Review Article

Pediatric Pharmacovigilance: Analysis of Adverse Event Trends in Children for Common Non-Steroidal Anti-Inflammatory Drugs (NSAIDs)

Kiran A. Junghare*, Priya S. Shinde, Akanksha B. Sapkal, Sheetal S. Patil, Sampada P. Deshmukh, Pranav V. Pawar, Amruta B. Bhagat
YSPM's Yashoda Technical Campus, Faculty of Pharmacy, Satara, Dist-Satara, Maharashtra, India.
***Corresponding author's E-mail:** kiranjunghare37@gmail.com

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ABSTRACT

Pediatric pharmacovigilance is a fundamental pillar of modern healthcare, necessitated by the distinct physiological and metabolic profiles of children that differentiate them from the adult population. Among the most frequently utilized therapeutic agents in pediatric medicine are Non-Steroidal Anti-Inflammatory Drugs (NSAIDs), specifically Ibuprofen, and the antipyretic Paracetamol. While these medications are globally recognized for their efficacy in managing fever and pain, ensuring their safety across various developmental stages remains a complex clinical challenge. This review provides a comprehensive analysis of the adverse event trends associated with these drugs by synthesizing data from robust global repositories like WHO VigiBase and national frameworks such as the Pharmacovigilance Programme of India (PvPI). By examining clinical literature and spontaneous reporting patterns, this study identifies critical safety signals, including Paracetamol-induced hepatotoxicity and Ibuprofen-linked nephrotoxicity, particularly in cases of dehydration or improper weight-based dosing. Furthermore, the analysis highlights the significant role of caregiver medication errors and off-label usage in the occurrence of preventable adverse drug reactions (ADRs). The study concludes that strengthening pediatric drug safety requires a multi-faceted approach involving enhanced spontaneous reporting, rigorous parental education, and the active involvement of clinical pharmacists in risk mitigation. Ultimately, these strategies are essential for optimizing therapeutic outcomes and ensuring the well-being of the pediatric population.

Keywords: Adverse Drug Reactions (ADRs), Drug Safety, Ibuprofen, NSAIDs, Paracetamol, Pediatric Pharmacovigilance.

INTRODUCTION

The landscape of pediatric therapeutics is inherently complex, primarily because the pharmacological response in children is dictated by a dynamic process of growth and maturation. For decades, the medical community operated under the flawed assumption that children were merely "miniature adults," leading to the widespread off-label use of many medications. However, it is now well-established that children possess unique physiological, metabolic, and psychological characteristics that significantly alter drug disposition[1]. Consequently, pediatric pharmacovigilance has emerged as a specialized and critical discipline, focused on monitoring the safety and efficacy of drugs in this vulnerable population.

Among the most ubiquitous medications in pediatric care are Non-Steroidal Anti-Inflammatory Drugs (NSAIDs) and antipyretics, with Paracetamol and Ibuprofen being the primary agents used for the management of fever and pain worldwide[2]. Their widespread availability as over-the-counter (OTC) products often fosters a public perception of absolute safety. However, the pharmacological reality is much more nuanced. While these drugs are highly effective when administered correctly, they carry a distinct risk profile that is often exacerbated by weight-based dosing complexities and developmental variations in hepatic and renal clearance[3].

Paracetamol (Acetaminophen) remains the first-line treatment for pediatric pyrexia due to its excellent safety record at therapeutic doses. Yet, it remains a leading cause of accidental poisoning and drug-induced liver injury in children, often due to cumulative dosing errors or the use of multiple formulations containing the same active ingredient[4]. On the other hand, Ibuprofen—a potent NSAID—is highly valued for its anti-inflammatory properties. Despite its benefits, its association with gastrointestinal distress and potential nephrotoxicity, particularly in children who are dehydrated or have underlying renal issues, necessitates constant clinical vigilance[5].

