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Beyond the Warning Label: Renal, Neurological, and Tendon Toxicity Associated with Diclofenac, Metronidazole, and Ciprofloxacin — A Review

Loso Judijanto
IPOSS Jakarta
Corresponding Author: Loso Judijanto losojudijantobumn@gmail.com

A R T I C L E I N F O

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A B S T R A C T

Diclofenac, metronidazole and ciprofloxacin are clinically valuable medicines, yet their adverse-event profiles are often presented as deterministic organ-damage warnings. This qualitative literature review interprets 60 peer-reviewed journal articles published from 2020 to 2026, comparing renal dysfunction associated with non-steroidal anti-inflammatory drugs, peripheral and central neurotoxicity associated with metronidazole, and fluoroquinolone-associated tendon disorders. Purposive, iterative source selection and reflexive thematic interpretation identified five themes: renal susceptibility and interacting prescriptions; heterogeneous neurological syndromes; tendon outcomes and molecule-specific uncertainty; methodological differences across safety evidence; and opportunities for prevention, risk communication and reporting. Cross-study contrasts are central to the interpretation. Canadian and Danish investigations produced different metronidazole-associated neurological risk estimates, while indication-specific fluoroquinolone comparisons yielded differing tendon outcomes. Evidence from carefully selected NSAID recipients likewise cautions against assuming inevitable kidney injury from exposure alone

INTRODUCTION

1. The Double-Edged Nature of Effective Pharmacotherapy

Medicines are valuable precisely because they modify human physiology or microbial survival, yet the same interventions can produce unintended injury when target selectivity is incomplete, exposure is excessive, physiological reserves are limited or monitoring fails. Drug safety is therefore more nuanced than classifying products as simply safe or dangerous. It requires assessment of clinical indication, probable therapeutic benefit, patient susceptibility, concomitant medication and the nature of an emerging symptom. Contemporary reviews of medication-related harm show that adverse reactions remain an important clinical and health-system burden, while a meaningful proportion of injury may be avoided through better prescribing and surveillance (Insani et al., 2021; Khalil and Huang, 2020; Hodkinson et al., 2020). Public-facing health information often communicates these risks through memorable one-drug, one-organ pictures. Such pictures may raise awareness, but they can also turn an association into an unconditional claim and obscure the distinction between transient symptoms, rare serious events and common complications of the underlying disease. The probability of an adverse reaction cannot be reconstructed from a drawing or an isolated relative-risk estimate. Studies of how patients interpret medication information suggest that additional context may sometimes decrease comprehension, while statistical concepts such as odds ratios and numbers needed to harm are frequently misunderstood; effective risk communication therefore requires careful selection of both language and quantitative framing (Kelly et al., 2022; Yount et al., 2024; Curran et al., 2022). The image motivating this review depicts diclofenac alongside injured kidneys, metronidazole alongside damaged peripheral nerves and ciprofloxacin alongside muscle pain. The three associations invite a productive scientific comparison because the drugs belong to different therapeutic classes and plausibly affect different tissues, although the specific outcome labels require refinement. Diclofenac is a non-steroidal anti-inflammatory drug, metronidazole is an antimicrobial active against anaerobic pathogens and certain protozoa, and ciprofloxacin belongs to the fluoroquinolone antibiotics. None should be regarded as universally harmful, and none can be evaluated apart from the illness being treated, its alternatives and the vulnerability of the recipient (LaForge et al., 2023; Daneman et al., 2021; Baggio and Ananda-Rajah, 2021).

2. The Urgency of a Comparative Clinical-Safety Perspective

Kidney injury associated with non-steroidal anti-inflammatory drugs is relevant because renal autoregulation can become particularly dependent on prostaglandins during reduced effective circulating volume or impaired perfusion. Renal consequences may be clinically silent until biochemical abnormalities appear, and the risk may be magnified by particular combinations of antihypertensives, diuretics and analgesics. This is not a claim that every dose of diclofenac causes kidney damage. Rather, it highlights the way ordinary prescribing decisions interact with dehydration, pre-existing chronic kidney disease, heart failure and medication combinations to create recognizable patterns of potentially preventable harm (Perazella and Rosner, 2022; Klomjit

and Ungprasert, 2022; Drożdżal et al., 2021). Neurological toxicity associated with metronidazole differs from renal toxicity both in its manifestations and in the sources from which it is recognized. Observational work has identified associations with neurologic diagnoses after exposure, while case reports and radiological investigations describe cerebellar dysfunction, encephalopathic presentations and peripheral sensory symptoms. Importantly, a subsequent Danish case-time-control investigation did not identify a statistically significant association, emphasizing the need to assess the comparator, diagnostic ascertainment and patient population rather than assuming universal agreement. The distinction between peripheral neuropathy and metronidazole-associated encephalopathy remains essential, as does consideration of liver disease, comorbidity and cumulative treatment exposure (Daneman et al., 2021; Andersen et al., 2024; Lee et al., 2024; Sørensen et al., 2020). Fluoroquinolone-associated tendon disorders pose a third pattern of potential injury. Tendinitis, tendon pain, tendon rupture and nonspecific myalgia are not interchangeable clinical terms, while pharmacovigilance databases and longitudinal studies do not always produce equivalent relative-risk estimates. Recent investigations range from cohort analyses showing positive associations to molecule-stratified and comparator-based studies finding heterogeneous or non-significant results for ciprofloxacin in certain populations. The practical question is not whether all fluoroquinolones inevitably damage tendon tissue, but how treatment selection and follow-up should incorporate a clinically recognized yet variable concern (Baik et al., 2020; Sangiorgio et al., 2024; Chang et al., 2022).

3. Review Aim, Questions and Contribution

This qualitative literature review addresses six connected questions: how diclofenac may impair renal physiology; what peripheral and central neurological syndromes may follow metronidazole use; how ciprofloxacin and related fluoroquinolones are associated with tendon injury; which patient and prescribing characteristics modify those risks; how conflicting forms of evidence should be interpreted; and which measures may prevent avoidable harm. The discussion deliberately crosses disciplinary boundaries, bringing together nephrology, infectious diseases, neurology, musculoskeletal medicine, pharmacoepidemiology and patient-safety research. It seeks a synthetic explanatory model rather than a pooled estimate across clinically incommensurable outcomes (Baker and Perazella, 2020; Quickfall et al., 2021; Duman et al., 2025; Coste et al., 2023). The article makes three contributions. First, it translates a simplified safety illustration into three precisely defined clinical risk domains while maintaining each medication's therapeutic role. Second, it compares the epistemic strengths of cohorts, meta-analyses, pharmacovigilance signals, pharmacological explanations and case descriptions, paying explicit attention to contradictory findings. Third, it offers an integrated preventive framework spanning patient evaluation, treatment selection, counseling, symptom recognition, drug review and event reporting. These contributions matter because better knowledge does not necessarily translate into fewer

adverse events unless it is incorporated into routine clinical processes (Hodkinson et al., 2020; Cervantes-Arellano et al., 2024; Sadeq et al., 2022).

LITERATURE REVIEW

1. Concepts of Drug-Related Injury and Causality

An adverse drug reaction is a harmful and unintended response associated with medicinal exposure, whereas the broader idea of an adverse drug event may include preventable errors and injury occurring during use without a definitively established pharmacological cause. These concepts become especially difficult to separate when the suspected outcome is common in the untreated population. Acute kidney injury can accompany sepsis and dehydration; sensory neuropathy can result from metabolic conditions; and tendon disorders develop through mechanical overload or degeneration. Sound attribution therefore requires clinical chronology, compatible findings, assessment of competing explanations and an appropriately cautious reading of population-level evidence (Insani et al., 2021; Khalil and Huang, 2020; Perazella and Rosner, 2022). The central conceptual distinction is between a safety signal, statistical association, biological plausibility and credible causal inference. A disproportionate share of spontaneous reports mentioning a drug and an outcome is useful for hypothesis generation, but the reporting system generally lacks a reliable exposed-population denominator and is vulnerable to stimulated reporting. Observational databases may estimate comparative risk if their design adequately handles measured confounders, ascertainment and time at risk, yet residual confounding remains possible. Mechanistic research strengthens plausibility but does not automatically establish the clinical incidence or severity of injury in humans (Davis et al., 2023; Coste et al., 2023; Jiao et al., 2024). Preventability is also an interpretive rather than purely pharmacological property. Some harm reflects unavoidable susceptibility despite appropriate care, while other events occur during unnecessary prescribing, excessive exposure, failure to identify interactions or delayed recognition of warning symptoms. The avoidability of a particular event cannot be determined from the identity of the medicine alone. Research on medication-related injury emphasizes the importance of health-system context, and studies of antibiotic-related adverse reactions suggest that improved prescribing quality and pharmacovigilance can influence the burden of preventable problems (Hodkinson et al., 2020; Tran et al., 2023; Curran et al., 2022).

2. The Pharmacological Basis of Diclofenac-Associated Kidney Injury

Diclofenac inhibits cyclooxygenase pathways and reduces prostaglandin formation, contributing to its analgesic and anti-inflammatory effects. In the kidney, however, prostaglandins help preserve perfusion under particular physiological stresses, especially by supporting afferent arteriolar vasodilatation. Suppression of this adaptive response can lower glomerular filtration in a patient whose renal blood flow is already compromised. Additional potential mechanisms include interstitial nephritis and other forms of drug-associated renal pathology, making it inaccurate to collapse the clinical spectrum into a single process of direct tissue poisoning (Perazella and Rosner, 2022; Klomjit and

Ungprasert, 2022; Drożdżal et al., 2021). The possibility of kidney injury depends strongly on baseline function and context. In stable, adequately hydrated patients with preserved renal reserve, a short exposure may carry a different risk profile from regular treatment during acute illness or in the presence of chronic kidney disease. The literature therefore emphasizes careful individual assessment rather than a universal dichotomy between forbidden and harmless NSAIDs. Differences among agents, prescribing patterns, outcome windows and the route of administration further complicate cross-study interpretation, particularly when studies explore chronic decline rather than acute, hemodynamically mediated deterioration (Teo et al., 2023; Baker and Perazella, 2020; Wan et al., 2021). A clinically important model is the so-called triple whammy, typically involving a diuretic, a renin–angiotensin system inhibitor and an NSAID. The diuretic can reduce effective volume, the renin–angiotensin inhibitor alters efferent arteriolar tone and NSAID-related prostaglandin suppression can diminish afferent vasodilatation. This combination may compromise the kidney's compensatory mechanisms. The explanatory model is compelling, but risk should still be assessed with reference to the patient, dose, treatment duration, clinical situation and the limitations of the studies used to identify the association (Calvo et al., 2023; Kunitsu et al., 2022; LaForge et al., 2023).

3. Metronidazole-Associated Neurological Syndromes

Metronidazole is widely used when anaerobic and selected protozoal pathogens are plausible treatment targets. Neurological safety literature distinguishes at least two clinically different forms of adverse outcome: peripheral neuropathy and a central neurotoxic syndrome often described as metronidazole-induced encephalopathy. Peripheral involvement may present as numbness, tingling, burning discomfort or altered distal sensation. Central involvement may include ataxia, speech disturbance, confusion or other neurological abnormalities, occasionally accompanied by characteristic magnetic resonance imaging findings. The diversity of presentations is one reason that a simple illustration of an injured peripheral nerve is insufficient to depict the whole spectrum (Sørensen et al., 2020; Quickfall et al., 2021; Ricci et al., 2020). The pathophysiology of metronidazole neurotoxicity is not completely settled. Proposed explanations include altered neuronal metabolism, oxidative injury and other effects on vulnerable neural structures, but mechanistic hypotheses should not be equated with established human causal pathways. Imaging reports have described signal changes involving the dentate nuclei and other structures, sometimes together with an initially puzzling clinical presentation. Such patterns may assist diagnosis when compatible clinical features and exposure history are present; they do not replace systematic evaluation for other toxic, infectious, metabolic or vascular causes of neurological dysfunction (Lala et al., 2021; Datta et al., 2022; Martins et al., 2024). Several reports suggest improvement after withdrawal of metronidazole, especially when an encephalopathic syndrome is recognized early, whereas some patients with prolonged peripheral neuropathy experience more persistent symptoms. Case-based evidence is valuable for recognizing unusual presentations but cannot establish how often they occur in

the population receiving appropriate treatment. Risk interpretation also needs to separate cumulative exposure from an assertion that a single numerical duration or dose automatically causes toxicity. Prospective data with careful neurological phenotyping are still needed to clarify susceptible subgroups and recovery trajectories (Sahu et al., 2025; Gussago et al., 2022; Takahashi et al., 2025).

4. Ciprofloxacin and Fluoroquinolone-Associated Tendon Harm

Ciprofloxacin inhibits bacterial DNA gyrase and topoisomerase IV and is effective against selected susceptible bacterial infections. Concerns about fluoroquinolone-associated musculoskeletal toxicity have led to scrutiny of tendonitis, rupture and symptoms that could be confused with nonspecific muscle pain. Achilles tendon manifestations receive particular attention, although other tendons can be affected. A biologically plausible process involves adverse effects on tenocyte function, extracellular-matrix maintenance and oxidative balance, but mechanisms inferred from cell or animal systems should not be treated as direct predictions of clinical event rates (Baggio and Ananda-Rajah, 2021; Duman et al., 2025; Jonville-Béra et al., 2025). Molecule- and indication-specific interpretation is essential. The fluoroquinolone class includes agents with different uses, pharmacokinetics and evidence profiles, so a class-level warning does not demonstrate an identical magnitude of tendon risk for every member. An active-comparator study among patients treated for community-acquired pneumonia observed a higher short-term association with tendon injury, whereas a later study from the same research group among patients treated for urinary tract infection did not demonstrate a statistically significant difference. Together with agent-stratified cohorts, these findings underscore potential variation across both drugs and the conditions prompting prescription (Baik et al., 2020; Fleming et al., 2024; Fleming et al., 2025; Sangiorgio et al., 2024).

5. Stewardship, Pharmacovigilance and Interpretive Synthesis

Antimicrobial stewardship is not simply a strategy for reducing prescription volumes. It asks whether an antimicrobial is warranted, whether the selected agent is appropriate for the likely pathogen and anatomical site, and whether dose, route and duration match the clinical indication. This approach protects effectiveness while limiting unnecessary exposure to potential toxicities. For metronidazole and ciprofloxacin, stewardship can be particularly relevant when long courses are contemplated, alternative agents exist or patients have vulnerability factors requiring closer review (Sharland et al., 2022; Sadeq et al., 2022; Azamgarhi et al., 2024). Pharmacovigilance supplies a complementary perspective because clinical trials and routine care observe different populations. Electronic health records can support detection of patterns and follow-up of clinically documented outcomes, while spontaneous reports may identify unexpected combinations of symptoms. However, neither information stream is self-interpreting. Duplicate reports, varying diagnostic thresholds, incomplete medication histories, confounding and uneven awareness affect what is seen. Educational interventions and active feedback may strengthen the culture of reporting without transforming every reported association into confirmed

causality (Putri et al., 2024; Cervantes-Arellano et al., 2024; Davis et al., 2023; Jiao et al., 2024). A qualitative synthesis is particularly suitable when the purpose is explanatory comparison rather than estimating one pooled treatment effect. The present topic contains multiple drug classes, organs, endpoints and research traditions; forcing them into a single numerical effect would sacrifice meaningful clinical distinctions. Reflexive thematic analysis offers a disciplined way to identify recurring concepts, examine contradictions and make the analyst's interpretive choices visible. Its value depends on transparent argumentation and a willingness to record exceptions rather than on mechanistic coding counts or the appearance of a systematic search (Braun and Clarke, 2021; Braun and Clarke, 2022; Byrne, 2022).

METHODOLOGY

1. Design and Epistemological Orientation

This article uses a qualitative literature review with a clinically interpretive, comparative orientation. It is not a systematic literature review, does not claim a comprehensive capture of all relevant publications and does not present a PRISMA flow diagram or a pooled effect size. The unit of interpretation is a proposition supported by a defined body of research, such as a plausible renal mechanism, a documented neurological syndrome or a contested comparative risk estimate. The aim is to build an explanatory account that is clinically useful without implying quantitative precision unsupported by the diverse studies being interpreted (Braun and Clarke, 2021; Braun and Clarke, 2022; Byrne, 2022). Peer-reviewed journal articles published from 2020 to October 2026 were eligible for consideration, with the revised purposively assembled reference base comprising 60 articles dated 2020–2026. Source identification combined iterative topic-oriented literature searching, citation chaining and targeted updates when newer studies clarified, reinforced or contested an interpretation. The source clusters covered NSAID-associated renal injury; metronidazole-associated peripheral or central neurological events; fluoroquinolone-associated tendon outcomes; and medication safety, pharmacoepidemiology, clinical communication and qualitative interpretive methods. Selection was based on relevance, clinical specificity, study design and the need to include conflicting evidence. This is not an exhaustive search or a preregistered review, and no PRISMA record counts or pooled summary effects are claimed (Braun and Clarke, 2022; Andersen et al., 2024; Fleming et al., 2025; Rieck et al., 2026).

2. Reading, Coding and Evidence Appraisal

Each paper was read for the clinical claim it could legitimately support, the population and drug exposure studied, the outcome's ascertainment and the type of inference available. Core analytic distinctions included mechanism versus observation, individual presentation versus population association, class effect versus molecule-specific effect and relative versus absolute risk. Studies with an explicit denominator or comparator were given greater weight for occurrence and comparative-risk arguments than isolated cases or disproportionality signals. The latter were nevertheless retained when they supplied distinctive

phenotypic information or a credible reason to investigate a harm more closely (Coste et al., 2023; Jiao et al., 2024; Daneman et al., 2021). Thematic interpretation proceeded through repeated comparison of arguments within and between drug groups. Initial codes such as renal hemodynamics, cumulative neurological exposure, tendon matrix dysfunction, susceptibility, problematic co-prescription, information limitations and preventive action were consolidated into broader themes. Disconfirming evidence was not discarded; discrepant fluoroquinolone results were specifically preserved as a test of the framework's explanatory capacity. This approach aligns with methodological guidance that regards theme development as an explicit analytical process rather than an automatically reproducible counting exercise (Braun and Clarke, 2021; Braun and Clarke, 2022; Byrne, 2022).

3. Boundaries and Safeguards

The review gives priority to human clinical relevance but consults mechanistic explanations where they help connect exposures and outcomes. It does not provide personalized treatment advice, substitute for product labeling or decide the suitability of an individual patient's medicine. Because the sources differ in geography, population, indications and outcome definitions, cross-drug ranking of absolute risk would be misleading. DOI-based links are supplied for traceability, although full-text access may require a subscription; neither journal publication nor indexing alone guarantees freedom from bias, and all interpretations should remain proportionate to study design (Wan et al., 2021; Baik et al., 2020; Davis et al., 2023). Several design-specific threats are especially important here. Confounding by indication arises when the infection or inflammatory condition prompting therapy independently alters the outcome risk, while exposure misclassification may occur if recorded prescriptions are not actually taken. Surveillance bias can exaggerate associations when monitored patients receive more laboratory tests or diagnostic coding, and reports collected following strong warnings may be disproportionately numerous. Finally, neurological and musculoskeletal endpoints range from symptoms to imaging abnormalities or surgically documented rupture. These limitations motivate triangulation rather than reliance on any one class of evidence (Davis et al., 2023; Coste et al., 2023; Jiao et al., 2024).

RESULTS

1. Theme I: Diclofenac and Renal Susceptibility

The first major theme is a dependence on renal physiological reserve rather than a deterministic response to diclofenac. Review literature consistently explains how cyclooxygenase inhibition can compromise prostaglandin-dependent renal hemodynamics in patients already experiencing impaired perfusion. Acute kidney injury may be temporally related to an NSAID, but the clinical context helps determine how convincingly the medicine contributed. Volume depletion, cardiovascular illness, baseline renal disease and concurrent drugs may jointly alter the probability of an adverse outcome. Such contextual dependence makes a blanket statement that a certain tablet strength inevitably produces kidney damage scientifically untenable (Perazella and Rosner, 2022;

LaForge et al., 2023; Klomjit and Ungprasert, 2022). The pattern of evidence spans physiological explanation, disease-specific observational research and comparative analyses of non-steroidal anti-inflammatory drugs. A review of NSAID-associated renal damage describes more than one renal pathway, while an analysis of the comparative risk of individual NSAIDs draws attention to important heterogeneity across exposures. A contemporary cohort involving patients with ankylosing spondylitis examined long-term NSAID associations with chronic kidney disease, illustrating how baseline inflammation, disease severity and treatment selection complicate interpretation. The combined literature supports renal caution without establishing one universal safe or toxic dose for all patients (Drożdżal et al., 2021; Wan et al., 2021; Hwang et al., 2024). A recent retrospective cohort of hospitalized medical patients adds a useful counterpoint to generalized NSAID risk statements. In that cohort, systemic NSAID users were younger and had fewer comorbidities than unexposed patients, and propensity-adjusted analyses did not detect a statistically significant increase in short-term acute kidney injury. This result should not be interpreted as proof of renal safety for all patients, because treatment selection, residual confounding and limited drug-specific ascertainment remain relevant. Rather, it supports the distinction between a biologically credible hazard and the observed risk among carefully selected recipients (Rieck et al., 2026; Baker and Perazella, 2020). Risk in patients with established chronic kidney disease merits particular emphasis. A population-based examination of NSAID prescribing in this population documents why analgesic use must be evaluated in relation to vulnerability and clinical practice, while research considering NSAID administration routes underscores the need to avoid generalizing all exposure contexts as equivalent. Renal toxicity may be influenced by systemic exposure as well as the illness prompting pain management. Furthermore, studies of children demonstrate that pediatric acute kidney outcomes warrant their own interpretation; findings in hospitalized children cannot be automatically transported to elderly adults or ambulatory patients (Gong et al., 2022; Armstrong et al., 2023; Teo et al., 2023). Combination therapy is a recurring and potentially modifiable determinant. A nested case-control study of diuretics, renin–angiotensin–aldosterone-system inhibitors and NSAIDs or metamizole investigated hospital admission for acute kidney injury, strengthening concern about convergent reductions in renal autoregulatory capacity. A Japanese adverse-event database study examined the timing of acute kidney injury reported with related combination regimens. These sources differ substantially in causal leverage: a clinically designed case-control investigation can estimate comparative associations, whereas spontaneous reports provide timing patterns but not reliable incidence. Considered together, they make co-prescription review a high-priority preventive task (Calvo et al., 2023; Kunitsu et al., 2022; Baker and Perazella, 2020). Kidney safety assessment therefore requires more than asking whether the patient takes diclofenac. Clinicians should consider the analgesic indication, existing renal disease, hydration status, concomitant medicines, possible acute illness and the appropriateness of monitoring. A symptom-free patient may still develop an abnormal creatinine result, while

oliguria or edema can signal a problem without being specific to NSAID exposure. The evidence supports personalized benefit–risk review and clinical follow-up rather than self-directed dose adjustment or categorical avoidance of all NSAIDs by everyone. This reflects a nuanced contemporary discussion of NSAID use in chronic kidney disease (Baker and Perazella, 2020; Perazella and Rosner, 2022; Armstrong et al., 2023). Clinical decision support also requires outcome-based evaluation rather than an assumption that more recommendations necessarily prevent injury. A randomized clinical trial of individualized early advice for hospitalized patients with acute kidney injury increased completion of several recommended care processes but did not significantly reduce the primary composite clinical outcome. Although this trial did not test diclofenac exposure specifically, it illustrates an important implementation distinction between improved documentation or adherence and demonstrable reductions in patient harm. Renal-prescribing safeguards should therefore be assessed for clinical effectiveness as well as operational uptake (Aklilu et al., 2024).The preceding renal synthesis is condensed in Figure 1 as a mechanism-and-modifier diagram. The arrows indicate a physiologically plausible pathway involving compromised renal perfusion, while the lower boxes depict heightened patient vulnerability and interacting medicines. This distinction helps the reader avoid interpreting a standard diclofenac tablet as proof that acute kidney injury must occur.

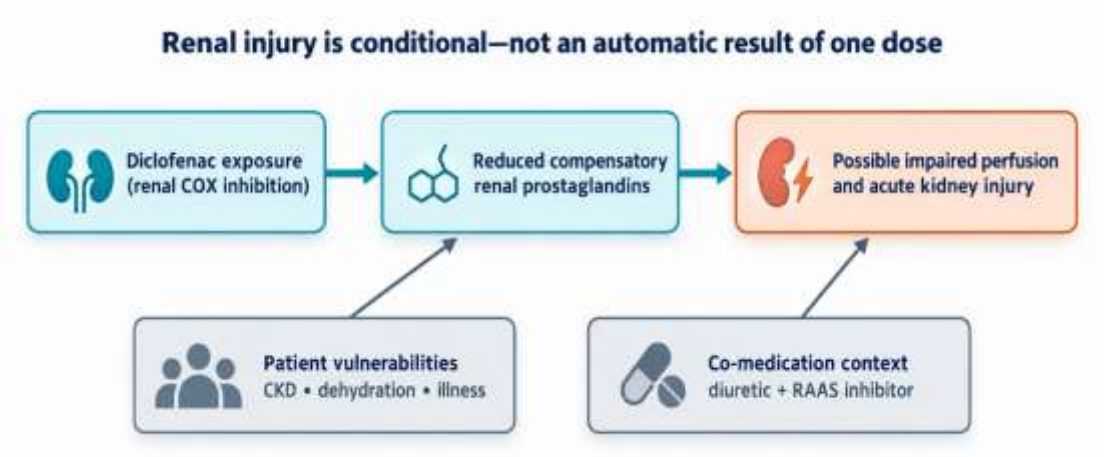

Figure 1. Context-Dependent Hemodynamic Pathway for NSAID-Associated Acute Kidney Injury.

Figure 1 summarizes how diclofenac-associated cyclooxygenase inhibition may reduce a protective renal response when patients are already susceptible to impaired perfusion. The two lower boxes are susceptibility and interaction modifiers, not additional proof that every exposed patient will develop acute kidney injury. This distinction explains why hydration, comorbidity and co-medication assessment are crucial before a categorical renal-safety claim can be made.

2. Theme II: Metronidazole and the Peripheral–Central Neurotoxicity Continuum

The second theme encompasses more than the peripheral-nerve injury shown in the original graphic. In a population-based nested case-control study among older adults treated with metronidazole, exposure was associated with a higher likelihood of documented neurological events relative to an antibiotic comparator; the absolute occurrence of clinically recognized diagnoses remained uncommon in that specific population. The analysis strengthens concern beyond isolated anecdotes yet cannot by itself resolve causality for every patient. Outcomes involving peripheral neuropathy and central neurological dysfunction should be considered separately, especially when presenting risk to patients or selecting a clinical monitoring strategy (Daneman et al., 2021; Quickfall et al., 2021; Sørensen et al., 2020). However, a nationwide Danish case-time-control study provides a materially different result. Among 476,066 first-time metronidazole prescriptions, the reported 100-day cumulative incidence was 0.016% for peripheral neuropathy and 0.002% for cerebellar dysfunction or encephalopathy; the estimated odds ratio for the combined neurological outcomes was 0.98 (95% CI 0.59–1.64), without a statistically significant association. The Canadian study of older adults reported an adjusted odds ratio of 1.43 (95% CI 1.26–1.63) compared with clindamycin, but its case definition, design and patient mix differ from those of the Danish investigation. Because the event definitions, time-related comparison strategies and populations are not equivalent, their estimates should be discussed as conflicting and non-interchangeable rather than averaged or selectively preferred (Daneman et al., 2021; Andersen et al., 2024). A more recent investigation of hospitalized patients explored the frequency and risk factors for metronidazole-associated neurological adverse events. It identified clinical susceptibility factors that included severe comorbidity, highlighting why adverse effects should not be assumed to depend on dose alone. A patient with significant liver dysfunction may have an exposure history and competing neurological differential diagnosis quite different from those of a healthy outpatient with a brief prescription. The observed frequency also reflects ascertainment and the population studied, not the probability for every recipient of an oral metronidazole tablet (Lee et al., 2024; Ji et al., 2024; Daneman et al., 2021). Peripheral neuropathy cases describe sensory symptoms that may appear during longer or repeated courses, sometimes persisting beyond medication withdrawal. A report of two patients with neuropathy reinforces the importance of cumulative exposure and formal clinical assessment of sensory abnormalities, but it is not a denominator-based study. Similarly, combined encephalopathy and polyneuropathy cases show that central and peripheral manifestations can coexist. Such observations are valuable for constructing symptom-aware clinical pathways, although the possibility of comorbidity-associated neuropathy, other neurotoxic medications and infection-related illness must remain part of the diagnostic assessment (Gussago et al., 2022; Sahu et al., 2025; Sørensen et al., 2020). Central toxicity frequently attracts attention because symptoms such as ataxia, dysarthria, confusion and altered mental status may trigger urgent neuroimaging. Published clinical and

radiological reports describe recognizable patterns in selected patients, including signal abnormalities in structures involved in coordination. A report emphasizing electroencephalographic observations further illustrates the diversity of investigations pursued when metronidazole-associated encephalopathy is suspected. However, imaging patterns do not independently prove a drug cause, and a credible diagnosis still requires temporal coherence, consideration of alternative neurological illnesses and clinical review of the medication history (Ricci et al., 2020; Lala et al., 2021; Datta et al., 2022). Recent reports also demonstrate that the phenotype is not uniform. Cases involving spondylodiscitis, cirrhosis and transient cortical lesions broaden the differential range and show why a single prototypical image should not dictate diagnosis. Patients may be receiving complex antibiotic regimens for prolonged infections, making attribution particularly demanding. Published descriptions often report improvement following withdrawal of the suspected agent, but clinical course and degree of recovery may differ across manifestations. These findings support early review of unexplained neurological symptoms during metronidazole therapy while avoiding an inference that every patient will recover fully and quickly (Martins et al., 2024; Ji et al., 2024; Takahashi et al., 2025). Across neurological reports, cumulative dose and treatment duration appear relevant but are insufficient as stand-alone diagnostic rules. The literature contains patients with different exposure histories and underlying illnesses; thresholds cited in narrative discussions are best considered heuristics rather than guarantees of safety below a specific value. Short courses should not be portrayed as devoid of any possible adverse event, while extended courses should receive proportionate clinical attention without automatic presumption of injury. Interpreting these data requires careful distinction between what cohort studies can estimate, what a case series can reveal and what mechanistic hypotheses remain unresolved (Daneman et al., 2021; Lee et al., 2024; Gussago et al., 2022).

3. Theme III: Ciprofloxacin, Tendon Pathology and Outcome Heterogeneity

The third theme is the need to replace the vague phrase muscle damage with defined musculoskeletal outcomes. Fluoroquinolone-associated tendinopathy may initially manifest as tendon discomfort or inflammation, while rupture represents a more severe structural event. Myalgia can coexist but is not synonymous with collagen disruption or loss of tendon integrity. Reviews describe possible oxidative stress and extracellular-matrix effects, although the relative contributions of these mechanisms in humans are incompletely established. The clinical implication is to identify the tissue and symptom under discussion before comparing published risk estimates or deciding what warning information should accompany treatment (Baggio and Ananda-Rajah, 2021; Duman et al., 2025; Jonville-Béra et al., 2025). A pharmacovigilance analysis of reports from 2016–2021 identified disproportionate reporting patterns for tendonitis and tendon rupture with fluoroquinolones. Such data are useful for identifying unusual or serious possible adverse events, but they do not contain a reliable total number of exposed, event-free individuals. Consequently, a reporting odds ratio must not be translated into a patient-level probability. The limitations are especially salient for drug classes that have received extensive

media attention, safety communications and labeling changes, which can influence the decision to report a suspected event (Shu et al., 2022; Jiao et al., 2024; Ly et al., 2023). Population-based results complicate any assertion of a single class-wide causal magnitude. A nationwide Taiwanese cohort reported a positive association between fluoroquinolone exposure and tendon disorders, while a study of approximately one million older US Medicare beneficiaries found a non-significant ciprofloxacin association for a combined tendon-rupture outcome under its specific analytical design. These observations do not automatically negate one another. Differences in molecule, comparator antibiotic, indication, ascertainment, follow-up window, age distribution and confounder control could create divergent estimates. The correct synthesis retains the possibility of a real risk while acknowledging genuine uncertainty about the magnitude in specific populations (Baik et al., 2020; Chang et al., 2022; Sangiorgio et al., 2024).
An indication-specific comparison further illustrates how study design influences apparent fluoroquinolone effects. Among patients treated for community-acquired pneumonia, Fleming and colleagues reported greater odds of tendon injury within one month for fluoroquinolone recipients than for non-fluoroquinolone recipients (odds ratio 1.419; 95% CI 1.188–1.698). Their subsequent study among patients with urinary tract infection did not find a statistically significant elevation in tendon-injury outcomes against alternative antibiotics. These estimates refer to different source populations and clinical decisions; they do not establish that one infection causes or protects against tendon damage. They instead reinforce the importance of indication-specific, active-comparator research, explicit time windows and transparent adjustment for potential confounding (Fleming et al., 2024; Fleming et al., 2025). A molecule-stratified systematic review and meta-analysis of Achilles tendon complications offers another perspective by examining agents separately, but its pooled estimates must be interpreted in light of the included studies and event definitions. Research focused on Achilles rupture continues to emphasize the need for careful exposure definitions and comparisons. Importantly, interpreting a relative increase without its baseline rate can overstate the perceived danger for low-risk patients, while ignoring a small absolute excess may be equally unwise when the potential consequence is severe. Treatment decisions therefore require both a clinically meaningful absolute context and adequate attention to seriousness (Sangiorgio et al., 2024; Rasmussen et al., 2024; Baik et al., 2020).
Certain clinical situations deserve closer appraisal even if the precise degree of risk is debated. Existing tendon pathology, recent tendon repair, advanced age and concomitant glucocorticoid therapy are relevant when clinicians review a fluoroquinolone prescription and consider an alternative. A matched cohort study of individuals undergoing primary tendon repair found higher rates of subsequent reoperation among those exposed to fluoroquinolones after repair, although the observational design cannot eliminate confounding by indication or other unmeasured differences. Research in adolescents, by contrast, shows why adult data should not be assumed to apply identically to younger groups with different baseline injury rates (Waters et al., 2023; Ross et al., 2021; Azamgarhi et al., 2024).

The consequences of a genuinely serious tendon event may also extend beyond the initial diagnosis. A Finnish analysis of compensated fluoroquinolone-related tendon injuries documented substantial healthcare use and economic burden among selected claimants. Its sample was defined by successful compensation claims, however, so the findings inform severity and service use among affected people rather than the incidence of injury across all fluoroquinolone prescriptions. Such evidence should supplement, not replace, denominator-based comparative-risk studies (Kuula, Backman and Blom, 2021; Baik et al., 2020). Regulatory and stewardship responses have also affected prescription practice. Evaluation of European label changes documents alterations in prescribing trends following safety-related restrictions or warnings, while contemporary reviews stress that antimicrobial selection must balance effectiveness against the possibility of serious adverse effects. Such interventions are not evidence that every prescribed course was inappropriate, nor should they be used to justify substituting a less-effective antibiotic for a serious infection. They do reinforce an evidence-based preference for choosing a fluoroquinolone only when its expected value is appropriate to the indication, susceptibility profile and available alternatives (Ly et al., 2023; Jonville-Béra et al., 2025; Azamgarhi et al., 2024). Figure 2 places the evidence supporting fluoroquinolone tendon concerns into three analytically separate categories. The study types answer different questions, and the final box shows why their conclusions should be interpreted together rather than treated as identical measures of risk. This comparison clarifies the apparent tension between pharmacovigilance signals and molecule-specific observational findings.

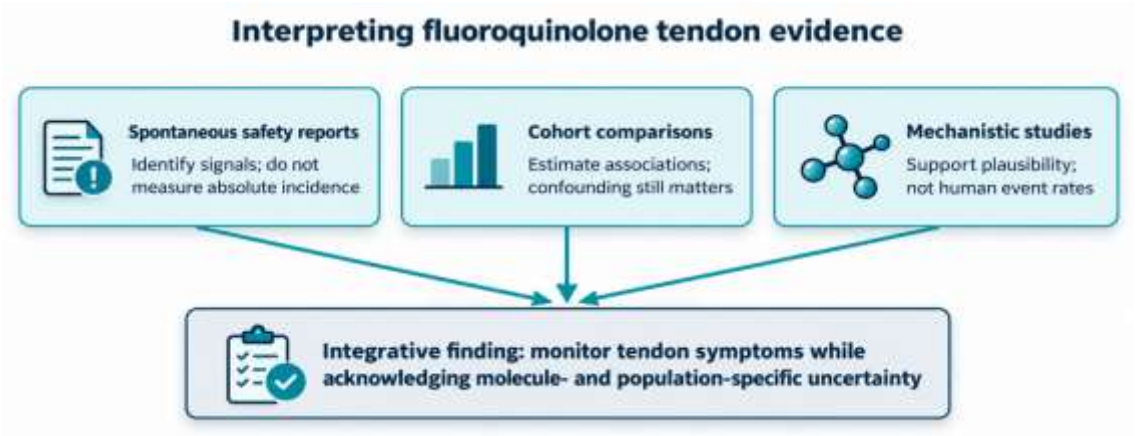

Figure 2. Triangulating Evidence Concerning Fluoroquinolone-Associated Tendon Events

Figure 2 illustrates why evidence about ciprofloxacin and tendon injury should be integrated by study purpose instead of pooled informally. Spontaneous reports may identify a safety signal, cohorts can make comparative estimates under particular assumptions, and mechanistic studies lend biological plausibility. The integrative judgment is therefore caution coupled with recognition of drug-specific and population-specific uncertainty.

4. Theme IV: Shared Risk Modifiers and Unequal Evidence Strength

The three drug classes reveal a common structure: exposure enters a biological system whose vulnerability is already shaped by other illnesses, medicines and physiological reserves. Diclofenac is especially important in settings of impaired renal autoregulation; metronidazole requires attention to neurological symptoms, exposure history and organ dysfunction; and ciprofloxacin warrants consideration of tendon vulnerability and treatment alternatives. The effect modifiers are not fully interchangeable, however. A patient's risk of NSAID-related acute kidney injury cannot be calculated from an estimate of fluoroquinolone-associated tendon rupture, and metronidazole-related encephalopathy cannot be collapsed into a generic measure of cumulative harm (LaForge et al., 2023; Lee et al., 2024; Duman et al., 2025). Evidence architecture also varies systematically across the three topics. Kidney research combines established physiology, clinical reviews, cohort comparisons and drug-interaction studies. Metronidazole reports contain important imaging and syndromic descriptions, supplemented by more informative population investigations that attempt to measure event occurrence. Fluoroquinolone safety combines pharmacovigilance, epidemiological comparison, mechanism-oriented reviews and post-repair cohorts. Each approach resolves some ambiguities while creating others. Recognizing which type of question each study can answer is more informative than giving all publications equal weight simply because they appear in peer-reviewed journals (Calvo et al., 2023; Daneman et al., 2021; Baik et al., 2020; Coste et al., 2023). Time is a further unifying dimension. Renal function may deteriorate during an acute physiological stress, a neurological syndrome may be recognized after cumulative or repeated antibiotic treatment, and tendon symptoms may prompt evaluation within a clinically relevant period surrounding fluoroquinolone exposure. However, the relevant window cannot be imposed identically across all three outcomes. Exposure onset, lag, discontinuation, repeated prescriptions and clinical follow-up must be appropriate to the particular event, while outcome coding can introduce delays or ambiguities. Poor temporal definitions can weaken even a very large observational dataset (Kunitsu et al., 2022; Lee et al., 2024; Rasmussen et al., 2024; Davis et al., 2023). The interpretive errors most likely to mislead patients are the absence of denominators, treating all reported events as confirmed drug causation and attributing a nonspecific symptom to a single medicine without differential diagnosis. In some cases, common symptoms such as pain, dizziness or sensory change may be effects of the underlying condition, competing medications or unrelated illness. Conversely, uncertainty should not justify ignoring a plausible warning sign with potentially serious consequences. A mature safety culture treats symptoms as reasons for timely assessment, not as proof of a single causal explanation (Insani et al., 2021; Coste et al., 2023; Jiao et al., 2024). This same interpretive problem affects how probability is communicated to patients. A review of lay understanding of statistics found that odds ratios, likelihood ratios and numbers needed to treat or harm often hinder comprehension, while percentage and frequency formats do not perform identically across audiences. Experimental medication-information research also

showed that adding qualitative contextual text may sometimes increase cognitive load and worsen comprehension of side-effect information. Consequently, clarity requires selective, tested messages and explicit denominators where available—not merely longer warning leaflets or more dramatic illustrations (Yount et al., 2024; Kelly et al., 2022).

5. Theme V: Prevention, Communication and Reporting

Preventive practice begins before a medicine is started. Reviewing the indication, likely benefit, patient comorbidities, potential interactions, prior adverse reactions, baseline symptoms and the availability of alternatives helps distinguish necessary exposure from avoidable exposure. This process is especially important in polypharmacy, in which changing one medicine may alter physiological risks created by several others. The goal is not indiscriminate refusal of useful drugs but a documented decision that the selected treatment provides a reasonable clinical benefit given the particular risk profile and circumstances (Hodkinson et al., 2020; Tran et al., 2023; Sadeq et al., 2022). Monitoring and patient communication are complementary rather than competing strategies. Where renal risk is clinically significant, assessment may include kidney function, volume status and the presence of acute illness; for metronidazole, new numbness, paresthesia, ataxia or confusion deserves prompt review; and for fluoroquinolones, new focal tendon pain or signs suggesting tendon injury warrants timely professional assessment. These warning cues are not substitute diagnostic criteria or instructions for self-treatment. Their usefulness depends on understandable language, realistic absolute-risk information when estimates are available, a reliable point of contact and a system that responds appropriately to patient concerns (Baker and Perazella, 2020; Quickfall et al., 2021; Baggio and Ananda-Rajah, 2021; Yount et al., 2024). Pharmacovigilance becomes more informative when clinicians document exposure timing, indication, co-medications, diagnostic findings, withdrawal and outcomes. Electronic record–based signals can help identify trends that may not be visible in isolated practice, whereas spontaneous reporting can bring unusual presentations into view. Neither source is intrinsically sufficient to establish incidence or a definitive causal claim. Continuing professional education and clearer institutional feedback may improve the completeness and utility of these reports, which can ultimately support safer choices for future patients (Putri et al., 2024; Cervantes-Arellano et al., 2024; Davis et al., 2023; Jiao et al., 2024). Figure 3 places the three medication classes in a common clinical-safety framework without suggesting that their toxicological mechanisms are equivalent. Each row shows a distinctive organ-specific outcome and the need for appropriate clinical assessment. The shared modifiers provide a bridge to the discussion of susceptibility, patient communication and safety reporting.

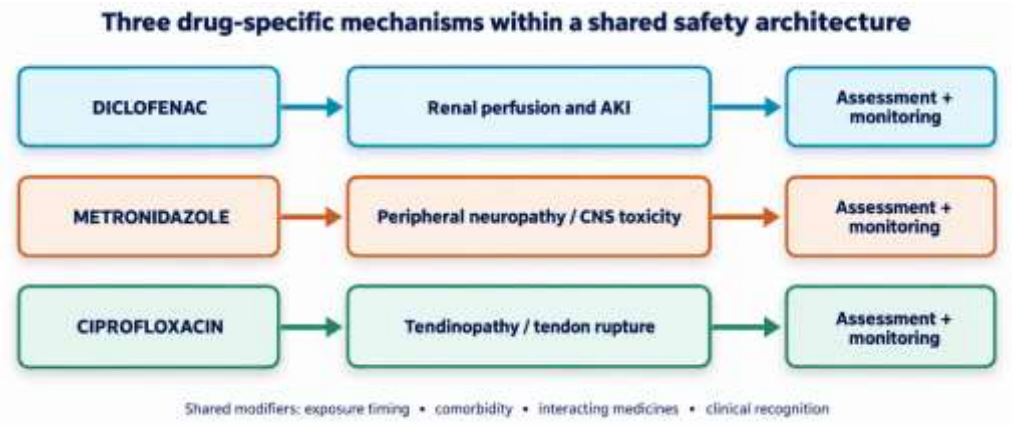

Figure 3. Comparative Organ-Specific Risks Within One Exposure–Susceptibility–Recognition Framework

Figure 3 places the three medications side by side while preserving their different clinical endpoints. Its connecting arrows represent the clinical task of identifying and assessing a suspected event, not a deterministic arrow from drug ingestion to damage. Across all three pathways, exposure timing, patient susceptibility, concomitant medications and the ability to recognize symptoms influence clinical interpretation.

DISCUSSION

1. Interpreting the Three Organ-Specific Signals Without Causal Overreach

The strongest conceptual conclusion is that the three drug–outcome relationships should be discussed at the level of distinct clinical syndromes, with the degree of causal certainty made explicit. Diclofenac-associated renal dysfunction has a convincing hemodynamic rationale in susceptible conditions, although drug exposure may not be the only cause of a specific kidney injury episode. Metronidazole-associated neurotoxicity spans peripheral and central findings for which the literature includes both population estimates and compelling but selected case reports. Ciprofloxacin-related tendon events are sufficiently important to inform prescribing, but cohort estimates are heterogeneous and cannot be converted into a universal risk figure (Perazella and Rosner, 2022; Daneman et al., 2021; Baik et al., 2020; Sangiorgio et al., 2024). This pattern answers the first three research questions by showing that the biological pathways are not parallel. Renal injury concerns an organ that continuously responds to circulatory conditions and medication-induced changes in vasoactive signals. Neurological toxicity involves clinically heterogeneous findings for which cumulative exposure, illness severity and neuroimaging may be relevant. Tendon toxicity is linked to extracellular-matrix integrity and injury outcomes that may be uncommon but consequential. The categories are therefore comparable as problems of medication safety, not as mechanistically identical processes or directly rankable outcome rates (Drożdżal et al., 2021; Ricci et al., 2020; Duman et al., 2025). The diclofenac literature supports an actionable distinction between risk factors and inevitable effects. Reduced kidney reserve, inadequate perfusion, volume disturbance and certain

drug combinations can make an NSAID less well tolerated, but risk reduction depends on balancing a genuine clinical indication with practical alternatives and patient-specific conditions. Population studies of chronic kidney disease require additional care because the diseases underlying analgesic use also affect renal outcomes. The notion of a single universally dangerous tablet strength would neglect both the pharmacological dose–response context and non-pharmacological influences on kidney function (Teo et al., 2023; Baker and Perazella, 2020; Wan et al., 2021; Hwang et al., 2024). The metronidazole literature likewise demands clinical and methodological specificity. Peripheral sensory complaints, encephalopathic symptoms and cerebellar signs differ in urgency, diagnostic work-up and prognosis, even when an exposure history raises suspicion. The Canadian positive association and Danish non-significant findings remind readers that a characteristic case phenotype and a reproducible population-wide excess are different propositions. Neither the absence of statistical significance in a single design nor a radiological pattern in an isolated case should decide causality for all clinical contexts; timely assessment and explicit consideration of competing explanations remain essential (Sørensen et al., 2020; Daneman et al., 2021; Andersen et al., 2024; Lee et al., 2024). For ciprofloxacin, the most informative response to conflicting studies is methodological examination, not selective citation. A class-level safety warning and a non-significant estimate for one molecule, comparator and population can coexist logically. The absence of statistical significance in one analysis does not demonstrate the absence of any risk, and a positive result in another cannot guarantee the same effect size everywhere. Explicitly comparing the studies' target populations, drugs, observation windows and outcome definitions is therefore more useful than selecting a dramatic headline or claiming that all evidence points in one numerical direction (Baik et al., 2020; Sangiorgio et al., 2024; Chang et al., 2022; Rasmussen et al., 2024).

2. An Integrated Exposure–Susceptibility–Recognition Framework

The thematic findings suggest a six-part pathway linking a therapeutic decision to an eventual clinical outcome. First, a valid indication establishes potential benefit. Second, molecule, dose, treatment duration and route define exposure. Third, comorbidities and concurrent medicines determine susceptibility. Fourth, organ-specific pharmacological or tissue processes create possible injury. Fifth, symptom recognition, laboratory findings or diagnostic evaluation determine whether harm becomes visible. Sixth, timely professional review, treatment modification when indicated and reporting shape prognosis and future prevention. This framework makes clear why the same drug can be appropriate for one patient while warranting extra precautions or an alternative in another (LaForge et al., 2023; Lee et al., 2024; Azamgarhi et al., 2024; Hodkinson et al., 2020). The model also distinguishes prevention opportunities from observational evidence about the event itself. Avoiding an unnecessary prescription acts before exposure, medication reconciliation modifies interacting risks, symptom education may accelerate recognition and clinical reporting helps improve future knowledge. None of these actions guarantees that injury cannot occur, but together they provide multiple opportunities to reduce preventable

harm. The model remains conceptual rather than a validated quantitative prediction tool; its purpose is to organize clinical reasoning and to suggest variables for empirical evaluation in future multi-site datasets (Tran et al., 2023; Cervantes-Arellano et al., 2024; Sadeq et al., 2022). Risk communication is best framed around expected benefit, plausible harm, uncertainty and a concrete plan for obtaining help. Informing a patient that NSAID-related acute kidney injury is more concerning during dehydration and certain co-prescriptions is more useful than saying diclofenac invariably damages the kidneys. Metronidazole counselling should accurately distinguish peripheral sensory symptoms from more urgent central neurological changes, while ciprofloxacin counselling should focus on new focal tendon symptoms rather than equating every episode of muscle soreness with rupture. When credible absolute-risk data exist, they should be communicated with an appropriate denominator and timeframe, recognizing that statistical terms may be misunderstood without explanation (Calvo et al., 2023; Quickfall et al., 2021; Baggio and Ananda-Rajah, 2021; Yount et al., 2024).

3. Why Relative, Absolute and Attributable Risk Must Not Be Confused

Relative-risk estimates describe comparisons between selected groups and do not directly reveal how many patients in routine care will experience an outcome. A clinically important relative increase may correspond to a small absolute increase if the baseline event is rare; conversely, even modest changes in common adverse events can matter at population scale. Attributable risk requires a credible counterfactual comparison, which is especially difficult when illness severity influences both prescription choice and harm occurrence. The material reviewed here therefore does not yield a unified absolute risk for the three drugs, and it should not be used to create an invented cross-drug hazard ranking (Coste et al., 2023; Baik et al., 2020; Sangiorgio et al., 2024). Selection of the comparator medicine is an underappreciated source of variation. Different antimicrobials may be prescribed for infections that differ in severity, anatomical site or likely pathogen, and those factors can themselves influence diagnostic testing and adverse-event risk. The contrast between positive short-term tendon associations among pneumonia patients and non-significant results among urinary tract infection patients is especially instructive because both investigations evaluated fluoroquinolones against treatment alternatives for a defined indication. Similarly, the Danish and Canadian metronidazole analyses answer related but not identical questions because they used different comparison structures and outcome ascertainment. Interpretation should therefore prioritize clearly specified target populations and clinically meaningful comparators over class-wide risk rankings (Andersen et al., 2024; Daneman et al., 2021; Fleming et al., 2024; Fleming et al., 2025). Pharmacovigilance reports are often even less suitable for numerical incidence claims. Reporting may intensify after publicity, duplicate events may be submitted, and the absence of a report should not be equated with the absence of harm. Conversely, an adverse-event report can be valuable because it describes a rare syndrome that would be difficult to capture in a small clinical trial. Good synthesis recognizes the

complementary roles: reports generate hypotheses and enrich clinical phenotypes, whereas appropriately designed population studies improve estimation of comparative occurrence and potentially test those hypotheses (Shu et al., 2022; Davis et al., 2023; Jiao et al., 2024). Table 1 summarizes three clinically important contrasts that should remain visible in a critical qualitative review. Each pair of studies addresses a related safety question but differs in population, indication or comparison design. The table is therefore an aid to interpreting heterogeneity, not a pooled estimate or a ranking of drug toxicity (Calvo et al., 2023; Andersen et al., 2024; Fleming et al., 2025).

Table 1. Contrasting Clinical Safety Findings and the Limits of Cross-Study Inference

Safety domain	Selected recent findings	Interpretive limitation
NSAID-associated AKI	A triple-whammy case-control study associated interacting prescriptions with AKI admissions; an inpatient NSAID cohort found no significant adjusted AKI difference among selected patients (Calvo et al., 2023; Rieck et al., 2026).	Drug combinations and baseline vulnerability differ. A null association in selected recipients does not establish universal renal safety.
Metronidazole neurological events	The Canadian nested case-control study estimated an adjusted odds ratio of 1.43; a Danish case-time-control analysis estimated 0.98 with a confidence interval including the null (Daneman et al., 2021; Andersen et al., 2024).	Different patients, comparators and neurological ascertainment prohibit averaging or direct comparison of absolute rates.
Fluoroquinolone tendon injury	A study of community-acquired pneumonia reported increased short-term tendon-injury odds; a subsequent study of urinary tract infections found no statistically significant elevation (Fleming et al., 2024; Fleming et al., 2025).	Underlying indications and active comparators differ. Neither result provides a universal ciprofloxacin-specific event rate.

The comparisons in Table 1 are deliberately heterogeneous, making transparent how clinical selection and outcome definitions can change apparent associations. A positive result should trigger assessment of bias and clinical relevance, while a non-significant estimate should not be presented as proof that a recognized adverse reaction cannot occur. The practical implication is calibrated precaution coupled with continued efforts to obtain better denominators, stronger comparators and clinically confirmed endpoints (Daneman et al., 2021; Rieck et al., 2026; Fleming et al., 2024).

4. Clinical Decisions, Prescribing Systems and Stewardship

For diclofenac and related NSAIDs, useful safeguards can include reviewing pre-existing kidney disease, diuretic and renin–angiotensin inhibitor use, and concurrent illness that affects volume status. Consideration of other

analgesic strategies and the minimum clinically necessary exposure should be individualized rather than imposed as a simplistic universal rule. Monitoring decisions must depend on clinical context, while an unexpected deterioration in kidney function requires broader assessment. A system that flags potentially hazardous combinations can assist clinicians, but automated alerts should remain focused enough to preserve their credibility and actionability (Calvo et al., 2023; Baker and Perazella, 2020; Kunitsu et al., 2022). For metronidazole, stewardship should emphasize the appropriateness of the indication and the need to revisit prolonged treatment plans. In patients who develop new unexplained sensory or central neurological symptoms, prompt clinical assessment may determine whether the medication contributes to the problem. The heterogeneity of manifestations means that merely asking about one symptom will miss some presentations, and complex infections can obscure attribution. Shared documentation among prescribers, pharmacists and patients is particularly useful when treatment extends across inpatient and outpatient settings (Daneman et al., 2021; Lee et al., 2024; Sahu et al., 2025; Sharland et al., 2022). For ciprofloxacin, a similar framework begins with microbiological and clinical appropriateness. A safety concern should inform the choice of antibiotic and duration, especially where tendon vulnerability or recent surgery is relevant, but must be weighed against the harms of ineffective infection treatment. Patient counseling should describe symptoms that warrant medical review without labeling all exercise-related discomfort as proof of antibiotic damage. Appropriate antimicrobial stewardship is therefore not synonymous with eliminating a drug class; it means choosing the safest effective regimen in the clinical context (Ly et al., 2023; Waters et al., 2023; Azamgarhi et al., 2024; Sadeq et al., 2022). At the organizational level, medication reconciliation, clinically informed prescribing support and pathways for responding to new symptoms are more robust than generic one-time warnings. Multidisciplinary input may be especially useful for people with impaired renal or hepatic function, interacting medicines or complicated infectious indications. A recent meta-analysis found that interactive educational strategies could improve adverse drug reaction reporting, although gains in report counts are not themselves evidence that adverse-event incidence declined. Randomized clinical evidence from acute kidney injury care likewise indicates that improved recommendation uptake need not translate into better short-term patient outcomes. Institutions should consequently monitor the quality of reporting and actual clinical outcomes, not merely alert frequency or training participation (Mongkhonmath et al., 2025; Aklilu et al., 2024; Putri et al., 2024).

Figure 4 translates the proposed prevention framework into a sequence that can be considered during prescribing and follow-up. It emphasises that a useful safety warning includes an indication check, individual risk review and an accessible response to concerning symptoms. It also represents documentation and adverse-event reporting as part of improving future care.



Figure 4. Clinical and Organizational Steps to Prevent Avoidable Medication-Related Harm

Figure 4 converts the thematic synthesis into a practical workflow beginning with a legitimate indication and moving through risk review, regimen choice, patient education and assessment of new symptoms. Reconciliation and reporting complete the learning loop by supplying information for the immediate clinical decision and future prescribing safeguards. The framework is conceptual, and its effectiveness should be evaluated in real-world implementation studies.

5. Methodological Limitations and Research Agenda

This article's own limitations follow from the purposeful qualitative design. The corpus was selected for relevance and interpretive diversity rather than through a preregistered, exhaustive database search, so selection bias and omission of potentially relevant studies remain possible. The included papers vary in baseline risk, geographic setting, healthcare databases and outcome definitions, and the synthesis does not provide formal certainty grades or meta-analytic estimates. Mechanistic claims remain inferential, and some neurological descriptions arise from selected case reports rather than controlled human exposure studies. These limitations are important for appropriately restrained conclusions, not reasons to disregard the clinical concerns entirely (Braun and Clarke, 2021; Braun and Clarke, 2022; Byrne, 2022). Future research should improve the capture of clinically validated endpoints rather than relying exclusively on billing codes or report frequencies. For kidney outcomes, useful designs would account for baseline creatinine, hydration-related events, co-medication changes and timing of analgesic exposure. For metronidazole, systematic neurological examination and longer follow-up could distinguish reversible encephalopathy from persistent peripheral neuropathy while evaluating cumulative exposure. For ciprofloxacin, research should compare clinically interchangeable antimicrobials with drug-specific exposure definitions and confirmed tendon outcomes, including exploration of interactions with corticosteroids and past tendon injuries (Perazella and Rosner, 2022; Lee et al., 2024; Sangiorgio et al., 2024; Waters et al., 2023). Comparative effectiveness and safety studies would also benefit from attention to implementation: whether electronic warnings change prescribing appropriately, whether patient counseling improves recognition and whether pharmacovigilance feedback leads to measurable reductions in harm. Better observational methods cannot

substitute for clinical judgment, but they can narrow uncertainty by making denominators, comparators and time windows explicit. Mixed-method research could examine how patients interpret alarming health graphics, whether their interpretation changes adherence and which formats best communicate rare but serious events without minimizing uncertainty or discouraging necessary care (Hodkinson et al., 2020; Cervantes-Arellano et al., 2024; Coste et al., 2023; Ly et al., 2023). Educational studies should examine which safety messages patients understand, remember and act upon without abandoning necessary treatment. Testing warning visuals against text-only explanations, using representative patient groups and measuring comprehension separately from anxiety or adherence would help distinguish beneficial vigilance from avoidable alarm. In parallel, interventions that increase reporting or guideline adherence should be tested against clinically confirmed harms rather than judged on process measures alone. These priorities follow from recent controlled and synthesis evidence on communication and medication-safety implementation (Kelly et al., 2022; Yount et al., 2024; Mongkhonmath et al., 2025; Aklilu et al., 2024).

CONCLUSIONS AND RECOMMENDATIONS

The safety relationships involving diclofenac, metronidazole and ciprofloxacin are clinically important, but the scientific meaning of each differs considerably. Diclofenac-associated kidney injury is strongly shaped by renal hemodynamics, physiologic reserve and co-prescribed medicines. Metronidazole has been associated with peripheral and central neurological syndromes whose manifestations, exposure patterns and recovery can differ. Ciprofloxacin-related tendon concerns require precise outcome terminology and a careful reading of heterogeneous fluoroquinolone studies. None of these observations supports the assertion that a specified tablet strength invariably produces organ damage in every patient.

The principal conclusion is that safer medication use emerges from the interaction of appropriate indication, individual vulnerability assessment, limited unnecessary exposure, clinical monitoring, patient understanding and meaningful adverse-event reporting. A drug warning should be sufficiently specific to encourage early assessment of concerning symptoms but calibrated enough to avoid turning a possible adverse reaction into inevitable harm. Relative-risk findings cannot replace absolute context, and spontaneous reporting cannot establish incidence without valid denominators. Healthcare institutions should integrate targeted interaction reviews, antimicrobial and analgesic stewardship, patient-centred symptom counselling and accessible follow-up into routine care. Researchers should prioritize validated outcomes, active-comparator designs, improved exposure measurement and long-term evaluation of patients who experience suspected harm. Future educational materials should communicate clinical syndromes and risk magnitudes accurately, while intervention studies should test whether better alerts, prescribing decisions and adverse-event reports result in measurable reductions in injury. Taken together, these priorities translate a memorable warning

illustration into a balanced agenda for rational prescribing, clearer uncertainty communication and prevention of avoidable medication harm.

FURTHER STUDY

This research still has limitations, so further studies are needed on the topic Beyond the Warning Label: Renal, Neurological, and Tendon Toxicity Associated with Diclofenac, Metronidazole, and Ciprofloxacin—A Review to improve this research and provide more insights for both the authors and the readers.

REFERENCES

Aklilu, A.M. et al. (2024) 'Early, individualized recommendations for hospitalized patients with acute kidney injury: a randomized clinical trial', JAMA, 332(24), pp. 2081–2090. Available at: https://doi.org/10.1001/jama.2024.22718

Andersen, M.A. et al. (2024) 'Association between first-time neurologic events and metronidazole treatment: a case-time control study', Clinical Therapeutics, 46(4), pp. 307–312. Available at: https://doi.org/10.1016/j.clinthera.2024.02.003

Armstrong, M.J. et al. (2023) 'Population-Based Analysis of Nonsteroidal Anti-inflammatory Drug Prescription in Subjects With Chronic Kidney Disease', Canadian Journal of Kidney Health and Disease, 10, 20543581221149621. Available at: https://doi.org/10.1177/20543581221149621

Azamgarhi, T. et al. (2024) 'Fluoroquinolones in orthopaedic infection: balancing risks and rewards', Journal of Antimicrobial Chemotherapy, 79(10), pp. 2413–2416. Available at: https://doi.org/10.1093/jac/dkae286

Baggio, D. and Ananda-Rajah, M.R. (2021) 'Fluoroquinolone antibiotics and adverse events', Australian Prescriber, 44(5), pp. 161–164. Available at: https://doi.org/10.18773/austprescr.2021.035

Baik, S. et al. (2020) 'Association between tendon ruptures and use of fluoroquinolone, and other oral antibiotics: a 10-year retrospective study of 1 million US senior Medicare beneficiaries', BMJ Open, 10(12), e034844. Available at: https://doi.org/10.1136/bmjopen-2019-034844

Baker, M. and Perazella, M.A. (2020) 'NSAIDs in CKD: Are They Safe?', American Journal of Kidney Diseases, 76(4), pp. 546–557. Available at: https://doi.org/10.1053/j.ajkd.2020.03.023

Calvo, D.M. et al. (2023) 'Effect of the combination of diuretics, renin-angiotensin-aldosterone system inhibitors, and non-steroidal anti-inflammatory drugs or metamizole (triple whammy) on hospitalisation due to acute kidney injury: A nested case-control study', Pharmacoepidemiology and Drug Safety, 32(8), pp. 898–909. Available at: https://doi.org/10.1002/pds.5621

Cervantes-Arellano, M.J. et al. (2024) 'Educational interventions in pharmacovigilance to improve the knowledge, attitude and the report of adverse drug reactions in healthcare professionals: Systematic Review and Meta-analysis', DARU Journal of Pharmaceutical Sciences, 32, pp. 421–434. Available at: https://doi.org/10.1007/s40199-024-00508-z

Chang, C.K. et al. (2022) 'Positive Association Between Fluoroquinolone Exposure and Tendon Disorders: A Nationwide Population-Based Cohort Study in Taiwan', Frontiers in Pharmacology, 13, 814333. Available at: https://doi.org/10.3389/fphar.2022.814333

Datta, A.K. et al. (2022) 'Metronidazole Induced Neurotoxicity: A clinico-radiological diagnosis', Sultan Qaboos University Medical Journal, 22(1), pp. 149–151. Available at: https://doi.org/10.18295/squmj.5.2021.080

Davis, S.E. et al. (2023) 'Use of Electronic Health Record Data for Drug Safety Signal Identification: A Scoping Review', Drug Safety, 46(8), pp. 725–742. Available at: https://doi.org/10.1007/s40264-023-01325-0

Fleming, V.H. et al. (2025) 'Risk of tendon injury in patients treated with fluoroquinolone (FQ) vs non-fluoroquinolone antibiotics for urinary tract infection (UTI)', Journal of Pharmacy Technology, 41(2), pp. 72–82. Available at: https://doi.org/10.1177/87551225241303848

Gong, J. et al. (2022) 'Nonsteroidal anti-inflammatory drugs associated acute kidney injury in hospitalized children: A systematic review and meta-analysis', Pharmacoepidemiology and Drug Safety, 31(2), pp. 117–127. Available at: https://doi.org/10.1002/pds.5385

Gussago, S. et al. (2022) 'Metronidazole and Peripheral Neuropathy: A Report of Two Cases of (Unusual) Side Effects', Cureus, 14(10), e30889. Available at: https://doi.org/10.7759/cureus.30889

Hodkinson, A. et al. (2020) 'Preventable medication harm across health care settings: a systematic review and meta-analysis', BMC Medicine, 18, 313. Available at: https://doi.org/10.1186/s12916-020-01774-9

Kelly, B. et al. (2022) 'Effects of additional context information in prescription drug information sheets on comprehension and risk and efficacy perceptions', Journal of Pharmaceutical Policy and Practice, 15, 15. Available at: https://doi.org/10.1186/s40545-021-00386-9

Khalil, H. and Huang, C. (2020) 'Adverse drug reactions in primary care: a scoping review', BMC Health Services Research, 20, 5. Available at: https://doi.org/10.1186/s12913-019-4651-7

Klomjit, N. and Ungprasert, P. (2022) 'Acute kidney injury associated with non-steroidal anti-inflammatory drugs', European Journal of Internal Medicine, 101, pp. 21–28. Available at: https://doi.org/10.1016/j.ejim.2022.05.003

Kunitsu, Y. et al. (2022) 'Time until onset of acute kidney injury by combination therapy with "Triple Whammy" drugs obtained from Japanese Adverse Drug Event Report database', PLOS ONE, 17(2), e0263682. Available at: https://doi.org/10.1371/journal.pone.0263682

Kuula, L.S.M., Backman, J.T. and Blom, M.L. (2021) 'Health service use and costs associated with fluoroquinolone-related tendon injuries', Pharmacology Research & Perspectives, 9(3), e00796. Available at: https://doi.org/10.1002/prp2.796

LaForge, J.M. et al. (2023) 'Non-steroidal Anti-inflammatory Drugs: Clinical Implications, Renal Impairment Risks, and AKI', Advances in Therapy, 40(5), pp. 2082–2096. Available at: https://doi.org/10.1007/s12325-023-02481-6

Lala, V.G. et al. (2021) 'Metronidazole-induced encephalopathy', South African Journal of Radiology, 25(1), 2016. Available at: https://doi.org/10.4102/sajr.v25i1.2016

Perazella, M.A. and Rosner, M.H. (2022) 'Drug-Induced Acute Kidney Injury', Clinical Journal of the American Society of Nephrology, 17(8), pp. 1220–1233. Available at: https://doi.org/10.2215/CJN.11290821

Putri, R.A., Ikawati, Z. and Rahmawati, F. (2024) 'An Awareness of Pharmacovigilance Among Healthcare Professionals Due to an Underreporting of Adverse Drug Reactions Issue: A Systematic Review of the Current State, Obstacles, and Strategy', Current Drug Safety, 19(3), pp. 317–331. Available at: https://doi.org/10.2174/0115748863276456231016062628

Quickfall, D. et al. (2021) 'Metronidazole-induced neurotoxicity', CMAJ, 193(42), E1630. Available at: https://doi.org/10.1503/cmaj.201671

Rasmussen, P.V. et al. (2024) 'Oral fluoroquinolones and the risk of Achilles tendon rupture', Journal of Sport and Health Science, 13(6), pp. 749–750. Available at: https://doi.org/10.1016/j.jshs.2024.04.001

Ricci, L. et al. (2020) 'Metronidazole Encephalopathy EEG Features: A Case Report with Systematic Review of the Literature', Brain Sciences, 10(4), 227. Available at: https://doi.org/10.3390/brainsci10040227

Rieck, K.M., Schroeder, D.R. and Mao, M.A. (2026) 'Inpatient NSAID exposure and development of acute kidney injury in medical inpatients: a retrospective cohort study', American Journal of Medicine Open, 15, 100119. Available at: https://doi.org/10.1016/j.ajmo.2025.100119

Ross, R.K. et al. (2021) 'Fluoroquinolone Antibiotics and Tendon Injury in Adolescents', Pediatrics, 147(6), e2020033316. Available at: https://doi.org/10.1542/peds.2020-033316

Sadeq, A.A. et al. (2022) 'Exploring Antimicrobial Stewardship Influential Interventions on Improving Antibiotic Utilization in Outpatient and Inpatient Settings: A Systematic Review and Meta-Analysis', Antibiotics, 11(10), 1306. Available at: https://doi.org/10.3390/antibiotics11101306

Sahu, P. et al. (2025) 'Metronidazole-induced encephalopathy and polyneuropathy', BMJ Case Reports, 18(4), e264913. Available at: https://doi.org/10.1136/bcr-2025-264913

Sangiorgio, A. et al. (2024) 'Achilles tendon complications of fluoroquinolone treatment: a molecule-stratified systematic review and meta-analysis', EFORT Open Reviews, 9(7), pp. 581–588. Available at: https://doi.org/10.1530/EOR-23-0181

Sharland, M. et al. (2022) 'The WHO AWaRe Antibiotic Book: providing guidance on optimal use and informing policy', The Lancet Infectious Diseases, 22(11), pp. 1528–1530. Available at: https://doi.org/10.1016/S1473-3099(22)00683-1

Shu, Y. et al. (2022) 'Fluoroquinolone-associated suspected tendonitis and tendon rupture: A pharmacovigilance analysis from 2016 to 2021 based on the FAERS database', Frontiers in Pharmacology, 13, 990241. Available at: https://doi.org/10.3389/fphar.2022.990241

Sørensen, C.G. et al. (2020) 'Metronidazole-induced encephalopathy: a systematic review', Journal of Neurology, 267(1), pp. 1–13. Available at: https://doi.org/10.1007/s00415-018-9147-6

Takahashi, S., Ishihara, S. and Tomimitsu, H. (2025) 'Metronidazole-induced encephalopathy with transient cortical lesions', Neurology and Clinical Neuroscience, 13, pp. 134–136. Available at: https://doi.org/10.1111/ncn3.12855

Teo, S.H. et al. (2023) 'Non-steroidal anti-inflammatory drugs in chronic kidney disease and risk of acute adverse kidney events according to route of administration', International Urology and Nephrology, 55(3), pp. 679–686. Available at: https://doi.org/10.1007/s11255-022-03344-9

Tran, H.N. et al. (2023) 'Preventability of Adverse Drug Reactions Related to Antibiotics: An Assessment Based on Spontaneous Reporting System', Therapeutic Innovation & Regulatory Science, 57(5), pp. 1104–1112. Available at: https://doi.org/10.1007/s43441-023-00552-y

Wan, E.Y.F. et al. (2021) 'Comparative Risks of Nonsteroidal Anti-Inflammatory Drugs on CKD', