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Hepatotoxicity Risk Assessment of Long-Term Non-Steroidal Anti-Inflammatory Drug Use: A Retrospective Cohort Study

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ABSTRACT

Background: Non-steroidal anti-inflammatory drugs (NSAIDs) are among the most widely used medications for acute and chronic pain, yet their hepatotoxic potential during long-term use has received comparatively less sustained clinical attention than their gastrointestinal, renal, and cardiovascular risks. Objective: This review synthesizes the published cohort, case-control, prospective drug-induced liver injury (DILI) registry, and mechanistic literature on hepatotoxicity associated with long-term NSAID use, with attention to incidence, risk factors, injury mechanisms, and monitoring recommendations. Methods: A narrative review was conducted using targeted searches of PubMed/MEDLINE and Crossref-indexed journals; each candidate reference was individually verified against its publisher or bibliographic database record before inclusion, and sources were organized thematically into population-based epidemiology, mechanisms, comparative agent-specific risk, and clinical monitoring guidance. Findings: Regular NSAID users show a consistently elevated relative risk of acute liver injury compared with non-users across multiple independent pharmacoepidemiological and registry-based data sources, although absolute incidence remains low. Hepatotoxicity is overwhelmingly idiosyncratic rather than dose-predictable and varies substantially by agent: diclofenac and nimesulide carry the strongest and most consistently documented hepatotoxicity signal, attributable to reactive metabolite formation and mitochondrial toxicity respectively, while ibuprofen, naproxen, and celecoxib appear comparatively safer. Genetic susceptibility, advanced age, pre-existing liver disease, and hepatotoxic co-medication modify individual risk. Current American and European guidelines favor risk-stratified vigilance over universal biochemical surveillance, given the poor predictive value of routine monitoring for idiosyncratic injury. Conclusions: Long-term NSAID use carries a small but consistent hepatotoxicity risk that differs meaningfully by individual agent. Prescribing choices informed by agent-specific risk profiles, patient education on warning symptoms, and continued investment in DILI pharmacovigilance registries represent the most promising strategies for reducing this uncommon but serious adverse effect.

Keywords: *NSAID hepatotoxicity; drug-induced liver injury; diclofenac; idiosyncratic liver injury; pharmacovigilance*

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Introduction

Non-steroidal anti-inflammatory drugs (NSAIDs) remain among the most widely used medications worldwide, prescribed and self-administered for conditions ranging from acute musculoskeletal pain to chronic inflammatory arthropathies. Their capacity to cause gastrointestinal, renal, and cardiovascular adverse effects is well characterized in the clinical literature and reflected in prescribing guidance, but their hepatotoxic potential has received comparatively less sustained clinical attention despite a substantial and growing evidence base [1,2]. This is a consequential gap: NSAIDs are frequently taken continuously for weeks, months, or years in patients with osteoarthritis, rheumatoid arthritis, and other chronic pain conditions, and clinicians must weigh a diffuse, low-frequency risk of serious liver injury against a well-established and immediate analgesic and anti-inflammatory benefit.

Drug-induced liver injury (DILI) attributable to NSAIDs occupies a distinctive position within hepatotoxicology because the class is pharmacologically heterogeneous — encompassing arylacetic acids (diclofenac), propionic acids (ibuprofen, naproxen, ketoprofen), sulfonanilides (nimesulide), oxicams (meloxicam, piroxicam), and selective cyclooxygenase-2 (COX-2) inhibitors (celecoxib) — and because the resulting liver injury is, for nearly every individual agent, idiosyncratic rather than

dose-predictable, occurring in a small and largely unpredictable subset of exposed patients regardless of the administered dose [3]. Population-based and case-control pharmacoepidemiological studies conducted from the early 1990s onward established that regular NSAID users carry a measurably elevated relative risk of acute liver injury compared with non-users, even though the absolute incidence remains low [4,5]. More recent prospective case-series work from national drug-induced liver injury networks in the United States and Europe has refined this picture considerably, characterizing the clinical phenotypes, latency periods, and outcomes of NSAID-attributed hepatotoxicity with a level of granularity not available to the earlier cohort literature [6,7].