In the Indian context, the Pharmacovigilance Programme of India (PvPI) has been instrumental in creating a structured framework for reporting Adverse Drug Reactions (ADRs) specifically in the pediatric sector[6]. Despite these institutional efforts, under-reporting remains a significant hurdle. This is often due to a lack of awareness among caregivers and a systemic gap in spontaneous reporting by healthcare professionals. Strengthening our understanding of these trends is not just a regulatory requirement but a fundamental necessity for protecting the health of the future generation[7].

METHODOLOGY

The structural integrity of this review is based on a systematic approach to evaluate pediatric safety data for Ibuprofen and Paracetamol. Given the physiological diversity in children, the methodology focuses on evidence that accounts for developmental variations in drug response, following the PRISMA (Preferred Reporting Items

for Systematic Reviews and Meta-Analyses) guidelines for academic rigor.

- **Literature Search and Data Sources**

A multi-database comprehensive search was conducted across PubMed/MEDLINE, ScienceDirect, Cochrane Library, and Google Scholar to identify relevant studies published between 2009 and 2024. The search strategy employed a combination of MeSH terms and Boolean operators: ("Pediatric Pharmacovigilance" OR "Drug Safety") AND ("NSAID" OR "Ibuprofen" OR "Paracetamol") AND ("Adverse Drug Reactions" OR "Signal Detection").

To integrate real-world clinical evidence, secondary safety data and spontaneous reports were synthesized from global repositories such as WHO VigiBase and national regulatory frameworks including the Pharmacovigilance Programme of India (PvPI)[6,8].

- **Study Selection (PRISMA Framework)**

The selection process followed a structured four-stage filtration (Identification, Screening, Eligibility, and Inclusion) as illustrated in Figure 1. As depicted in the PRISMA workflow[9], the systematic process began with the identification of 345 records, which were subsequently refined to 310 after duplicate removal. During the screening phase, 130 full-text articles were rigorously assessed for eligibility based on predefined inclusion criteria.

This filtration ultimately resulted in the inclusion of 45 high-quality studies—comprising randomized controlled trials (RCTs), observational cohorts, and systematic reviews—for final qualitative analysis and synthesis.

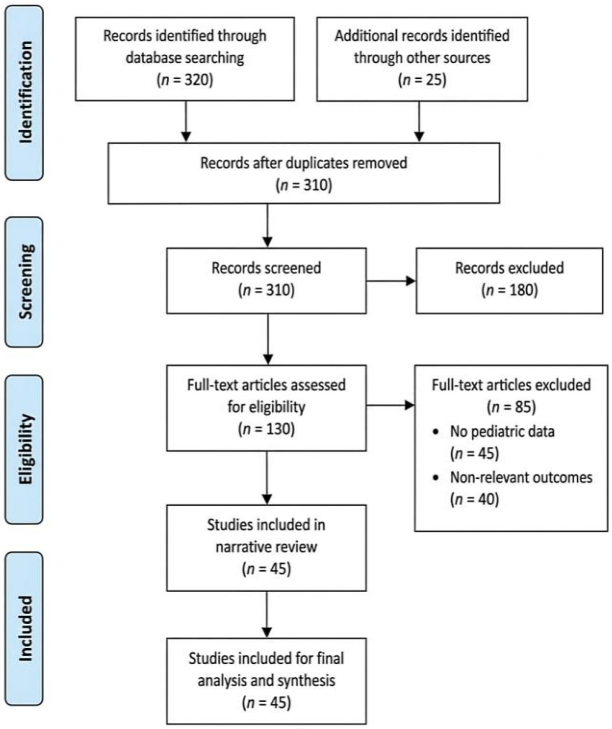

Figure 1: PRISMA flow diagram illustrating the literature search, screening, and study selection process for the present review.

- **Inclusion and Exclusion Criteria**

To ensure high-level evidence, specific criteria were established:

Inclusion Criteria: Studies involving children aged 0–18 years, focus on Paracetamol or Ibuprofen monotherapy/ combination, and reports of serious adverse events (e.g., SJS, TEN, AKI, or Hepatotoxicity).

Exclusion Criteria: Case reports with insufficient clinical data, studies published in languages other than English, and gray literature without peer-review validation.

