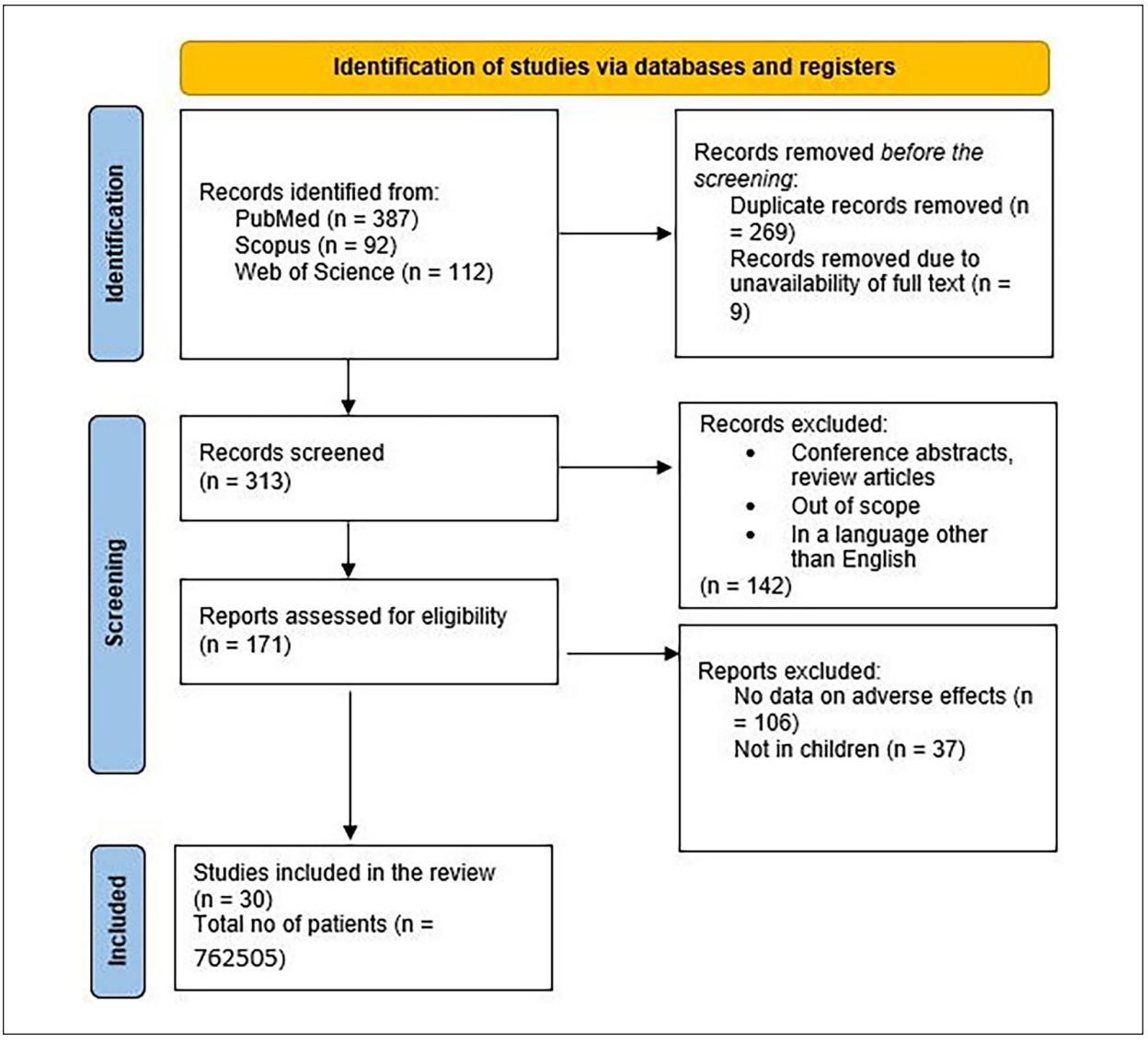

Figure 1. Search results from different databases.