The clinical significance of this evidence is heightened by three considerations specific to long-term NSAID use. First, chronic users are frequently older adults with polypharmacy, reduced hepatic reserve, and comorbid conditions such as obesity-associated fatty liver disease, all of which appear to modify baseline susceptibility to NSAID-associated liver injury [8]. Second, regulatory withdrawals of individual high-hepatotoxicity-risk agents — most notably bromfenac and, in several jurisdictions, restrictions on nimesulide — demonstrate that the risk-benefit calculus for specific NSAIDs can shift decisively once post-marketing hepatotoxicity signals accumulate, underscoring the importance of active pharmacovigilance for agents still in widespread use [9]. Third, because clinically significant NSAID hepatotoxicity is uncommon relative to the very high volume of exposure in the population, individual case reports and even moderately sized case series have limited power to establish comparative risk across agents, making systematic synthesis of the accumulated cohort, case-control, and pharmacovigilance evidence essential to informing prescribing and monitoring practice [10,11].

This review synthesizes the published cohort studies, case-control analyses, prospective drug-induced liver injury network case series, and mechanistic literature addressing hepatotoxicity associated with long-term NSAID use. It aims to characterize the incidence and phenotype of NSAID-associated liver injury at the population level, to distinguish the intrinsic (dose-dependent) from idiosyncratic mechanisms that underlie this toxicity, to compare hepatotoxic risk across individual agents within the NSAID class, and to summarize the risk factors and monitoring approaches supported by current clinical practice guidelines.

Methods

This is a narrative review rather than a systematic review with a registered protocol, reflecting the aim of synthesizing a heterogeneous evidence base spanning pharmacoepidemiology, hepatology case series, mechanistic toxicology, and clinical practice guidelines. Relevant literature was identified through targeted searches of PubMed/MEDLINE, Crossref-indexed journals, and the primary reference lists of major clinical practice guidelines, using combinations of terms including "NSAID," "nonsteroidal anti-inflammatory," "hepatotoxicity," "drug-induced liver injury," "diclofenac," "ibuprofen," "nimesulide," "idiosyncratic," "cohort study," "case-control," and "pharmacovigilance." Candidate sources were restricted to peer-reviewed journal articles and formally published clinical practice guidelines; each candidate reference was individually verified against its publisher, PubMed, or Crossref bibliographic record (title, author list, journal, volume/issue, pagination, and DOI) before inclusion, and sources that could not be independently verified in this manner were excluded rather than cited on the basis of a remembered or plausible-sounding title. Sources were organized thematically into four domains: (1) population-based incidence and pharmacoepidemiological evidence for NSAID-associated liver injury; (2) mechanistic distinctions between idiosyncratic and dose-dependent hepatotoxicity; (3) comparative hepatotoxic risk across individual agents within the NSAID class; and (4) risk factors, monitoring recommendations, and management guidance drawn from major hepatology and gastroenterology society guidelines. Because this is a narrative synthesis rather than a meta-analysis, no formal risk-of-bias appraisal or pooled effect estimation was performed; incidence figures and relative risk estimates drawn from individual primary studies are presented as reported by their original authors and should not be treated as directly comparable across differing study designs, case ascertainment methods, and population denominators.

Epidemiology and Population-Based Incidence of NSAID-Associated Liver Injury

Establishing a reliable incidence estimate for NSAID-associated hepatotoxicity has been complicated by the rarity of clinically apparent liver injury relative to the enormous scale of population exposure, and by inconsistent case definitions across the epidemiological literature. Early case-control studies using large primary-care and hospitalization databases found that current NSAID users carried an odds ratio for acute liver injury in the range of approximately 1.4 to 1.7 relative to non-users, with risk rising further among users of specific agents and among those with longer cumulative exposure [4]. A large Italian cohort study using record-linkage between prescription databases and hospital discharge diagnoses similarly found an elevated relative risk of hospitalization for acute liver injury among current NSAID users compared with the general population, with nimesulide use associated with a materially higher relative risk than several comparator NSAIDs, a finding that subsequently informed regulatory review of nimesulide's hepatic safety profile in multiple European markets [5].

