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A Comprehensive Review of Ibuprofen and Its Adverse Effects

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Abstract

Non-steroidal anti-inflammatory drugs (NSAIDs), particularly ibuprofen, are widely used for analgesia and antipyresis but remain a major cause of gastrointestinal (GI) injury across age groups. Data derived from the FDA Adverse Event Reporting System and real-world pharmacovigilance analyses consistently identify safety signals linking ibuprofen to gastric, small-bowel, and intestinal barrier damage. Clinical reviews and case reports,including instances of acute hemorrhagic gastritis and pre-pyloric perforation in young children,highlight the spectrum of NSAID-induced pathology, ranging from mild dyspepsia to life-threatening complications. Studies examining mechanistic pathways show that ibuprofen increases biomarkers of intestinal permeability even when systemic inflammation is suppressed. Risk is further modulated by factors such as dose, duration, hypoxic stress, and postoperative use, prompting trials like PERISAFE to evaluate adverse outcomes after major orthopedic surgery. Pediatric-focused research underscores additional concerns, including hypersensitivity reactions, prescribing variability, and potential associations between ibuprofen administration and asthma development or exacerbation. Together, the evidence emphasizes the need for cautious NSAID use, appropriate patient selection, and implementation of preventive strategies such as gastro protective agents and enhanced monitoring to mitigate ibuprofen-related GI and systemic adverse effects.

Keywords
Ibuprofen, NSAID, Adverse drug reaction (ADR), Gastrointestinal bleeding.

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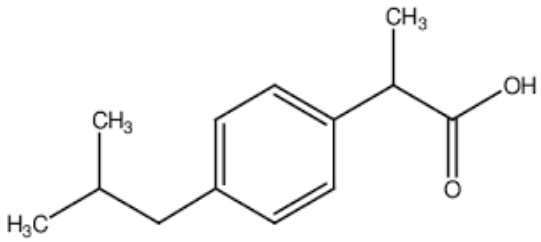
INTRODUCTION

Ibuprofen is one of the most widely used non-steroidal anti-inflammatory drugs (NSAIDs) belonging to the propionic acid derivative class. It is chemically designated as (±)-2- (p- isobutylphenyl) propionic acid, with the molecular formula $C_{13}H_{18}O_2$. It was first synthesized in 1961 by Dr. Stewart Adams and colleagues at the Boots Pure Drug Company in Nottingham, United Kingdom, and was introduced to the market in 1969 under the brand name Brufen.



Ibuprofen

Ibuprofen exerts its pharmacological effects primarily through the inhibition of cyclooxygenase (COX-1 and COX-2) enzymes, which are responsible for the biosynthesis of prostaglandins— key mediators of inflammation, pain, and fever. By blocking these enzymes, ibuprofen provides effective analgesic (pain-relieving), antipyretic (fever-reducing), and anti-inflammatory actions[1].

Ibuprofen is a chiral compound, existing as two enantiomers S (+)-ibuprofen, which is pharmacologically active, and R (-)-ibuprofen, which is inactive but can undergo enzymatic conversion in vivo to the active form. The drug is rapidly absorbed after oral administration, with a peak plasma concentration reached within 1–2 hours. Clinically, ibuprofen is used to treat a wide range of conditions such as rheumatoid arthritis, osteoarthritis, dysmenorrhea, dental pain, headache, and musculoskeletal disorders. It is available in various dosage forms including tablets, capsules, suspensions, and topical gels, allowing flexibility in administration. Despite its therapeutic benefits, ibuprofen's long-term or excessive use can lead to adverse effects such as gastrointestinal irritation, renal impairment, and cardiovascular complications, largely due to its non-selective COX inhibition[2]. Harish R. Kayatwar, Aboli A. Dagamwar, et.al 3 ,2023 conducted a comprehensive overview of the adverse effects associated with ibuprofen, a commonly used non-steroidal anti-inflammatory drug (NSAID) belonging to the propionic acid derivative class. The authors describe that while ibuprofen is widely used for its analgesic, antipyretic, and anti-inflammatory properties, its extensive and often unsupervised use can lead to several adverse drug reactions (ADRs). The review highlights that the most frequent ADRs are gastrointestinal disturbances such as abdominal pain, nausea, vomiting, gastric ulceration, and bleeding, resulting from inhibition of prostaglandin synthesis. It also notes renal complications, including acute renal failure and electrolyte imbalance, as well as cardiovascular risks like hypertension, oedema, and potential exacerbation of heart failure during prolonged or high-dose use. In addition, rare hypersensitivity reactions, hepatic toxicity, and haematological effects such as anaemia and thrombocytopenia are discussed. The authors emphasize that many ADRs are dose-dependent and can be minimized through rational prescribing, patient education, monitoring of therapy, and proper reporting under pharmacovigilance programs. The review concludes by underscoring the necessity for healthcare professionals to be vigilant regarding ibuprofen's risk profile to ensure safe and effective patient care.