Others

Studies identified fractures in 431 cases[30] (0.81%), as well as mental health problems such as anxiety (n=432,0.81%) and depression (n=273, 0.51%).[47] Additionally, 4429(8.33%) cases of asthma were reported among 80 870 children using PPIs.[28,34,46] In more severe instances, 962 (1.8%) cases of acute kidney injury were noted among 11 496 children taking PPIs.[45] Furthermore, less common side effects in children on PPIs included headaches (n=51, 0.09%), dizziness (n=7, 0.01%), arthralgia (n=4, 0.007%), irritability (n=4, 0.0078%), tooth problems (n=7, 0.0137%), and asthenia. Significant side effects associated with PPI use in the pediatric population are presented in Table 3.

Side Effects Associated With Short and Long-Term Use

The common side effects reported in studies with short-term use of PPIs[18,23,26,28,29,31,32,34,37,38,40-44] (<12 weeks) are upper respiratory tract infections (31.4%), diarrhea (11.16%), vomiting (9.56%), cutaneous manifestations (9.56%), fever (7.16%), headache (6.38%), GI infections (5.58%), constipation (4.78%), and abdominal pain (3.58%). Other short-term side effects are nausea, anemia, dysmenorrhea, arthralgia, tachycardia, GERD, anemia, and urinary tract infections. Asthma is the most common side effect reported in long-term use of PPIs (>12 weeks). Other side effects of long-term use are fractures (7.56%), anxiety (7.48%), and depression

Table 3. Table Representing the Number of Events for Each Significant Side Effect Along With Their Proportion in Total Adverse Effects.

Adverse effects	Number of events	Proportion %
Viral pathogen	14607	27.46%
Respiratory tract complications	10547	19.8%
Gastrointestinal complications	9445	17.75%
Asthma	4430	8.33%
ENT infection	3721	6.99%
Bacterial pathogen	3177	5.97%
Kidney or urinary tract infections	2799	5.26%
Traumatic injuries	1106	2.07%
Hospital acquired AKI	962	1.8%
Anxiety	433	0.81%
Fracture	431	0.81%
Skin infections	361	0.68%
Depression	273	0.51%
Musculoskeletal infections	203	0.38%
Nervous system infections	200	0.37%
Diarrhea	67	0.12%
Vomiting	59	0.11%
Headache	50	0.09%
Abdominal pain	51	0.09%
Fever	42	0.08%
Rash	45	0.08%
Constipation	24	0.05%
Eczema	19	0.04%
Regurgitation	16	0.03%
Cough	14	0.03%
Nausea	11	0.02%
Somnolence	8	0.02%

(4.78%). Some rare side effects like urticaria, insomnia, and erosive esophagitis were also found to be associated with long-term use.[19-22,24,25,33,46,47] Various side effects associated with short and long-term use of PPIs are depicted in Figure 2.

Discussion

In the current systematic review on PPI usage in the pediatric population, 53 190 (6.98%) adverse effects were encountered out of 761 906 participants. The 5 most common adverse effects were respiratory tract complications, gastrointestinal complications, urinary tract infections, asthma, and ENT infection. Gastrointestinal, respiratory, skin, central nervous system, and musculoskeletal system infections, asthma, fractures, and psychiatric adverse effects were a few significant side effects of using PPI in the pediatric population, as depicted in Figure 3.