- **Data Extraction and Causality Assessment**

Data were extracted using a standardized template focusing on patient demographics, dosage regimens, ADR type, and clinical outcomes. Identified ADR trends were evaluated using the WHO-UMC Causality Assessment Scale and the Naranjo Algorithm to ensure scientific plausibility between drug exposure and the observed clinical outcomes. This systematic evaluation minimizes bias and strengthens the correlation between NSAID administration and pediatric safety signals[10].

Overview Of Common NSAIDs Used in Pediatrics

The therapeutic management of pain and pyrexia in the pediatric population is a critical aspect of clinical practice, with Non-Steroidal Anti-Inflammatory Drugs (NSAIDs) serving as the frontline intervention. Unlike adult medicine, where a vast array of NSAIDs is available, the pediatric pharmacological landscape is notably more selective. This restriction is primarily due to the unique developmental physiology of children, where certain agents pose a risk of severe systemic complications, such as Reye's Syndrome or acute metabolic imbalances[11].

- **Therapeutic Classifications and Clinical Utility**

Pediatric NSAIDs are generally categorized based on their chemical structure and their specific affinity for Cyclooxygenase (COX) isoenzymes.

Para-aminophenol Derivatives (Paracetamol): While Paracetamol (Acetaminophen) is not a classical NSAID due to its minimal peripheral anti-inflammatory activity, it remains the most utilized antipyretic globally. Its high safety margin at therapeutic doses makes it the preferred first-line agent for neonates and infants[12]. Propionic Acid Derivatives (Ibuprofen): Ibuprofen is the primary representative of this class in pediatrics. It is highly valued for its dual-action profile—providing robust anti-inflammatory effects alongside antipyretic action[13].

Fenamates (Mefenamic Acid): Occasionally utilized for short-term symptomatic relief of high-grade fever, though its usage is often reserved for older children due to a more pronounced adverse effect profile compared to Ibuprofen.

- **Comparative Pharmacodynamics and Dosing Paradigms**

The efficacy of these agents is intrinsically linked to weight-based dosing precision. Clinical errors often arise from a failure to recognize the maturational changes in hepatic and renal clearance that occur from infancy through adolescence[14].

Table 1: Comparative Clinical Profile of First-line Pediatric Analgesics

Pharmacological Parameter	Paracetamol (Acetaminophen)	Ibuprofen (Propionic Acid)
Dosing Schedule	10–15 mg/kg every 4–6 hours	5–10 mg/kg every 6–8 hours
Mechanism of Action	Central COX-3 inhibition	Peripheral COX-1 & COX-2 inhibition
Anti-inflammatory Effect	Negligible	Potent
Metabolic Pathway	Hepatic (Glucuronidation/Sulfation)	Hepatic (CYP2C9 Oxidative Pathway)
Elimination Half-life	~2–3 hours (age-dependent)	~1.8–2 hours
Max Daily Limit	75 mg/kg (up to 4g in adolescents)	40 mg/kg (up to 2.4g)

- **Rationale for Selection in Pharmacovigilance**

From a pharmacovigilance perspective, the widespread availability of these drugs as Over-the-Counter (OTC) products necessitates rigorous monitoring. The "perceived safety" of these agents often leads to cumulative dosing errors by caregivers. While Paracetamol is remarkably safe, its metabolic byproduct (NAPQI) poses a risk of hepatotoxicity if glutathione stores are depleted. Conversely, Ibuprofen's inhibition of peripheral prostaglandins requires caution in children with compromised hydration status to prevent acute kidney injury[15].

Adverse Drug Reactions Associated with NSAIDS In Children

The surveillance of Adverse Drug Reactions (ADRs) in the pediatric population is a multifaceted challenge, primarily due to the physiological heterogeneity across different age groups—from neonates to adolescents. While Paracetamol and Ibuprofen are cornerstones of pediatric therapy, their safety profile is contingent upon multiple factors, including genetic predisposition, nutritional status, and pre-existing clinical conditions[16].

- **Organ-Specific Toxicity Patterns**

Adverse events associated with these agents are typically categorized by the organ systems they affect. In children, the hepatic and renal systems are the most vulnerable due to the maturational stages of drug-metabolizing enzymes and filtration rates.