Table No: 1 Types of Adverse Drug Reaction

TYPE OF ADRS	CHARACTERISTICS	EXAMPLES
Type A	Dose-related Related to a pharmacological action of drug Predictable from known pharmacology	Nephrotoxicity caused by aminoglycosides Anticholinergic effect of tricyclic antidepressants
Type B	Not dose-related Uncommon No relation to a pharmacological action of the drug	Penicillin induced urticaria Anticonvulsant hypersensitivity syndrome reaction

Type C	Un common Long term exposure of drugs	Hypothalamic- pituitary-adrenal axis suppression by corticosteroids
Type D	Prolonged exposure to a drug	Tardive dyskinesia caused by antipsychotic medication
Type E	Termination of treatment	Tachyphylaxia

Zachary J. Mckenna, et.al 4, 2023, conducted a study on Ibuprofen Increases Markers of Intestinal Barrier Injury but Suppresses Inflammation at Rest and After Exercise in Hypoxia. This study examines the effects of ibuprofen on intestinal barrier function and inflammation in a hypoxic environment, particularly under conditions of rest and post-exercise. The findings suggest that while ibuprofen increases markers of intestinal barrier injury, it simultaneously suppresses inflammatory responses both at rest and after exercise-induced stress in hypoxia. The research highlights a dual effect of ibuprofen, where it may compromise intestinal permeability and contribute to gut dysfunction, while also moderating the inflammatory response, a common consequence of exercise in low-oxygen conditions. These results underscore the need for caution when using nonsteroidal anti- inflammatory drugs (NSAIDs) like ibuprofen, especially in athletes or individuals exposed to hypoxic environments, as the potential gastrointestinal risks may outweigh the anti-inflammatory benefits. Further studies are needed to better understand the long-term implications of ibuprofen use in such contexts.

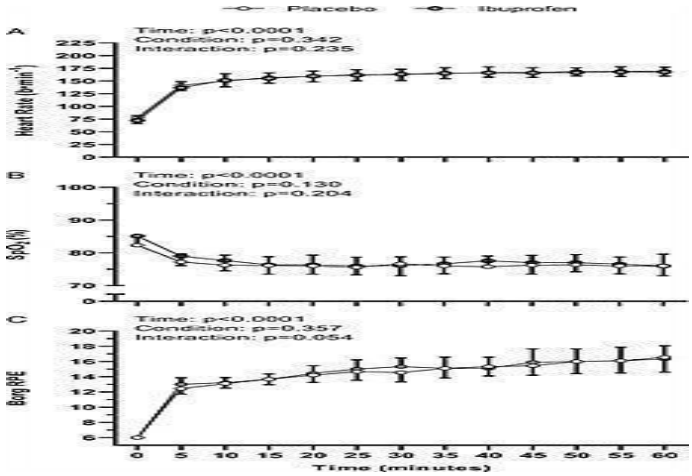


Figure 1: Physiological responses during exercise in placebo and ibuprofen trials. Heart rate (A), SpO2 (B), and Borg RPE (C). Data were analysed using two-way (time–condition) repeated-measures ANOVAs. Data are reported as mean and SD. n = 9 for all panels. RPE, rating of perceived exertion.

Wajeeh Uddin, et.al 5, 2025, published a paper on Over-the-Counter Ibuprofen-Induced Pre- Pyloric Gastric Perforation in a 28-Month-Old Child: A Rare Paediatric Case. The article presents a rare case of pre-pyloric gastric perforation in a 28-month-old child, attributed to the overuse of over-the-counter ibuprofen. Despite its common use for fever and pain relief in paediatric populations, ibuprofen can, in rare instances, lead to severe gastrointestinal complications, such as gastric perforation. In this case, the child was administered ibuprofen for several days to treat mild symptoms of fever and discomfort, leading to acute abdominal pain and vomiting. Imaging and surgical intervention revealed a perforation in the pre- pyloric region of the stomach. The child was promptly treated with surgical repair and a course of antibiotics. This case underscores the need for careful dosing and monitoring when using ibuprofen in young children, as well as awareness of its potential to cause serious gastrointestinal complications, even in the absence of underlying conditions.

Digvijay Dalavi,Ayan Sayyad et al 6,2023,published an article on A Comprehensive Overview Of Ibuprofen. It provides an in-depth and systematic analysis of one of the most widely used non-steroidal anti-inflammatory drugs (NSAIDs). The authors present a detailed account

of ibuprofen's chemical properties, pharmacokinetics, and mechanism of action, highlighting its ability to inhibit cyclooxygenase (COX-1 and COX-2) enzymes and subsequently reduce prostaglandin synthesis responsible for pain, fever, and inflammation. The review effectively integrates pharmacological insights with clinical data, outlining ibuprofen's therapeutic applications in the management of pain, inflammation, and fever, while also addressing its potential adverse effects such as gastrointestinal irritation, renal impairment, and cardiovascular risks. Furthermore, the article emphasizes appropriate dosing strategies, contraindications, and recent advances in ibuprofen formulations. Overall, the review serves as a comprehensive and authoritative resource that consolidates current knowledge on ibuprofen, offering valuable guidance for both clinical practitioners and pharmaceutical researchers.

Mahesh R Gore,Ajit D Nagare,Yogesh J Musale,et al 7,2023,published a paper on Study Of Ibuprofen Drug Related With Pharmacovigilence. The study focuses on evaluating the pharmacological properties, therapeutic uses, and safety concerns associated with Ibuprofen while highlighting the vital role of pharmacovigilance in ensuring patient safety. Ibuprofen, a commonly used non-steroidal anti- inflammatory drug (NSAID), is known for its analgesic, antipyretic, and anti-inflammatory actions. The article explains its mechanism of action, primarily through inhibition of the cyclooxygenase (COX) enzymes, leading to a reduction in prostaglandin synthesis , the mediators responsible for pain, fever, and inflammation.The research emphasizes that while Ibuprofen is widely available and generally considered safe at recommended doses, inappropriate or prolonged use can result in adverse drug reactions (ADRs), such as gastrointestinal irritation, ulceration, renal impairment, cardiovascular risks, and hypersensitivity reactions. The authors review reported ADR cases and provide a discussion on their frequency, severity, and contributing factors such as patient age, dosage, and concomitant medications. A key focus of the paper is the importance of pharmacovigilance systems in detecting, assessing, understanding, and preventing such ADRs. In conclusion, the authors stress that pharmacovigilance plays a crucial role in promoting rational drug use and minimizing drug-related risk.

Table 2: Pharmacokinetic data of Ibuprofen

Bioavailability	**80-100% by mouth.87% rectal**
Protein binding	98%
Metabolism	Liver.
Onset of Action	30 min
Elimination of half life	2-4 hr.
Excretion	Urine -95%.

Maria Oana Mărginean, Lorena Elena Meliț,et al 8,2018,published an article on Ibuprofen, a Potential Cause of Acute Hemorrhagic Gastritis in Children -A Case Report.This case report describes a 6-year-old boy who presented with hematemesis, abdominal pain and loss of appetite, after being given multiple doses of Ibuprofen for fever in a short time interval, contrary to recommended dosing guidelines. Diagnostic work-up revealed marked gastric mucosal friability and digested blood in the gastric corpus and fornix on endoscopy, while histopathology showed reactive changes in the corporal gastric mucosa. Although no active bleeding source was identified endoscopically, the clinical picture was consistent with acute hemorrhagic gastritis likely induced by ibuprofen. Treatment with intravenous proton pump inhibitors and fluid replacement led to clinical recovery. The authors conclude that even in the absence of recognised overdose, ibuprofen may precipitate upper gastrointestinal bleeding in children and emphasise that parents should avoid unsupervised administration of ibuprofen for fever management without paediatric consultation.

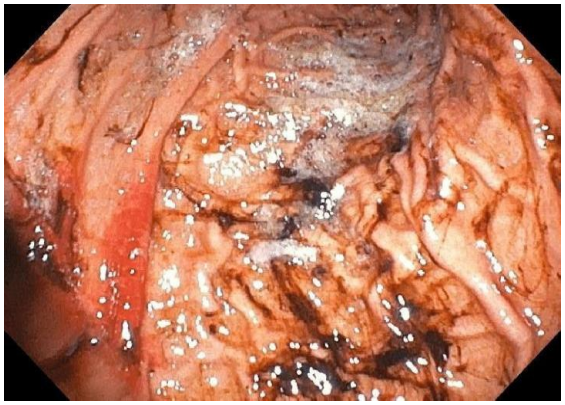


Fig 2

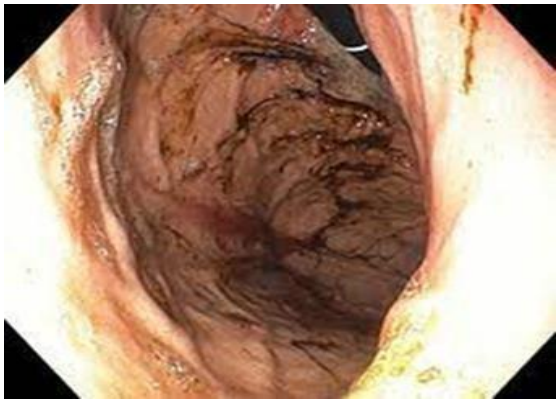


Fig 3

Fig 2: The endoscopic aspect of digested blood in gastric corpus

Fig 3: The endoscopic aspect of digested blood in gastric corpus and fornix without an active binding site.

Rabia Bushra and Nousheen Aslam 9, 2010 conducted a study on an Overview of Clinical Pharmacology of Ibuprofen, tracing its origin as the first propionic acid derivative introduced in 1969. The article describes the drug's mechanism of action as a non-selective inhibitor of COX-1 and COX-2 enzymes, which underlies its ability to reduce pain, inflammation, and fever. The authors detail pharmacokinetic properties: ibuprofen is rapidly absorbed (peak serum levels in 1–2 hours), highly protein-bound (>90%), extensively metabolized in the liver, and eliminated mainly via urinary metabolites, with a half-life of about 1.8–2 hours. They also outline a wide range of therapeutic uses from pain relief in dysmenorrhea, headache, arthritis, and dental pain to special indications like patent ductus arteriosus closure in premature infants. Regarding safety, the review notes that ibuprofen is generally well tolerated, but can still lead to gastrointestinal, renal, and hematological adverse effects; it also has significant drug–drug interactions (with e.g. warfarin, anti-hypertensives) and some food drug interactions (e.g. with certain beverages). The authors conclude that, because of its favorable safety profile and broad clinical utility, ibuprofen remains one of the safest and most widely used NSAIDs when used appropriately.

Motoki Kei and Yoshihiro Uesawa 10, 2025 conducted a study on Comprehensive Analysis of Gastrointestinal Injury Induced by Nonsteroidal Anti-Inflammatory Drugs Using Data from FDA Adverse Event Reporting System Database. The study evaluated the frequency, patterns, and seriousness of GI adverse events linked to various NSAIDs by applying disproportionality analysis methods. Their findings highlighted that non-selective NSAIDs exhibited strong signals for upper-GI complications such as bleeding, ulceration, and perforation, while COX-2 inhibitors showed comparatively lower risk. The study emphasizes the need for careful NSAID selection, dose optimization, and gastro protective strategies for high-risk patients. Overall, the work provides valuable insight into real-world NSAID safety profiles and informs clinical decision-making regarding GI risk management.

Jay L Goldstein and Bryon Cryer 11, 2015 conducted a study on Gastrointestinal Injury Associated with NSAID use: A Case Study and Review of Risk Factors and Preventive Strategies. Nonsteroidal anti-inflammatory drugs (NSAIDs) are widely used for their analgesic and anti- inflammatory effects, yet they remain a major cause of gastrointestinal (GI) injury, ranging from mild dyspepsia to severe complications such as ulcers, bleeding, and perforation. The article highlights that both traditional NSAIDs and COX-2 inhibitors carry GI risks, particularly in elderly patients, those with a history of ulcers, and individuals taking concomitant medications like corticosteroids or anticoagulants.

The case study further demonstrates how chronic NSAID exposure can precipitate serious GI outcomes if preventive measures are not implemented. The authors emphasize strategies such as using the lowest effective NSAID dose, co-prescribing proton pump inhibitors (PPIs), testing and eradicating *Helicobacter pylori* where indicated, and considering alternative analgesics in high-risk patients to minimize adverse effects. This article underscores the need for risk assessment and proactive gastroprotection in routine NSAID therapy.

Christina C. W. Laursen, Troels H. Lunn, et al 12, 2025, conducted a study on The Adverse Effects Associated with Ibuprofen Use After Major Orthopaedic Surgeries- A Detailed Statistical Analysis Plan for the PERISAFE Randomized Clinical Trial. The article presents a rigorously pre- specified statistical

analysis plan (SAP) for the PERISAFE trial, a large (n = 2,904), randomized, double-blind, placebo-controlled, multicenter clinical trial investigating the safety of an 8-day postoperative ibuprofen regimen (400 mg three times daily) in patients undergoing hip or knee arthroplasty. Their primary outcome is a comprehensive 90-day composite endpoint that includes serious adverse events such as death, myocardial infarction, stroke, venous thromboembolism, renal failure, major bleeding, and gastrointestinal ulcer, ensuring that both cardiovascular and bleeding risks are captured. Secondary endpoints include hospital- free days, a patient-reported diary of ibuprofen- and opioid-related side effects during the intervention, and 90-day health-related quality of life. The authors propose robust analytical methods: mixed-effects generalized linear models for binary outcomes, van Elteren tests for count data, mixed-effects linear regression for continuous data, and an exploratory win-ratio approach for the composite endpoint, adjusting for site, and with a pre- planned interim analysis after 1,400 participants. They further define both a modified intention-to- treat and a per-protocol population, while detailing procedures for missing data handling, interaction testing, and assumptions checks. Two independent blinded statisticians will conduct parallel analyses to minimize bias. Strengths of this SAP include its transparency, methodological rigor, and adherence to good clinical practice, which together will enhance the credibility and reproducibility of the PERISAFE trial's findings. However, despite the large sample size, the authors acknowledge potential limitations: uncertainty around the true incidence of the composite outcome and heterogeneity in the clinical relevance of individual components. Overall, this well-developed SAP lays a solid foundation for evaluating the balance between ibuprofen's analgesic benefits and its potential harms in the vulnerable postoperative arthroplasty population.

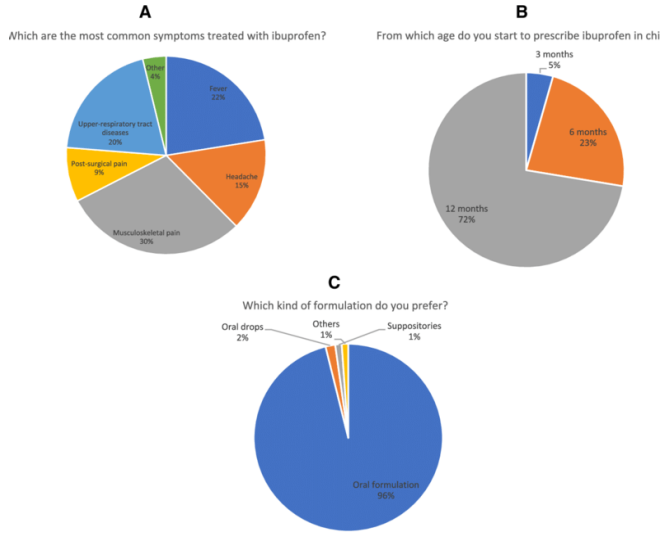
Xudong Xia, Jingjing Wang, et al 13,2025, conducted a valuable pharmacovigilance-based comparison of ibuprofen-associated adverse event (AE) profiles in children versus adults, using over a decade of real-world data from the Henan Province Adverse Drug Reaction Monitoring Center (2010–2023). They apply disproportionality analysis (ROR and PRR) to identify risk signals for ibuprofen in children (0–17 years) and in adults (≥ 18 years), uncovering that while gastrointestinal, neurological, and skin-related AEs are common across both groups, the frequency and nature of these events differ substantially. Notably, children show a higher reporting rate of rash and pruritus, and the authors identify a novel safety signal in pediatric users—significant decreases in white blood cell count (ROR = 12.72, PRR = 12.63). In adults, they also detect gender-specific patterns: headache and dizziness emerge predominantly in males, while abdominal discomfort and pruritic rash appear more in females. The study's strengths include its large sample size, age stratification, and rigorous statistical methods, which together enable detection of age- and sex-specific safety profiles. However, as with any spontaneous-reporting system, there is potential for reporting bias and lack of causality confirmation, limiting the ability to draw definitive conclusions. Overall, the paper offers critical insights that could guide clinicians toward more tailored monitoring of ibuprofen's safety, especially in vulnerable pediatric populations.

Sevgi Sipahi Cimen, Esra Yucel, et al 14,2023, deliver a valuable clinical investigation into immediate- type ibuprofen hypersensitivity in a pediatric cohort, evaluating 50 children (median age 7 years) with suspected ibuprofen allergy using systematic drug provocation tests (DPTs) and classifying reactions per pediatric allergy guidelines. They find that ibuprofen hypersensitivity is confirmed in 34% of cases, with angioedema being the most frequent clinical manifestation. Importantly, the study also identifies older age and male gender as independent risk factors for confirmed ibuprofen allergy.

Among those with confirmed hypersensitivity, a significant subgroup demonstrates cross-intolerance to other NSAIDs, underscoring the complexity of NSAID hypersensitivity in children. Their work further highlights that adult-based classification system for NSAID hypersensitivity may not be fully applicable to pediatric populations, supporting a need for tailored pediatric diagnostic frameworks. Strength of the study lies in its real-world, prospective diagnostic approach, while limitations include the relatively small sample size and the reliance on parental consent for certain tests (such as aspirin DPT) which could bias the classification. Overall, this study contributes critical insight into the epidemiology, risk stratification, and clinical management of ibuprofen allergy in children.

Massimo Martinelli, Lucia Quaglietta et al 15, 2021 conducted a survey of 181 Italian pediatricians found that almost all (98%) use paracetamol—not ibuprofen—as first-line treatment for fever, though about 29% still alternate or combine ibuprofen with paracetamol, mainly when paracetamol alone is insufficient or to prolong effect. Ibuprofen is most commonly prescribed for musculoskeletal pain (30%), upper respiratory infections (20%), headaches

(15%) and post-surgical pain (9%). Around 35% of the respondents reported adverse events in children on ibuprofen (191 events in total), most frequently gastrointestinal issues (like GI bleeding [15.7%], epigastric pain [15.1%], nonspecific abdominal pain [11%], nausea/vomiting [11%]), followed by allergic reactions (skin rash 21%, other hypersensitivity, angioedema). More serious but less frequent events included kidney damage (3.1%), complicated infections, empyema, soft tissue infection, and disseminated intravascular coagulation. About 12 % of adverse-event cases required hospitalization, and in nearly 28% of cases the problems were linked to incorrect dosing, prolonged therapy, or wrong administration frequency. The authors conclude that



while most pediatricians are reasonably cautious, the relatively high rate of alternating paracetamol and ibuprofen and errors in ibuprofen use call for better education and more careful prescribing.

Fig 4: Ibuprofen: Indications, age and formulations. A) Main indication for prescribing ibuprofen; B) Starting age for Ibuprofen prescription; C) Ibuprofen used formulations.

Toshio Watanabe Yasuhiro Fujiwara et al 16 2020 conducted a review to explore how NSAIDs frequently harm the small intestine, particularly in chronic users: capsule endoscopy studies show that about 50%of long-term NSAID users develop mucosal breaks. The pathophysiology involves not only prostaglandin inhibition (due to COX blockade) but also mitochondrial damage from the topical action of the drug; this impairs the intestinal barrier, allowing bacteria (especially Gram-negative) to invade. Immune activation via Toll-like receptor 4 (TLR4) and the NLRP3 inflammasome leads to cytokine release (e.g., TNF-α, IL-1β) and neutrophil infiltration, resulting in ulceration. Clinically, many patients remain asymptomatic, though some present with bleeding, strictures, or anemia. The only therapy with proven benefit in human studies is misoprostol, but even its protection is limited the authors call for new treatments, particularly those targeting the innate immune response.

Luke Baxter, Maria M. Cobo et al 17, 2024 Conducted A systematic review and meta-analysis of 24 studies (in children aged 0–18) found that ibuprofen use does not significantly increase the risk of developing asthma when compared with other active comparators (like paracetamol), both in short term and long-term follow-ups. However, when ibuprofen was used without an active comparator in short-term settings (e.g., to treat fever or bronchiolitis), it appeared to reduce asthma-like symptoms in otherwise healthy children, but potentially worsen symptoms in children who already have asthma. No clear long-term effects were observed in either group. The authors note that these findings rely on a small number of influential studies, especially in key clinical contexts, and call for more rigorous research (both clinical trials and observational) to better underestimate influence development or exacerbation of asthma.

CONCLUSION

The reviewed articles provide a comprehensive overview of the effects and risks associated with ibuprofen, a widely used non-steroidal anti-inflammatory drug (NSAID). A recurring theme across the studies is the potential for ibuprofen to cause a variety of adverse drug reactions (ADRs), including gastrointestinal disturbances (such as bleeding, ulcers, and gastritis), renal complications, and cardiovascular risks. These effects are often dose-dependent, highlighting the importance of appropriate dosing, patient education, and monitoring, especially for vulnerable populations like children and the elderly. Several studies underscore the dual effects of ibuprofen, where it may suppress inflammation and pain, but also compromise intestinal barrier function, potentially leading to gut dysfunction or even perforations, particularly in children and long-term users. For instance, one case study illustrated how inappropriate use of ibuprofen in a young child led to severe gastrointestinal complications, underscoring the need for careful dosing and surveillance in paediatric patients.

Additionally, there is growing evidence that ibuprofen can lead to hypersensitivity reactions, and the risk of adverse events such as anaemia and thrombocytopenia may be exacerbated by concurrent use with other medications.

Pharmacovigilance, therefore, plays a crucial role in detecting and managing these risks. Studies also highlighted the importance of balancing ibuprofen's analgesic and anti-inflammatory benefits with its potential harms, especially in postoperative settings or among athletes. The review concludes that while ibuprofen remains an effective and widely used NSAID, its safety profile requires careful consideration, particularly in long-term or high-dose use. Healthcare professionals must be aware of its ADR risks, apply appropriate therapeutic strategies, and ensure patient education to mitigate harm. Further research is necessary to better understand the long-term implications of ibuprofen use, particularly in specific populations like children and those in high-risk clinical situations.

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