Proton pump inhibitors (PPIs) work by blocking the proton pump (H+/K+ ATPase) in the parietal cells of the stomach, which reduces acid generation in the stomach. Reduced stomach acid output may make it easier for ingested bacteria and other pathogens to survive and spread throughout the gut since stomach acid acts as a natural barrier against them. This increases the risk of acquiring GI infections.[49]

There have been significant modifications in the GI microbiota linked to PPI use. Reduced stomach acidity may cause some bacteria to proliferate in the stomach and small intestine and may even alter the microbiological makeup of the colon. Studies have shown that, as compared to non-PPI users, oral and upper GI tract commensals are more abundant, while gut commensals are less abundant in PPI users.[50] In the case-control study of 19 children, the use of PPIs (proton pump inhibitors) was significantly higher in the *Clostridioides difficile* positive group compared to the negative group, with an odds ratio of 4.5 [95% confidence interval of 1.4-14.4][35]

This results in gastrointestinal infections, as reported in a few studies. In an RCT consisting of 42 participants, conducted by Tammara et al in 2011, pantoprazole use was associated with adverse effects of gastroenteritis (3,

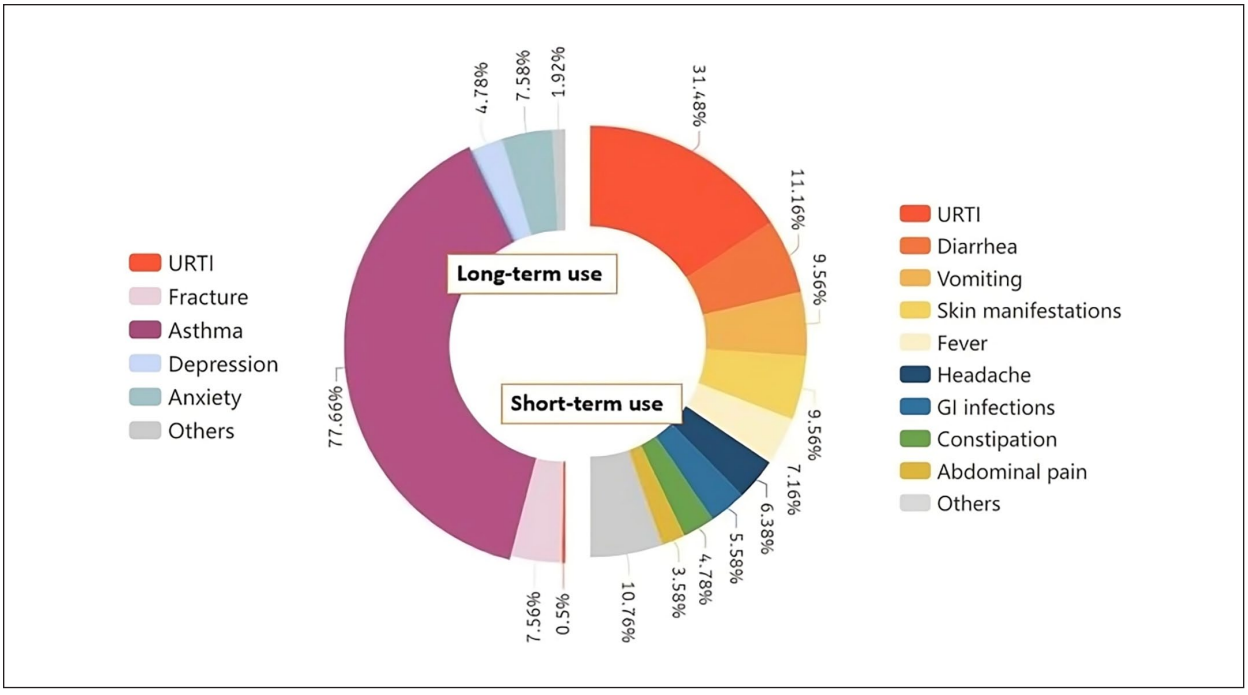

Figure 2. Pie chart depicting the adverse effects associated with short and long-term use of PPIs.
Abbreviation: URTI, upper respiratory tract infection.

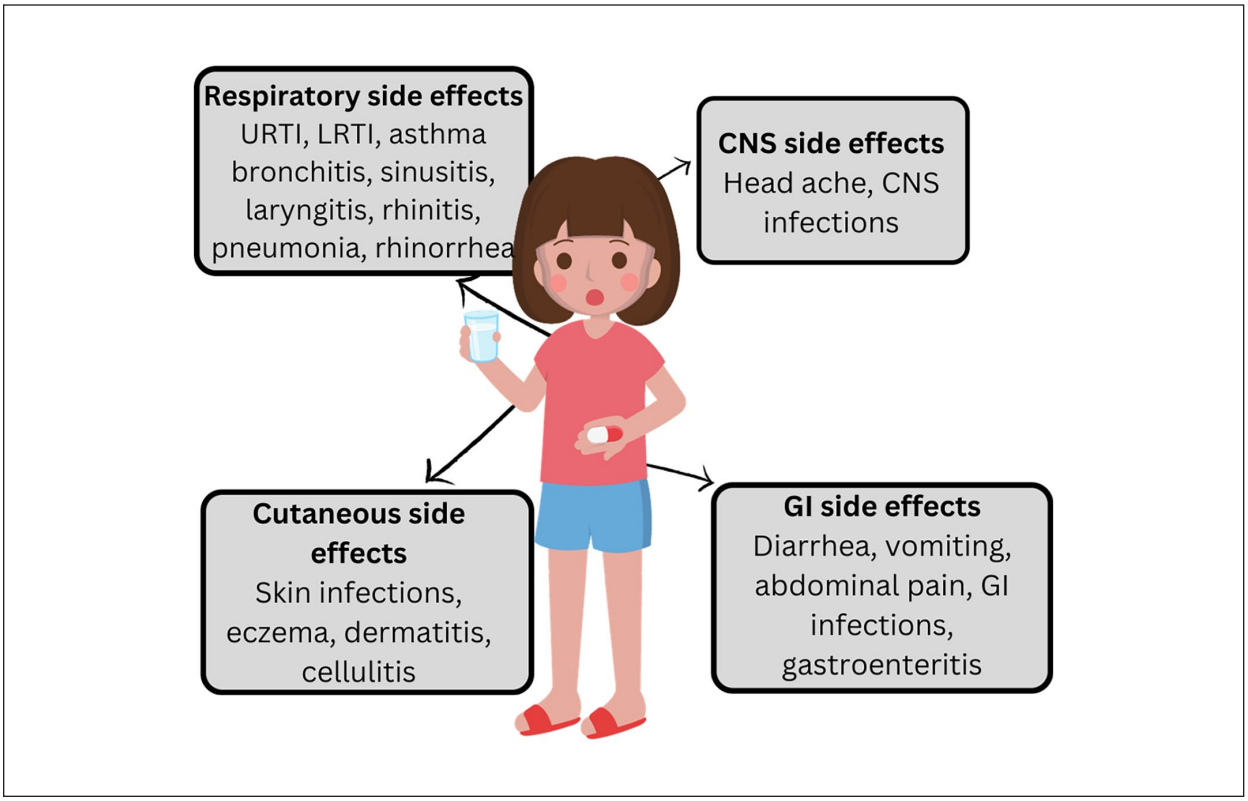

Figure 3. Important side effects reported due to the use of PPIs in the pediatric population.

8.33%) and GIT infections (2, 5.55%).[18] Similarly, in 2023, a cohort study conducted in France by Lassalle et al concluded that PPI use in infants causes adverse effects of digestive tract infection in about 9412 (1.5%) participants.[30]

Overall, in the pediatric population, the most common organisms associated with PPI-related infections include *Clostridioides difficile*, which causes diarrhea and can lead to severe complications. Salmonella and Campylobacter are also the leading causes of bacterial gastroenteritis. Escherichia coli causes severe foodborne illnesses in children, leading to symptoms like diarrhea and abdominal pain. Some of the viruses, like rotavirus and norovirus, may also cause gastroenteritis in young children.[51]

PPIs promote the colonization of bacteria like streptococcus and lactobacillus in the stomach by reducing gastric acid production which helps bacteria enter the lungs through invasion or aspiration, leading to respiratory tract infections.[52] This has been reported in a cohort study conducted in France in the year 2023 with total participants of 606 645, among which 10 446 (3.6%) lower respiratory tract infections have occurred as adverse effects of PPI.[30] A randomized control study for assessing the efficacy and safety of lansoprazole reported both upper respiratory tract infections (35%) and lower respiratory tract infections (13%) as adverse events following PPI use in children.[39] Similarly, Haddad et al while studying the efficacy and safety of rabeprazole maintenance therapy in children found upper respiratory tract infection as an adverse effect in 13% of the population[25] and among 54 adverse effects in a study by Tolia et al, the most common adverse effect was pharyngitis (23%).[41]

Apart from Gastrointestinal and respiratory infections, various other systemic infections have also been reported in a few studies. In a cohort study conducted by Lassalle et al on 606 645 individuals, 360 (0.059%) individuals have shown skin infections, 203 (0.034%) cases of musculoskeletal infections, and, 200 (0.033%) cases of CNS infections were reported.[30] From this study, it is evident that the people who were on ongoing PPI therapy were at more risk than people without exposure. Among the past users, the median (IQR) interval between cessation of PPI use and the onset of major infections was 9.7 months. With increasing time elapsed since stopping PPI treatment (withdrawal since ≤3 months: aHR, 1.13; 95% CI, 1.10-1.16; withdrawal since >12 months: aHR, 1.03; 95% CI, 1.01-1.05), the risk of serious infections gradually decreased.

As discussed earlier, the use of proton pump inhibitors PPIs in children can result in the alteration of both intestinal and lung microbiomes by inhibiting gastric acid secretions. Dysbiosis, which refers to the disruption of the microbial balance resulting from the reduced diversity in specific microbiomes is known to provoke asthma flare.[46] This was reported in a cohort study among 80 870 participants, in which patients on PPI use had a higher incidence rate of asthma (21.8 events per 1000 person-years) compared with the non-initiators. Asthma risk was significantly increased across all age groups who initiated PPIs and was greatest among young children ≤6 months old (HR, 1.83; 95% CI, 1.65-2.03) and 6 months to <2 years old (HR, 1.91; 95% CI, 1.65-2.22; $P < .001$).[46] Similarly, in a randomized control study conducted by James et al, subjects with a mean age of 14.2 years were randomized to receive oral rabeprazole. The tolerability was assessed in terms of adverse events. 8.3% of the total cases had asthma as a treatment-emergent side effect.[28] To summarize, the PPI-exposed peers experienced a substantially greater rate of getting asthma (n = 4430, 8.33% of total adverse effects), in the current study.

This is also supported by a systemic review conducted by Robinson and Ruffner which reported that there is a relationship between the risk of allergic diseases in children, such as food allergies, asthma, and eosinophilic esophagitis, and PPI exposure during pregnancy and childhood. However, uncontrolled confounding is still a possibility, and further prospective research would be helpful to determine the exact extent of this effect.[53]

A study by Wang et al reported that starting PPIs was associated with a 2.6-fold increased risk of depression and anxiety in children when compared to non-PPI users. The study cohort included 29 320 children who initiated PPI treatment and 29 320 matched children who did not. Among the study cohorts, 273 (0.93%) developed depression, and 432 (1.47%) developed anxiety. On the other hand, just 123 (0.42%) subjects developed depression and 168 (0.57%) developed anxiety among non-PPI users. PPI use was linked to both immediate and delayed risks of depression and anxiety. The amplitude of the connection was greater in younger age groups, increasing considerably with a longer duration of PPI usage, but was similar among individual PPIs. Furthermore, the risk was gradually reduced but remained considerable even 1 year after the PPIs were discontinued.[47]

Although some researchers have suggested that PPI may cause decreased bone density and exacerbated osteoporosis, this impact is far from proven. Further confusion arises from the fact that elderly people seem to experience bone effects more readily, leading some to speculate that younger patients are better able to offset the effects of PPI on bone.

Examining a child's fracture risk using PPI is complicated by the fact that the location and mechanism of pediatric fractures vary significantly from those of adult fractures. Because of this, it is essential to take fracture sites into account while researching children, since their presentation patterns may vary from those of adults. Malchodi et al in 2019 reported an elevated risk of fracture in early life in newborns exposed to PPI and histamine blockers, contrary to Freedberg et al in 2015 who showed no relationship between fracture risk and PPI use in children.[54,55]

PPI use in children has been recognized as an efficient intervention for Barrett's esophagus, eosinophilic esophagitis (EoE), Zollinger-Ellison syndrome, Helicobacter pylori in conjunction with other medications, duodenal ulcers, gastroesophageal reflux disease (GERD), and nonsteroidal anti-inflammatory-induced ulcer-related prophylaxis.[56] However, each year, the administration of PPIs increases in both Western and Eastern nations, leading to a potential risk of inappropriate utilization. The prevention of gastric duodenal ulcers in individuals without risk factors, stress ulcer prophylaxis in non-intensive care facilities, and overuse due to lack of awareness among patients are the main causes of PPI overuse.[57] Being offered over-the-counter increases the patient's risk of long-term, unmonitored use. Prolonged use of PPIs causes various adverse effects in children, including, systemic infections, decreased bone density, hypersensitivity reactions, and increased risk of allergic diseases.[56] Mitigation of potential long-term PPI risk could be attempted by periodic evaluations of children on long-term PPI therapy, to make sure they are administered the lowest dosage necessary to control their illness.[55] Clinicians must evaluate carefully the situation in which they're prescribing PPIs and whether or not they're clinically indicated.

Limitations

The inference from our studies and the representativeness of our findings are compromised by the paucity of research on the use of proton pump inhibitors in the pediatric population. Owing to missing data, several original research articles were disqualified. The adverse effects associated with PPI use have been documented in very few articles. Even if the data from more comprehensive, well-designed research are not yet available, our analysis offers an up-to-date, exploratory summary of the available data.

Conclusion

PPIs are effective in treating both acute and chronic diseases, however, they are commonly overprescribed and freely accessible in many nations. Hence, proton pump inhibitors must be used judiciously in children after evaluating the benefits and adverse outcomes. Healthcare practitioners should take into account the possible risks associated with PPIs despite their evident benefits in the prevention and treatment of upper gastrointestinal symptoms in children. Thus, PPI must only be prescribed when indicated and physicians are encouraged to be mindful about educating patients while deciding whether to begin using PPIs. To corroborate these findings, further prospective studies in children with PPI therapy are essential.

Author Contributions

DA: Contributed to conception and design; Drafted the manuscript; critically revised the manuscript; Gave final approval; Agrees to be accountable for all aspects of work ensuring integrity and accuracy.
DJS: Contributed to analysis; Drafted the manuscript; Gave final approval.
MS: Contributed to analysis; Drafted the manuscript; Gave final approval.
RBS: Contributed to analysis; Drafted the manuscript; Gave final approval.
SSMA: Contributed to conception and design; critically revised the manuscript; Gave final approval: Agrees to be accountable for all aspects of work ensuring integrity and accuracy.
MKM: Contributed to analysis; Drafted the manuscript; Gave final approval.
MS: Contributed to analysis; Drafted the manuscript; Gave final approval.
MSSV: Contributed to analysis; Drafted the manuscript; Gave final approval.
AS: Contributed to conception and design; Contributed to analysis; Drafted the manuscript; Gave final approval; Agrees to be accountable for all aspects of work ensuring integrity and accuracy.
SG: Contributed to analysis; Drafted the manuscript; Gave final approval.
SSR: Contributed to analysis; Drafted the manuscript; Gave final approval.

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Protocol was prepared. Registration is done on PROSPERO.

Provenance and Peer Review

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Assistance With the Study

None

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Supplemental Material

Supplemental material for this article is available online.

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