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RENAL EFFECTS OF NON-STEROIDAL ANTI-INFLAMMATORY DRUGS: A NARRATIVE REVIEW OF CLINICAL EVIDENCE AND PUBLIC HEALTH IMPLICATIONS IN INDONESIA

Mohamed Yousef Ahmed Eltarjaman[1]*, Diana Laila Ramatillah[1], Kashif Ullah Khan[2]
[1] Faculty of Pharmacy, Universitas 17 Agustus 1945 (UTA'45) Jakarta, Indonesia
[2] Institute of Pharmaceutical Sciences, Khyber Medical University, Peshawar, Pakistan

Abstract
Non-steroidal anti-inflammatory drugs (NSAIDs) are widely used to treat pain, inflammation, and fever in both clinical and community settings. In Indonesia, these medicines are among the most frequently purchased drugs, available through both prescription and over-the-counter channels. Their easy access and frequent long-term use have raised concerns about kidney safety, especially for people with hypertension, diabetes, or previous kidney impairment. This narrative review explores evidence on the renal effects of NSAID exposure across Indonesian clinical contexts. Literature from 2015 to 2025 was identified through searches in Scopus, PubMed, ScienceDirect, Google Scholar, and local university repositories. Overall, renal complications have been reported after both short-term and longer-term NSAID exposure. Hospital studies in Indonesia report acute kidney injury linked to dehydration, infection, or inappropriate dosing, while outpatient data demonstrate gradual declines in kidney function when laboratory monitoring is lacking. Primary care prescribing studies in Indonesia report that most NSAID recipients are female (approximately 58–76%), although hospital pharmacovigilance data do not show consistent demographic patterning of renal injury. Self-medication with NSAIDs remains common, further increasing renal risk in these populations. Recent Indonesian studies also point to risks related to prescribing in primary care, medication-related harm in hospitals, and gaps in medication-safety governance. Despite national and international guidelines discouraging NSAID use in high-risk patients, routine renal monitoring is not consistently practiced. Strengthening pharmacist counselling, structured renal monitoring protocols, and public education strategies may significantly reduce preventable kidney injury while preserving appropriate and equitable access to NSAID therapy in Indonesia.

***Keywords**: NSAIDs, kidney injury, renal monitoring, chronic kidney disease, Indonesia*

Corresponding author:
Mohamed Yousef Ahmed Eltarjaman,
Faculty of Pharmacy, Universitas 17 Agustus 1945 (UTA'45) Jakarta, Indonesia
Email ID: Eltrjman@gmail.com

QR CODE

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INTRODUCTION:

Non-steroidal anti-inflammatory drugs (NSAIDs) are among the most widely used medicines for the management of pain, fever, and inflammation in clinical and community settings16. They are commonly prescribed for musculoskeletal disorders, osteoarthritis, postoperative recovery, and chronic inflammatory conditions, and they are also easily purchased without prescription in many countries, including Indonesia7,23,48. Indonesian outpatient studies also document long-term NSAID use among patients with chronic inflammatory diseases such as rheumatoid arthritis, reinforcing the importance of repeated exposure pathways14.

NSAIDs produce analgesic and anti-inflammatory effects by inhibiting cyclooxygenase enzymes and reducing prostaglandin synthesis25. While this mechanism is therapeutic, prostaglandins also support renal hemodynamics by maintaining renal blood flow and glomerular filtration, especially during physiological stress11. Clinical research has shown that NSAID exposure can increase the risk of acute kidney injury in patients with hypertension, diabetes, dehydration, cardiovascular disease, or pre-existing kidney impairment1,12,29,32. Evidence from long-term cohort studies has also linked prolonged or high-dose NSAID use to a gradual decline in kidney function and higher incidence of chronic kidney disease 8,41.

These concerns are highly relevant in Indonesia, where NSAIDs are consistently reported among the most frequently dispensed analgesics in outpatient departments and community pharmacies31,36,40. Patterns of self-medication are common, and studies from Southeast Asia show that individuals often continue NSAID use for extended periods without medical supervision, even when living with chronic illnesses such as diabetes or hypertension6,10,40. Despite repeated NSAID exposure, outpatient follow-up does not consistently include routine monitoring of renal biomarkers such as serum creatinine and estimated glomerular filtration rate39. At the same time, kidney disease prevalence in Indonesia continues to rise, and many renal complications are detected only when already advanced, reducing opportunities for early intervention21,22.