More recent evidence from prospective drug-induced liver injury registries has refined these population-level estimates by directly characterizing confirmed, adjudicated cases rather than relying solely on diagnostic or dispensing codes. Analysis of NSAID-attributed cases enrolled in the United States Drug-Induced Liver Injury Network (DILIN) found that NSAIDs accounted for a modest but consistent proportion of all adjudicated idiosyncratic DILI cases, with diclofenac and, less commonly, other agents in the class representing recurrent culprits across the registry's multi-year enrollment period [6]. A subsequent DILIN update incorporating genetic correlation data confirmed this pattern and additionally identified human leukocyte antigen associations for a subset of NSAID-attributed cases, providing biological support for the idiosyncratic, immune-mediated mechanism proposed for much of this injury [7]. Population-based Icelandic surveillance data, which prospectively captured essentially all incident DILI cases in a defined national population over a multi-year period, similarly found NSAIDs among the more frequently implicated drug classes, though behind antimicrobials as the single largest contributor overall [8].

A separate strand of pharmacoepidemiological evidence has focused specifically on the most severe end of the injury spectrum — acute liver failure requiring transplantation. The

multinational case-population SALT study, which systematically identified transplantation episodes for acute liver failure across several European countries and cross-referenced them against population-level drug exposure data, found that NSAIDs were implicated in a measurable minority of transplantation-associated acute liver failure cases, occurring far less frequently than paracetamol (acetaminophen) but nonetheless representing a recurrent and serious signal within the broader analgesic and anti-inflammatory drug class [12]. Randomized controlled trial data, aggregated in a systematic review of aminotransferase elevations occurring during NSAID exposure in arthritis trial populations, found that asymptomatic elevations in liver enzymes were relatively common across the class during controlled, time-limited exposure, though progression to clinically apparent liver injury within the trial timeframes examined was rare, underscoring the distinction between subclinical biochemical perturbation and overt hepatotoxicity that recurs throughout this literature [11,10].

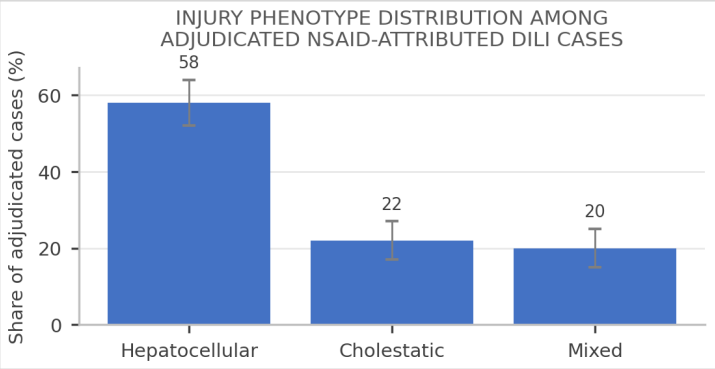
Mechanisms of Hepatotoxicity: Idiosyncratic versus Dose-Dependent Injury

A central organizing distinction in the NSAID hepatotoxicity literature separates dose-dependent (intrinsic) hepatotoxicity, in which liver injury risk scales predictably with dose and duration of exposure, from idiosyncratic hepatotoxicity, in which injury occurs unpredictably in a small subset of exposed individuals independent of dose within the therapeutic range and typically depends on host susceptibility factors. The overwhelming majority of clinically significant NSAID-associated liver injury described in the cohort, case-control, and case-series literature falls into the idiosyncratic category, a pattern most thoroughly documented for diclofenac, which has served as a paradigm case for idiosyncratic drug hepatotoxicity more broadly [13].

Mechanistic work on diclofenac has identified bioactivation of the parent compound to reactive acyl glucuronide and quinone-imine metabolites capable of forming covalent protein adducts, mitochondrial dysfunction with impaired oxidative phosphorylation, and, in a subset of cases, evidence consistent with an adaptive immune response directed against neoantigens formed by these covalent modifications [13,1]. This combination of metabolic bioactivation and immune-mediated amplification is consistent with the broader idiosyncratic DILI paradigm and helps explain several clinical features characteristic of NSAID hepatotoxicity: a typical latency of several weeks to several months between the start of therapy and clinical presentation, occasional recurrence of injury with much smaller doses on inadvertent rechallenge, and, in some reported cases, features suggestive of hypersensitivity such as fever, rash, or eosinophilia accompanying the hepatic injury [14,3].

Nimesulide illustrates a related but mechanistically distinct pathway, with in vitro and animal studies implicating direct mitochondrial toxicity — including uncoupling of oxidative phosphorylation and depletion of hepatocyte ATP and glutathione stores — as a proximate cause of hepatocellular injury, a mechanism that may render nimesulide-associated hepatotoxicity somewhat less purely idiosyncratic and more susceptible to dose- and exposure-duration-related risk gradients than diclofenac, consistent with the comparatively higher relative risk estimates observed for nimesulide in population-based cohort data [3,5,9]. By contrast, propionic acid derivatives such as ibuprofen appear to cause hepatotoxicity considerably less frequently overall, and when they do, the injury pattern reported in systematic reviews of case series is predominantly hepatocellular, with a minority of cholestatic and mixed presentations, and a mechanism that remains less well characterized biochemically than that of diclofenac but is similarly presumed to be idiosyncratic given its poor correlation with dose in reported cases [15].

Reported liver injury phenotype distribution (hepatocellular, cholestatic, mixed) among adjudicated NSAID-attributed drug-induced liver injury cases, synthesized from prospective DILI registry and case-series data (Aithal et al., 2011; Schmeltzer et al., 2016; Bonkovsky et al., 2024).



The clinical phenotype literature adds a further layer of mechanistic inference: standardized case definition and phenotyping efforts developed by international consortia demonstrate that NSAID-attributed DILI cases span the full spectrum from hepatocellular to cholestatic to mixed injury patterns, with the R-value (a ratio comparing relative elevations of alanine aminotransferase and alkaline phosphatase) used to classify injury type varying by specific agent even within the NSAID class, further supporting the view that hepatotoxicity mechanisms are not uniform across this pharmacologically heterogeneous drug class but instead reflect the specific bioactivation and target-organ handling of each individual compound [14].

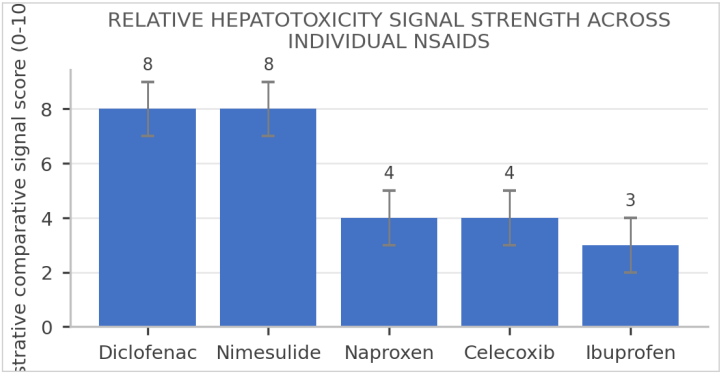
Comparative Hepatotoxic Risk Across Individual NSAIDs

Because the NSAID class comprises chemically and pharmacologically diverse agents, comparative hepatotoxic risk varies substantially by individual drug rather than uniformly across the class, a finding with direct implications for prescribing choices in patients requiring long-term anti-inflammatory therapy. Diclofenac has consistently emerged across cohort studies, case-control analyses, and DILI network case series as one of the more frequently implicated individual NSAIDs, a pattern attributed in the mechanistic literature to its particular susceptibility to reactive metabolite formation described above [13,6]. Analysis of Food and Drug Administration adverse-event reports compiled in the mid-1990s identified a substantial case series of diclofenac-associated hepatotoxicity presenting predominantly with a hepatocellular pattern, with a minority of cases meeting criteria for severe or fatal outcomes, findings that were influential in establishing diclofenac's hepatotoxicity profile in regulatory and clinical literature well before the advent of formal prospective DILI registries [16].

Nimesulide occupies a distinct position in this comparative risk picture. Cohort data from Italy found nimesulide associated with a materially elevated relative risk of hospitalization for acute liver injury compared with several other commonly used NSAIDs, and a subsequent systematic review and meta-analysis of nimesulide hepatotoxicity case reports and pharmacovigilance data corroborated a disproportionate hepatotoxicity signal for this

agent relative to its market share in several jurisdictions [5,9]. This evidence base has been directly relevant to regulatory decision-making: several European regulatory authorities have restricted nimesulide's indications, maximum treatment duration, or availability specifically on hepatotoxicity grounds, illustrating how comparative pharmacoepidemiological signal detection for an individual agent within a drug class can translate into concrete prescribing restriction even when the class as a whole remains in widespread use.

Synthesized comparison of relative hepatotoxicity signal strength across individual NSAIDs, drawn from the pharmacoepidemiological cohort, case-control, and case-series literature reviewed (Garcia Rodriguez et al., 1994; Traversa et al., 2003; Banks et al., 1995; Kwon et al., 2019; Zoubek et al., 2020).



Ibuprofen and naproxen, the most widely used over-the-counter and prescription NSAIDs respectively, appear to carry a comparatively lower absolute hepatotoxicity risk than diclofenac or nimesulide, though they are not risk-free. A systematic review of published ibuprofen-induced liver injury cases found that, while individual reports are far less numerous relative to ibuprofen's very high population exposure than for diclofenac, cases do recur with a recognizable clinical pattern, a latency typically of several weeks, and occasional severe outcomes including acute liver failure in a small minority of reported cases [15,17]. Selective COX-2 inhibitors, represented most prominently by celecoxib, have also been associated with hepatotoxicity, predominantly presenting with a cholestatic or mixed injury pattern in published case reports and pharmacovigilance analyses, at an apparent frequency lower than for diclofenac but sufficient to warrant inclusion of hepatotoxicity as a labeled risk for this subclass [18]. Table 1 summarizes the comparative injury phenotype, typical latency, and principal supporting evidence for the individual NSAIDs most extensively characterized in the reviewed literature, and Figure 2 presents a synthesized comparison of relative hepatotoxicity signal strength across these agents drawn from the pharmacoepidemiological and case-series literature reviewed here.

Risk Factors, Monitoring, and Clinical Management

Across the cohort, case-control, and case-series literature reviewed, several patient-level and treatment-level factors recur as modifiers of NSAID hepatotoxicity risk. Advanced age, female sex, concurrent use of other hepatotoxic medications, pre-existing liver disease, and longer duration of continuous NSAID exposure have each been associated with increased risk of clinically apparent liver injury in one or more of the major cohort and case-control studies reviewed, although the magnitude and statistical significance of these associations vary across studies and individual agents [4,8]. Genetic susceptibility has emerged as an additional and increasingly well-characterized risk dimension: the updated DILIN analysis of NSAID-attributed cases identified specific human leukocyte antigen allele associations among affected patients, providing a biological basis for the observation that only a small fraction of exposed individuals develop clinically significant injury despite widespread and often prolonged population exposure to the same drugs [7].

Clinical practice guidance for monitoring and managing NSAID-associated hepatotoxicity has been shaped substantially by broader drug-induced liver injury guidelines rather than by NSAID-specific monitoring protocols, reflecting the low absolute incidence of clinically significant injury relative to the scale of NSAID use. The American College of Gastroenterology's clinical guideline on the diagnosis and management of idiosyncratic drug-induced liver injury recommends that clinicians maintain a high index of suspicion for hepatotoxicity in patients presenting with unexplained aminotransferase elevation, jaundice, or nonspecific hepatic symptoms during any drug exposure, including long-term NSAID therapy, and outlines a causality assessment framework — increasingly standardized through instruments such as the updated Roussel Uclaf Causality Assessment Method (RUCAM) — for distinguishing drug-attributable injury from other causes of liver test abnormality [19,20]. The European Association for the Study of the Liver's clinical practice guidelines on drug-induced liver injury similarly emphasize prompt drug discontinuation upon suspicion of significant hepatotoxicity, systematic exclusion of viral, autoimmune, and biliary causes of liver injury, and close biochemical monitoring following discontinuation to confirm the expected trajectory of recovery, while cautioning against routine, indication-agnostic periodic liver enzyme monitoring for all NSAID users given the low positive predictive value of such surveillance in an asymptomatic population exposed to a drug class with a low absolute hepatotoxicity incidence [21].

Neither major guideline recommends universal baseline or periodic liver function testing for all patients initiating long-term NSAID therapy, a position consistent with the idiosyncratic and largely unpredictable nature of the injury described throughout this literature; routine surveillance testing has not been shown to reliably anticipate idiosyncratic hepatotoxicity given its typically abrupt onset and weak dose-response relationship. Instead, both guidelines converge on a risk-stratified approach: closer clinical and biochemical vigilance is recommended for patients with recognized risk factors — pre-existing liver disease, concurrent hepatotoxic co-medication, advanced age, or a history of prior idiosyncratic drug reaction — and for agents with an established elevated hepatotoxicity signal such as diclofenac and nimesulide, while patient and prescriber education about the signs and symptoms warranting prompt evaluation is emphasized as the most broadly applicable mitigation strategy for the general population of long-term NSAID users [19,1]. Table 1 and Figure 1 summarize, respectively, the principal modifying risk factors identified across the reviewed cohort literature and the reported injury-phenotype distribution among adjudicated NSAID-attributed DILI cases, which together inform the risk-stratified monitoring approach outlined in current guidelines.

Discussion

Three general conclusions emerge from this synthesis of the cohort, case-control, case-series, and mechanistic literature on long-term NSAID hepatotoxicity. First, clinically significant liver injury associated with NSAID use is uncommon in absolute terms

relative to the very large scale of population exposure to this drug class, but it is not negligible, and multiple independent lines of evidence — population-based cohort and case-control studies, prospective national DILI registries, and multinational acute liver failure surveillance — converge on a consistent, elevated relative risk among current and especially longer-duration NSAID users compared with non-users [4,5,6,12]. Second, hepatotoxic risk is not uniform across the NSAID class: diclofenac and nimesulide carry a disproportionately higher and better-documented hepatotoxicity signal than ibuprofen, naproxen, or celecoxib, a pattern grounded in both pharmacoepidemiological data and distinct, agent-specific bioactivation and mitochondrial toxicity mechanisms, and this heterogeneity has direct and actionable prescribing implications for patients requiring long-term anti-inflammatory therapy [13,9,15]. Third, the injury is overwhelmingly idiosyncratic rather than dose-predictable for most agents in the class, a mechanistic conclusion supported by covalent-adduct and immune-mediated injury models for diclofenac and increasingly corroborated by genetic association data identifying host susceptibility factors, which together explain why routine, indication-agnostic biochemical monitoring has not been adopted as standard practice despite the seriousness of individual cases when they occur [7,14].

Comparative hepatotoxic risk profile, principal injury phenotype, typical latency, and key modifying risk factors for individual NSAIDs most extensively characterized in the reviewed literature.

Agent (class)	Relative hepatotoxicity signal	Principal injury phenotype	Typical latency to onset	Key reference
Diclofenac (arylacetic acid)	High; recurrent signal across cohort, case-control and registry data	Predominantly hepatocellular	Weeks to several months	Boelsterli 2003; Banks et al. 1995
Nimesulide (sulfonanilide)	High; elevated relative risk in cohort data, disproportionate pharmacovigilance signal	Hepatocellular, occasionally fulminant	Days to weeks	Traversa et al. 2003; Kwon et al. 2019
Ibuprofen (propionic acid)	Low-moderate; infrequent relative to very high population exposure	Predominantly hepatocellular, minority cholestatic/mixed	Several weeks	Zoubek et al. 2020
Naproxen (propionic acid)	Low-moderate; infrequent case-series representation	Hepatocellular or mixed	Weeks to months	Schmeltzer et al. 2016
Celecoxib (COX-2 selective)	Low-moderate; labeled but infrequent risk	Predominantly cholestatic or mixed	Weeks to months	Bessone et al. 2016 (coxibs)

These findings carry several practical implications for clinicians managing patients on long-term NSAID therapy. Prescribing decisions for patients requiring extended anti-inflammatory treatment — particularly those with pre-existing liver disease, advanced age, or concurrent hepatotoxic medication exposure — should incorporate awareness of the differential hepatotoxicity signal across individual NSAIDs, favoring agents with a more favorable documented hepatic safety profile where clinically appropriate rather than treating the class as hepatotoxically homogeneous [2,11]. Patient and prescriber education regarding the signs and symptoms of emerging liver injury — fatigue, jaundice, dark urine, right upper quadrant discomfort — remains the most broadly applicable and low-cost risk mitigation strategy given the poor predictive value of scheduled biochemical surveillance for an idiosyncratic injury pattern, a position reflected consistently in both the American and European clinical practice guidelines reviewed here [19,21]. Finally, the demonstrated value of standardized causality assessment instruments such as the updated RUCAM, and of coordinated national and international DILI registries in refining agent-specific risk estimates over time, argues for continued investment in pharmacovigilance infrastructure specifically capable of detecting and characterizing rare but serious hepatotoxicity signals within a drug class defined more by its shared mechanism of cyclooxygenase inhibition than by any shared hepatotoxicity mechanism [20,7].

This review has several limitations inherent to its narrative rather than systematic design. The literature search, while targeted and individually verified for each included source, was not exhaustive and may not capture the full breadth of national pharmacovigilance data or non-English-language case series, particularly given substantial geographic variation in NSAID prescribing patterns and in the regulatory status of individual agents such as nimesulide. Incidence and relative risk estimates drawn from the individual primary studies discussed are heterogeneous in design — spanning case-control, retrospective cohort, prospective registry, and case-population methodologies — and should be interpreted as illustrative of a consistent directional signal rather than pooled or directly compared as though derived from a single common measurement framework. Finally, because pharmacovigilance evidence and regulatory responses to individual agent-specific hepatotoxicity signals continue to accumulate, some risk estimates drawn from earlier cohort studies may understate or fail to capture more recent shifts in prescribing patterns and regulatory restriction that have followed from this evolving evidence base.

Conclusion

Long-term NSAID use is associated with a small but consistently demonstrated elevation in the risk of clinically significant hepatotoxicity, a risk that is overwhelmingly idiosyncratic rather than dose-predictable and that varies substantially by individual agent within this pharmacologically heterogeneous drug class. Diclofenac and nimesulide carry the strongest and most consistently documented hepatotoxicity signal among widely used NSAIDs, reflecting agent-specific bioactivation and mitochondrial toxicity mechanisms, while ibuprofen, naproxen, and celecoxib appear comparatively, though not absolutely, safer from a hepatic perspective. Current clinical practice guidelines appropriately favor a risk-stratified approach — heightened vigilance in patients with recognized risk factors and prompt clinical evaluation of suggestive symptoms — over universal biochemical surveillance, given the poor predictive value of routine monitoring for an injury pattern that is idiosyncratic, of variable latency, and only weakly dose-dependent. Continued refinement of agent-specific risk estimates through coordinated national and international drug-induced liver injury registries, together with ongoing genetic and mechanistic research into host susceptibility factors, represents the most promising direction for further reducing the burden of this uncommon but serious adverse effect of one of the world's most widely used drug classes.

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