Hepatic Complications (Paracetamol-induced): Paracetamol remains a leading cause of drug-induced liver injury (DILI) in children globally. At therapeutic doses, it is metabolized via glucuronidation and sulfation. However, in cases of cumulative overdose, the production of the toxic metabolite N-acetyl-p-benzoquinone imine (NAPQI) exceeds the neutralizing capacity of glutathione, leading to centrilobular hepatic necrosis[17].

The specific metabolic transformation and the transition to the toxic NAPQI pathway during an overdose are visually detailed in Figure 2.

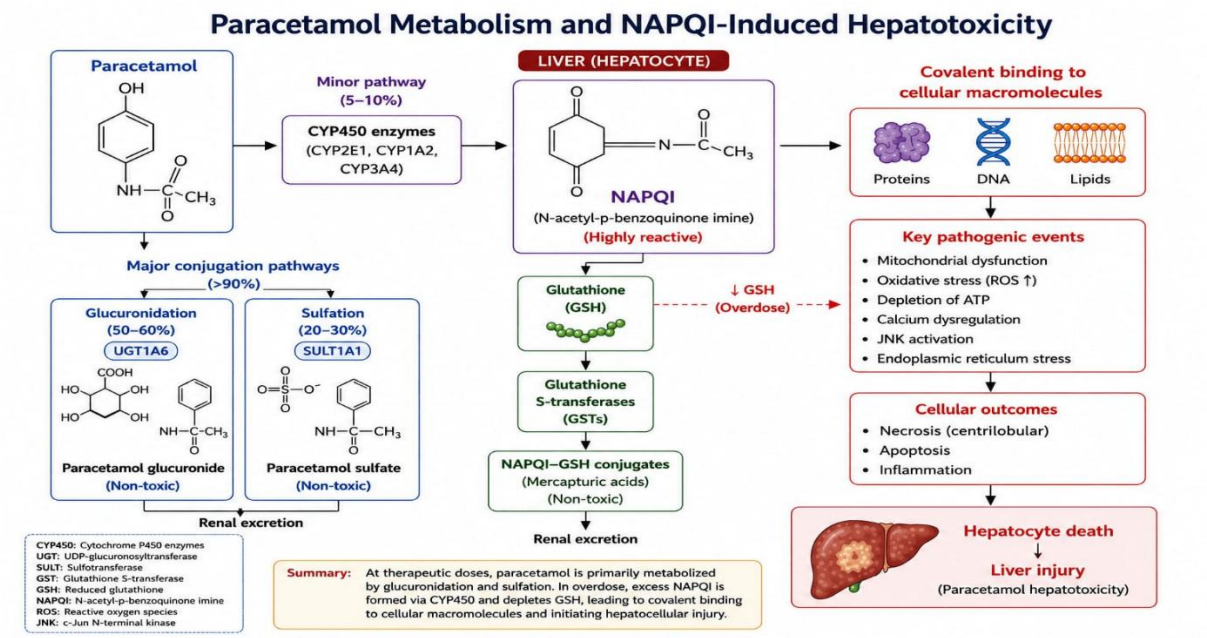

Figure 2: Metabolic pathway of Paracetamol highlighting the transition to toxic NAPQI formation during overdose.

Renal Insult (Ibuprofen-induced): Ibuprofen's mechanism involves inhibition of prostaglandin synthesis. In a dehydrated child, prostaglandins are vital for maintaining renal blood flow. Their inhibition can lead to acute kidney injury (AKI) and electrolyte imbalances, a trend increasingly noted in hospitalized pediatric patients[18].

- **Hypersensitivity and Dermatological Reactions**

Though rare, cutaneous ADRs represent some of the most severe safety signals in pediatric pharmacovigilance.

Stevens-Johnson Syndrome (SJS) and Toxic Epidermal Necrolysis (TEN): These are life-threatening mucocutaneous reactions. Ibuprofen has been identified in several safety signals as a potential trigger for SJS in genetically susceptible children[19].

Fixed Drug Eruptions (FDE): Paracetamol is frequently linked to localized skin reactions, which, although less severe than SJS, necessitate immediate discontinuation and future avoidance.

- **Gastrointestinal and Hematological Risks**

Unlike adults, children are generally less prone to chronic gastric ulcers from NSAIDs, yet acute gastrointestinal bleeding and dyspepsia remain significant risks, especially with prolonged Ibuprofen use[20]. Additionally, rare hematological ADRs, such as thrombocytopenia and neutropenia, have been documented in spontaneous reporting databases.

Table 2: Summary of Common vs. Serious ADRs in Pediatric NSAID Therapy

Systemic Category	Common Adverse Events	Serious / Life-Threatening
Gastrointestinal	Nausea, Vomiting, Abdominal pain	Gastric bleeding, Hematemesis
Hepatic	Transient elevation of AST/ALT	Acute Liver Failure (NAPQI)
Renal	Decreased urine output	Acute Kidney Injury (AKI)
Dermatological	Urticaria, Mild Rash	SJS / TEN
Neurological	Irritability, Dizziness	Aseptic Meningitis (Rare)

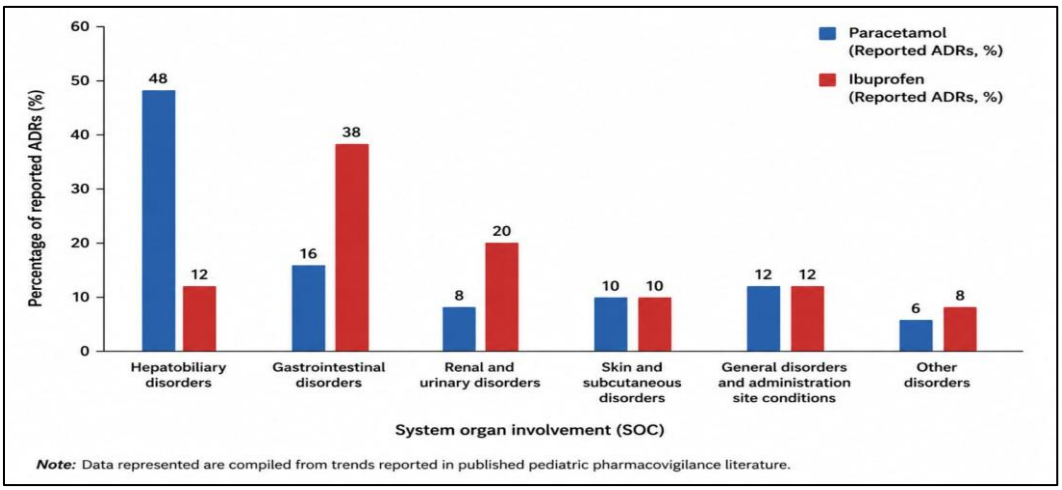

Figure 3: Comparative distribution of reported pediatric adverse drug reactions (ADRs) associated with paracetamol and ibuprofen according to system organ involvement based on pharmacovigilance trend analysis.

- **Clinical Factors Influencing ADR Severity**

The "Severity" of an ADR in children is often exacerbated by medication errors. Data from the Pharmacovigilance Programme of India (PvPI) suggests that a significant percentage of pediatric ADRs are "preventable," arising from dosing inaccuracies rather than the drug's intrinsic toxicity[21].

Pharmacovigilance Data Analysis and Reporting Trends

The analysis of pediatric safety data reveals critical insights into the patterns of adverse drug reactions (ADRs) that are often missed in clinical trials. Unlike adult pharmacovigilance, pediatric data reporting is significantly influenced by caregiver observations and the healthcare professional's clinical suspicion.

Recent trends indicate that while reporting rates have increased globally, the quality of reports concerning infants and neonates remains a challenge due to the complexity of identifying non-specific symptoms as ADRs[22].

- **Global and National Reporting Patterns**

According to the WHO–UMC global database (VigiBase)[8], NSAIDs consistently rank among the leading classes of drugs associated with pediatric ADR reports. In the Indian context, the Pharmacovigilance Programme of India (PvPI)[6] has demonstrated a gradual rise in spontaneous ADR reporting.

However, under-reporting continues to remain a major challenge. Available evidence suggests that for every serious ADR reported, several clinically relevant mild-to-moderate reactions remain undocumented[23].

- **Trend Analysis: Paracetamol vs. Ibuprofen**

Data analysis demonstrates distinct differences in the adverse reaction profiles of the two most commonly used pediatric NSAIDs, namely paracetamol and ibuprofen. Paracetamol-associated ADR reports are predominantly related to accidental dosing errors by caregivers, frequently resulting in hepatic involvement. In contrast, ibuprofen is more commonly associated with gastrointestinal disturbances and transient renal impairment, particularly during dehydration-prone conditions[24].

As illustrated in Figure 3, a comparative analysis of system organ involvement (SOC) reveals significant trends in pediatric ADR reporting. Paracetamol-associated reactions are predominantly hepatobiliary (48%), highlighting its risk for liver involvement. Conversely, Ibuprofen demonstrates a higher frequency of gastrointestinal (38%) and renal (20%) adverse effects compared to paracetamol. This graphical data, compiled from pharmacovigilance literature, underscores the importance of organ-specific monitoring.

- **The Impact of "Off-Label" Use on Data**

A substantial proportion of pediatric pharmacovigilance data indicates that ADRs occur more frequently when medicines are prescribed or administered "off-label," meaning outside the approved age group, dosage range, or formulation specifications. Statistical analyses suggest that the absence of pediatric-specific dosage forms frequently necessitates the splitting or manipulation of adult tablets, thereby increasing the risk of dosing inaccuracies and safety concerns. Such practices contribute significantly to the generation of safety signals reported in national and international databases[25].

Risk Factors Associated with Pediatric NSAID-Induced ADRs

Identifying children who are most vulnerable to adverse drug reactions is a cornerstone of safe pediatric practice. The risk profile of NSAID therapy in children is not uniform; it is influenced by a complex interplay of biological, clinical, and external factors. Recognizing these risks allows clinicians and pharmacists to personalize therapy and prevent avoidable harm[26].

- **Biological and Genetic Vulnerabilities**

Individual variability in drug metabolism significantly impacts a child's susceptibility to toxicity.

Genetic Polymorphisms: Variations in genes encoding enzymes like CYP2C9 and CYP2E1 can alter the metabolic rate of NSAIDs. "Slow metabolizers" may experience prolonged systemic exposure, increasing the risk of adverse events even at standard doses[22].

Developmental Maturity: Neonates and young infants have immature hepatic glucuronidation and lower renal filtration rates. This physiological immaturity reduces their capacity to clear toxic metabolites, such as NAPQI, making them more prone to liver and kidney injury[17].

- **Clinical and Environmental Risk Factors**

The patient's current clinical state can act as a catalyst for severe ADRs.

Dehydration Status: Dehydration is a critical risk factor for Ibuprofen-induced acute kidney injury (AKI). In a dehydrated state, renal blood flow is prostaglandin-dependent; inhibiting these prostaglandins with NSAIDs can lead to rapid renal failure[18].

Nutritional Depletion: Malnourished children often have lower glutathione stores. Since glutathione is essential for neutralizing toxic paracetamol metabolites, its depletion significantly lowers the threshold for hepatotoxicity[27].

Pre-existing Comorbidities: Children with underlying asthma are at a higher risk for NSAID-induced bronchospasm, while those with cardiac or hepatic dysfunction require specialized monitoring for systemic complications[28].

- **Dosing and Administrative Errors**

A substantial portion of pediatric risks is linked to the practical challenges of medication administration.

Weight-Based Complexity: Calculation errors in mg/kg dosing are a leading cause of accidental overdose. The narrow therapeutic window of paracetamol in infants makes even minor calculation errors clinically significant[21].

Household Measuring Tools: The use of non-standardized household spoons instead of graduated oral syringes frequently leads to inaccurate dosing, which is a major driver of preventable ADR signals reported to national databases[29].

The Role of Clinical Pharmacists in Pediatric Pharmacovigilance

The integration of clinical pharmacists into the pediatric multidisciplinary team is a decisive factor in enhancing drug safety and mitigating the risks associated with NSAID therapy. As medication experts, pharmacists bridge the gap between clinical diagnosis and safe therapeutic execution, particularly in the complex environment of pediatric weight-based dosing[29]. Beyond mere dispensing, their role has evolved into active bedside clinical surveillance, ensuring that each dose of analgesic is tailored to the child's unique physiological state.

- **Prescription Audit and Dose Optimization**

Clinical pharmacists perform a vital "gatekeeping" role by auditing prescriptions for accuracy. In pediatrics, this involves a meticulous review of dose-to-weight ratios to prevent sub-therapeutic dosing or toxicity. By cross-verifying the patient's renal and hepatic status with the prescribed drug's clearance profile, pharmacists can

preemptively adjust regimens for high-risk NSAIDs, thereby reducing the incidence of acute kidney injury (AKI)[18]. This proactive intervention is critical in neonatal and infant care, where renal filtration rates are still maturing.

As illustrated in Figure 4, the clinical pharmacist follows a systematic 7-step workflow to ensure medication safety. This cycle begins with a comprehensive prescription audit and extends to post-discharge follow-ups, creating a continuous loop of safety monitoring for pediatric patients.

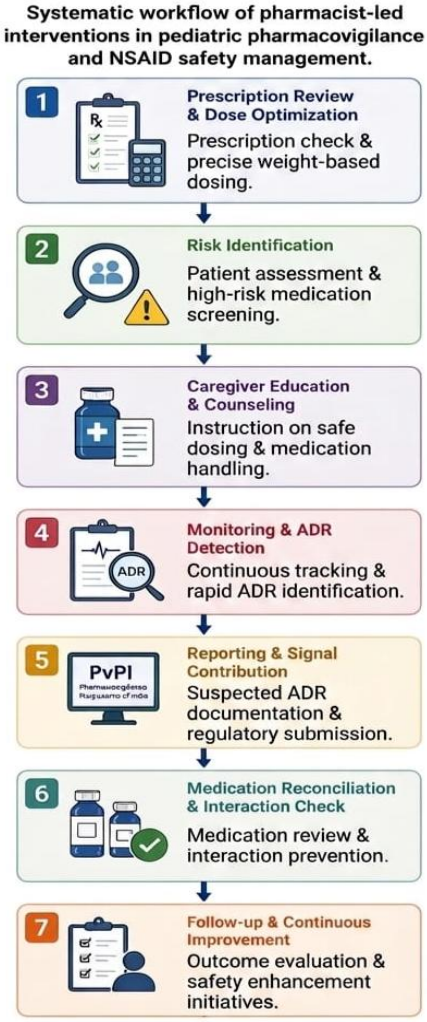

Figure 4: Systematic workflow of pharmacist-led interventions in pediatric pharmacovigilance and NSAID safety management.

- **Spontaneous Reporting and Signal Detection**

Spontaneous reporting remains the backbone of pediatric pharmacovigilance. Clinical pharmacists are uniquely positioned to identify subtle Adverse Drug Reactions (ADRs) that may be overlooked during routine bedside care. Their expertise in causality assessment allows them to distinguish between disease symptoms and true drug-induced events. Their involvement in documenting "suspected" reactions and uploading them to national repositories like the Pharmacovigilance Programme of India (PvPI)[6] ensures that emerging safety signals for pediatric NSAIDs are captured and analyzed at a regulatory level[30].

- **Caregiver Education and Risk Communication**

A significant portion of pediatric ADRs stems from caregiver errors in home settings. Pharmacists play an educational role by demonstrating the correct use of oral syringes over household spoons and counseling on the "hidden" presence of Paracetamol in various Over-the-Counter (OTC) cough and cold preparations[31]. Effective risk communication involves simplifying complex pharmacological concepts into actionable advice for parents, thereby preventing accidental double-dosing or cumulative toxicity[32].

- **Medication Reconciliation and Prevention of Polypharmacy**

Children with chronic conditions often undergo complex treatments involving multiple providers. Clinical pharmacists perform medication reconciliation to identify potential drug-drug interactions between NSAIDs and other therapeutic agents (e.g., aminoglycosides or diuretics). In a hospital setting, this oversight is crucial for preventing "prescribing cascades" and synergistic nephrotoxicity, ensuring that the pediatric patient's overall treatment plan remains cohesive, safe, and effective[33].

Prevention And Safety Strategies for NSAID Use in Children

The mitigation of NSAID-induced adverse drug reactions (ADRs) in pediatric populations is a fundamental safety imperative. Effectively preventing systemic toxicity requires a synergistic approach that integrates precision dosing, clinical vigilance, and proactive caregiver engagement.

- **Precision Dosing and Weight-Based Optimization**

The cornerstone of safety in pediatric pharmacotherapy is the strict transition from empirical age-based dosing to precise weight-based (mg/kg) calculations. Evidence suggests that even minor deviations in dosage can predispose neonates and infants to acute renal stress. Clinicians must utilize standardized volumetric measuring tools and avoid the "rounding up" of doses, particularly in children with borderline body mass index (BMI) or pre-existing constitutional vulnerabilities[34].

- **Vigilant Assessment of Hydration and Renal Perfusion**

Given that NSAIDs exert their effects by inhibiting renal prostaglandins—which are crucial for maintaining glomerular filtration during periods of stress—hydration status must be evaluated prior to therapy initiation. In febrile illnesses where dehydration is a common complication, NSAID therapy should be judiciously suspended or delayed until normovolemia is restored to prevent drug-induced acute kidney injury (AKI)[18].

- **Rational Selection and Minimum Effective Exposure**

A "safety-first" strategy involves adhering to the principle of the lowest effective dose for the shortest clinically necessary duration. Rational drug selection should prioritize NSAIDs with well-characterized safety profiles in children, while avoiding the concurrent administration of multiple NSAIDs or other nephrotoxic agents (e.g., aminoglycosides).

Such polypharmacy significantly elevates the risk of synergistic organ damage[35].

- **Strategic Caregiver Counselling and Error Prevention**

Preventative strategies must extend beyond the hospital ward into the domestic environment. Comprehensive counseling sessions led by pharmacists can drastically reduce accidental toxicity. Caregivers should be educated on identifying the early clinical markers of ADRs and cautioned against the "therapeutic duplication" often seen when combining prescription NSAIDs with over-the-counter (OTC) medications[36].

CONCLUSION

The therapeutic landscape of pediatric medicine relies heavily on the efficacy of Non-Steroidal Anti-Inflammatory Drugs (NSAIDs); however, their safety profile remains a complex clinical challenge. This review emphasizes that children are not merely "small adults" but a distinct patient population with unique physiological and developmental vulnerabilities. The evidence gathered underscores that while NSAIDs are indispensable for managing pain and inflammation, the risk of severe adverse drug reactions (ADRs)—particularly drug-induced acute kidney injury—demands constant clinical vigilance.

The pivotal role of the clinical pharmacist emerges as a cornerstone in bridging the gap between therapeutic intent and patient safety. Through proactive interventions such as meticulous weight-based dose optimization, systematic prescription audits, and comprehensive caregiver counseling, the clinical pharmacist acts as a critical safeguard against preventable medication errors. Furthermore, the integration of structured reporting systems like the Pharmacovigilance Programme of India (PvPI) is essential for the early detection of emerging safety signals in the pediatric demographic.

In conclusion, ensuring the safe use of NSAIDs in children requires a shift from reactive management to a proactive safety culture. By fostering a multidisciplinary approach that combines clinical expertise with compassionate caregiver engagement, the healthcare system can minimize the systemic risks of NSAID therapy. Future efforts should continue to prioritize personalized dosing strategies and robust pharmacovigilance to protect the health and well-being of the pediatric population.

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