Given these patterns, there is a need to synthesize existing evidence on NSAID-related renal outcomes within the Indonesian context. A narrative review focused on Indonesia can clarify current knowledge, identify gaps in monitoring and prescribing practices, and support clinical decision making for patient groups at increased renal risk.

RESEARCH METHODOLOGY:

SEARCH STRATEGY

This narrative review was developed through a semi-structured literature search to identify current evidence on the renal effects of non-steroidal anti-inflammatory drugs in different clinical contexts in Indonesia. Several major academic databases were searched: Scopus, PubMed, ScienceDirect, and Google Scholar. To capture Indonesian evidence that may not be indexed consistently in major databases, supplementary searching via Google was used to locate relevant local journals and university thesis repositories (e.g., the UGM repository). This approach helped broaden coverage of Indonesian clinical and community contexts alongside established clinical, pharmacological, and nephrology literature. The search period focused on publications from 2015 to 2025 to capture both foundational mechanisms and recent clinical trends. Studies published in Indonesian were translated into English when necessary.

The search used combinations of controlled vocabulary and free-text keywords. The core terms included “NSAIDs”, “non-steroidal anti-inflammatory drugs”, “kidney function”, “renal impairment”, “acute kidney injury”, “chronic kidney disease”, “renal biomarkers”, “primary care”, “hospital patients”, “long-term use”, “over-the-counter NSAIDs”, “high-dose NSAIDs” , “Southeast Asia” and “Indonesia”. Boolean operators were applied to refine search results. An example search string used on PubMed was: (NSAIDs OR non-steroidal anti-inflammatory drugs) AND (kidney OR renal OR acute kidney injury OR chronic kidney disease) AND (primary care OR outpatient OR hospital OR long-term use OR over-the-counter).

The retrieved records were screened for relevance based on titles, abstracts, and full-text review when necessary. Studies were selected according to their relevance to renal outcomes associated with NSAID exposure, with particular attention to applicability within Indonesian or comparable Southeast Asian healthcare contexts. Duplicate records and studies not meeting inclusion criteria were excluded from the final synthesis.

INCLUSION AND EXCLUSION CRITERIA

Studies were included if they reported clinical outcomes related to renal function following NSAID exposure in humans. Publications were considered regardless of study design, as long as they provided measurable or clinically interpretable renal outcomes. Studies were excluded if they focused only on animal experiments, or non-renal adverse effects. Priority was given to peer-reviewed journal articles. High-quality clinical reviews and 4

systematic reviews were also considered when primary data supported their conclusions. Theses and dissertation studies were also carefully included due to the limited number of peer-reviewed studies published in Indonesia.

The database search was supplemented by manual screening of reference lists from relevant papers to identify additional sources that were not captured through keyword searches. This approach helped ensure that evidence across different clinical settings and patient groups was represented.

LIMITATIONS

Because this is a narrative review, the goal is thematic synthesis rather than exhaustive study capture or formal risk-of-bias scoring. Some Indonesian evidence may also be underrepresented in indexed databases, and the quality of local reports can vary. To address this, the search included local repositories and reference-list screening to improve coverage of Indonesia-relevant findings.

RESULTS:

Prevalence and Patterns of NSAID Use in Indonesia

NSAIDs are among the most widely used medications in Indonesia, both by prescription and through over-the-counter (OTC) access. Several local studies indicate that NSAID consumption remains high among patients with chronic illnesses and those engaging in self-medication. For instance, Kamal (2020) and Sinuraya (2023) reported a significant association between long-term NSAID use and chronic renal failure in Yogyakarta, where self-medication with analgesics was common among CKD patients. Similarly, a community-based survey in Central Java found that nearly 60% of individuals self-medicate with analgesics, often without knowledge of renal safety concerns24. Primary care data further illustrate how NSAIDs are routinely prescribed in outpatient settings. In Jambi City, musculoskeletal disorders accounted for 52% of NSAID prescriptions, with diclofenac sodium as the most frequently used drug, and high compliance with rational prescribing indicators for indication and dosing34. However, evidence from other Puskesmas settings shows inconsistent prescribing quality, including inappropriate NSAID selection and dosing frequency, indicating substantial variation in primary care practice across regions37. Primary-care prescribing audits suggest that most NSAID recipients are female, ranging from 58.0% in Poli-Polia Puskesmas to 76% in Putri Ayu Puskesmas34,37.

Hospital-based research supports these findings. Rudang (2024) identified inappropriate NSAID use as a frequent drug-related problem (DRP) among CKD patients in Medan hospitals38, while Apriani (2019) observed dosing inaccuracies of NSAIDs in 35% of CKD inpatients in a Jakarta military hospital 4. Collectively, these studies highlight inadequate clinical monitoring and public awareness as key contributors to the persistent use of nephrotoxic drugs.

Pathophysiological Mechanisms of NSAID-Induced Renal Dysfunction

The renal toxicity of NSAIDs is primarily attributed to their inhibition of cyclooxygenase (COX) enzymes, which impairs prostaglandin synthesis and reduces renal blood flow. Indonesian pharmacology reviews emphasize this mechanism, noting that COX-1 and COX-2 inhibition decreases afferent arteriolar vasodilation, particularly under states of dehydration or comorbidity15.

Pathophysiologically, NSAIDs may trigger acute interstitial nephritis (AIN), papillary necrosis, and hemodynamically mediated acute kidney injury (AKI). Similar mechanisms are supported internationally, where studies have shown that both systemic and topical NSAIDs were independently associated with acute kidney injury in adults with chronic kidney disease, highlighting that renal risk persists across different routes of administration12,18,45.

Importantly, pharmacodynamic variability and co-morbid factors (e.g., concurrent ACE inhibitors or diuretics) amplify renal risk in Indonesian CKD populations 3.

Clinical Outcomes: NSAID Use and Chronic Kidney Disease Progression

Chronic kidney disease vulnerability in Indonesia is strongly shaped by underlying metabolic and cardiovascular conditions. A cross-sectional study in Tangerang identified diabetes mellitus and kidney stones as dominant predictors of chronic kidney disease, indicating that NSAID-related renal injury often occurs within pre-existing high-risk populations rather than in isolation13.

Indonesian clinical data on NSAID-related renal outcomes show mixed but concerning trends. Muharni (2025) observed a non-significant yet clinically relevant association between long-term NSAID use and CKD progression in Riau Province, suggesting underpowered sample sizes may obscure true risk35. Conversely, Agussalim (2025) identifies unsupervised medication use, including NSAIDs, as a significant contributing factor to chronic kidney disease (CKD) progression and risk among hemodialysis patients in Indonesia2. This is supported by recent hospital-based data from Universitas Indonesia Hospital, which indicate that nephrotoxic drugs remain frequently prescribed to

CKD patients despite established renal risk. Kusumawardani (2025) found that 71.4% of 5

CKD outpatients received at least one potentially nephrotoxic medication, including NSAIDs in 5.8% of cases30. Although most prescriptions were guideline-compliant, approximately 20% were inappropriate, often associated with polypharmacy and incomplete renal monitoring. These findings suggest that the persistence of nephrotoxic prescribing patterns in tertiary care settings may continue to place Indonesian CKD patients at risk of drug-induced renal decline.

Hospital data from East Kutai and Makassar provide nuanced insights. Some findings indicate no significant correlation between NSAID use and acute renal failure incidence, while others note subclinical renal function decline with cumulative exposure17. Other International studies corroborate these observations, demonstrating increased CKD risk and faster eGFR decline among chronic NSAID users, particularly those with hypertension or diabetes19,33,46. Additionally, in a large cohort of nearly 4,000 CKD patients, Zhan (2020) reported that time-updated NSAID use was associated with higher risks of kidney function decline and hospitalization, particularly among Black participants and those with reduced baseline eGFR50.

EPIDEMIOLOGICAL AND PUBLIC HEALTH CONTEXT IN INDONESIA

National surveys such as *RISKESDAS* (2018) report a CKD prevalence of 0.38%, representing a rising national health burden27. This figure appears lower than the regional average, as a systematic review by Suriyong (2022) estimated that CKD stages 3-5 affect approximately 12% of adults in Southeast Asia and 11.2% across low- and middle-income countries in Asia overall. The meta-analysis highlighted that CKD prevalence in Southeast Asia is comparable to global levels and continues to increase alongside non-communicable disease burdens43. Although national surveys in Indonesia do not directly link NSAID exposure to CKD incidence, complementary research by Hustrini (2023) and Agussalim (2025) suggests that unsupervised medication use, including NSAIDs, is a contributing factor to CKD progression in Indonesian populations.

In a different study, Yang (2016) highlighted that in many Asian countries, including Indonesia, acute kidney injury (AKI) frequently arises from preventable causes such as nephrotoxic drug exposure, infections, and delayed clinical recognition49. These patterns suggest that NSAID-Similar challenges are seen across other health systems in Asia and the Middle East. In Bahrain, associated AKI in Indonesia may be amplified by systemic challenges in early detection and renal service accessibility. Beyond pharmacological risks, environmental and geochemical factors may further exacerbate kidney vulnerability in tropical populations. Wimalawansa & Dissanayake (2019) proposed that chronic kidney disease of multifactorial origin (CKDmfo) in agricultural and peri-equatorial regions is driven by long-term exposure to environmental nephrotoxins, dehydration, malnutrition, and hard water containing high ionic components. These overlapping stressors may interact with NSAID-induced reductions in renal perfusion, compounding the overall burden of kidney disease in Indonesia's rural and low-resource settings47.

Data from hospital and community-level studies reveal that public access to NSAIDs without adequate pharmacovigilance persists despite national regulations. Public health interventions in Indonesia also demonstrate that medication-related kidney risk is shaped by governance and self-medication systems. Following the national pediatric kidney injury crisis linked to contaminated syrup formulations, community-based interventions targeting pharmaceutical technical staff and professional associations showed measurable improvements in knowledge regarding safe self-medication practices and medication risk communication42. This widespread availability may partly explain the continued association between NSAID use and renal morbidity in Indonesia.

REGULATORY AND CLINICAL GUIDELINE FRAMEWORKS

Indonesia follows both national and international standards in managing CKD and drug safety. The *Pedoman Nasional Pelayanan Kedokteran Tata Laksana Penyakit Ginjal Kronik (2023)*, issued by the Ministry of Health, recommends strict avoidance of NSAIDs in CKD patients, aligning with KDIGO (2024) global guidelines26,27. Regulatory assessments by BPOM, such as the MOVI-COX® NSAID evaluation, underscore the need for heightened post-marketing surveillance of nephrotoxic drugs in Indonesia9. Despite these measures, clinical implementation remains inconsistent, highlighting the necessity of stronger pharmacovigilance, physician education, and patient awareness. Primary care studies in Indonesia show that guideline-aligned NSAID prescribing is achievable, but variability across health centers indicates the need for standardized implementation and monitoring mechanisms34,37.

Husain (2025) found that 17.4% of CKD patients in primary care received at least one inappropriate

NSAID prescription. Their mixed-method analysis revealed that inappropriate use stemmed from intersecting patient, physician, and system factors including limited renal pharmacology knowledge among primary care physicians, patient demand for fast pain relief, and insufficient prescribing oversight20. These findings mirror Indonesian patterns of patient-driven self-medication and limited routine renal monitoring, indicating that systemic and educational interventions are essential across comparable healthcare contexts.

Based on the synthesized findings, Table 1 summarizes practical renal-safety actions for NSAID use in Indonesian clinical settings.

Patient Group	Key Renal Risk Factors	Suggested Action	Suggested Monitoring Interval	Safer Alternatives
Patients with diagnosed CKD (eGFR <60 mL/min/1.73 m²)	Reduced renal reserve; RAAS inhibitor use; diuretics; polypharmacy	Avoid NSAIDs whenever possible; if unavoidable, use lowest dose for shortest duration	Baseline serum creatinine and eGFR; repeat within 3-7 days of initiation	Paracetamol; Topical NSAIDs (cautiously; systemic absorption still possible); non-pharmacologic therapy
Elderly patients (≥65 years)	Age-related decline in GFR; dehydration risk; multiple comorbidities	Avoid long-term use; ensure hydration; review concurrent medications	Baseline renal function; recheck within 1-2 weeks if repeated use	Paracetamol; physiotherapy; topical analgesics
Patients with hypertension or cardiovascular disease	RAAS inhibitors; diuretics; fluid imbalance	Avoid chronic NSAID therapy; monitor blood pressure and renal function	Baseline renal function; repeat after 1-2 weeks if therapy continues	Paracetamol; non-NSAID analgesics as clinically appropriate
Patients with diabetes mellitus	Diabetic nephropathy risk; microalbuminuria; hyperfiltration injury	Avoid prolonged NSAID use; assess albuminuria when available	Baseline creatinine/eGFR; reassess within 1-2 weeks for repeated use	Paracetamol; dose-adjusted analgesics
Patients on ACE inhibitors/ARBs + diuretics ("triple whammy" risk)	Impaired autoregulation of renal perfusion	Avoid NSAID co-prescribing; pharmacist medication review recommended	Check renal function within 3-5 days of exposure	Non-NSAID analgesics; non-pharmacologic pain management
Patients with dehydration, infection, or acute illness	Reduced renal perfusion; hypovolemia	Withhold NSAIDs during acute illness; encourage fluid replacement	Monitor renal function if NSAIDs were recently used	Paracetamol (short-term); re-evaluate after recovery
Chronic self-medication users (OTC)	Prolonged unsupervised exposure; lack of laboratory monitoring	Pharmacist counselling; limit package size; public education	Recommend renal function testing if use >1-2 weeks	Pharmacist-guided therapy; non-drug strategies

Monitoring intervals are pragmatic practice-based suggestions; local protocols and patient severity should guide timing.

These monitoring intervals are pragmatic, risk-stratified suggestions informed by KDIGO principles (risk minimization/avoidance in CKD) and common nephrology/pharmacovigilance practice, adapted to the Indonesian context. Implementation of such structured monitoring may significantly reduce preventable NSAID-associated renal injury.

DISCUSSION / CRITICAL SYNTHESIS

Evidence across the reviewed literature demonstrates that renal effects associated with NSAID exposure occur in a wide range of clinical and community contexts, extending beyond long-term pain management. Indonesian and international studies indicate that prolonged NSAID use without renal monitoring can lead to a gradual decline in kidney function, even among outpatients without pre-existing renal disease. Muharni (2025) reported a clinically relevant association between long-term analgesic/NSAID exposure and renal outcomes in Riau Province, although statistical significance may be limited by sample size. Hospital-based data from East Kutai show that acute kidney injury (AKI) may develop even during short courses of NSAIDs when dehydration, infection, or concurrent nephrotoxic drug use are present17. These observations are consistent with international findings that renal injury can occur with both acute and chronic NSAID exposure when physiological stressors coexis12,19. In addition, hospital pharmacovigilance studies further demonstrate that renal injury is frequently part of broader medication-related organ toxicity. Observational hospital data using structured causality assessment methods have identified medication-related kidney impairment associated with commonly prescribed inpatient drug classes, including NSAIDs, diuretics, antibiotics, and cardiovascular agents, reinforcing the role of polypharmacy in renal risk44.

Patterns of vulnerability appear consistent across regions. Adults with hypertension, diabetes, cardiovascular disease, or a history of renal impairment have the highest likelihood of developing NSAID-related renal injury. In

Indonesian studies, these comorbidities were frequently identified among patients using NSAIDs for musculoskeletal or general pain complaints38. Age-related decline in renal reserve further heightens sensitivity to prostaglandin inhibition, leading to reductions in glomerular filtration rate (GFR) and sodium retention. The combination of NSAIDs with diuretics or agents affecting the renin-angiotensin-aldosterone system (RAAS) represents an especially important risk factor for renal dysfunction in this population3. The mechanism is well established: cyclooxygenase inhibition impairs vasodilatory prostaglandin synthesis, which reduces renal perfusion pressure, particularly under hypovolemic or hypoperfused states15.

The accessibility of NSAIDs in Indonesia, both through prescription and over-the-counter sales, amplifies these risks. Surveys and hospital audits show that self-medication with analgesics is common, often extending for several weeks or months without medical supervision4,24. National data from *RISKESDAS* (2018) and *RISKESDAS* (2023) confirm increasing CKD prevalence, but laboratory follow-up for patients who repeatedly receive NSAID prescriptions remains inconsistent in many hospitals and clinics27. Several reports describe individuals presenting to tertiary hospitals with moderate-to-severe renal impairment following unsupervised NSAID use for musculoskeletal pain or fever management, often compounded by underlying hypertension or diabetes2,21.

Taken together, the literature suggests that risk depends less on NSAIDs alone and more on the context of exposure: dose, duration, hydration status, comorbidity, and concurrent nephrotoxic drugs. Prolonged or repeated use, inadequate hydration, unrecognized comorbidities, and polypharmacy involving other nephrotoxic drugs collectively increase the likelihood of renal injury. Regular monitoring of serum creatinine or estimated GFR is inexpensive and widely available in Indonesia but remains underutilized in outpatient care. Establishing structured renal monitoring protocols for repeated NSAID users could substantially reduce iatrogenic kidney injury.

Clinical pharmacy services have a particularly important role in risk mitigation. Pharmacists in outpatient and community settings are positioned to identify high-risk users, review medication histories, and counsel patients on hydration, dose limits, and avoidance of concurrent nephrotoxic agents. In hospitals, pharmacist-led medication review programs have demonstrated measurable reductions in drug-related problems among CKD patients38. At the regulatory level, both the *Pedoman Nasional Pelayanan Kedokteran Tata Laksana Penyakit Ginjal Kronik* (2023) and KDIGO (2024) guidelines emphasize avoiding NSAIDs in patients with reduced renal function, reinforcing the importance of coordinated monitoring and counselling within Indonesian clinical systems26,28.

However, similar patterns of non-adherence to NSAID prescribing guidelines have been reported internationally 5 . found that 27% of adults with CKD in Alberta, Canada, were prescribed at least one NSAID over a 7-year period, and only one in five received follow-up renal function testing within 30 days of prescription. These findings illustrate that even in health systems with established monitoring frameworks, inappropriate NSAID use among CKD patients remains common. This global trend highlights the need for stronger clinical governance and prescriber education to align practice with renal safety recommendations.

RESEARCH GAP AND FUTURE DIRECTIONS

Despite expanding international evidence on NSAID-related renal risk, population-specific outpatient data in Indonesia remain limited. Existing studies primarily focus on general prescribing patterns, hospital-based drug-related problems, or national CKD prevalence data, but few have examined renal biomarker outcomes within defined high-risk outpatient populations. Furthermore, structured renal monitoring protocols for repeated NSAID users are inconsistently implemented across Indonesian primary care settings. These gaps highlight the need for focused observational research evaluating renal function changes in clinically vulnerable subgroups to inform safer prescribing frameworks and targeted monitoring strategies in Indonesian healthcare systems.

CONCLUSION:

This narrative review synthesizes evidence from Indonesian and international studies to clarify how non-steroidal anti-inflammatory drug (NSAID) exposure influences renal function across diverse clinical contexts. The findings indicate that renal impairment associated with NSAIDs arises through both acute and chronic mechanisms, often under conditions of dehydration, comorbidity, or concurrent drug use that compromise renal perfusion. Even at therapeutic doses, NSAIDs can precipitate acute kidney injury in hospitalized patients and contribute to gradual kidney function decline among long-term users, particularly in the presence of hypertension, diabetes, or cardiovascular disease.

In Indonesia, where NSAIDs are widely available both by prescription and over the counter, patterns of unsupervised or prolonged use remain a central determinant of renal risk. Hospital-based evidence shows that inappropriate dosing and lack of renal

function monitoring are frequent, while population surveys confirm that community self-medication persists despite public health guidance. These trends are compounded by limited laboratory follow-up in outpatient settings, meaning that early renal impairment often goes undetected until clinically significant decline has occurred.

The reviewed literature supports a clear preventive direction. The primary risk factors are modifiable, and early renal injury can often be reversed when monitoring and counselling are integrated into care. Routine assessment of serum creatinine and estimated glomerular filtration rate during repeat NSAID prescribing, coupled with pharmacist-led reviews of concurrent medications, represents an achievable and cost-effective approach to minimize iatrogenic kidney injury. Public education on hydration, dosing limits, and the dangers of combining multiple NSAIDs is equally critical for reducing community-level risk.

Within Indonesia's evolving health system, aligning clinical practice with national *Pedoman Nasional Pelayanan Kedokteran Tata Laksana Penyakit Ginjal Kronik* (2023) and international KDIGO (2024) renal safety guidelines offers a practical framework for safer NSAID use. Consistent implementation of these measures across primary care, hospital, and pharmacy settings can help preserve access to effective analgesia while substantially reducing preventable renal morbidity.

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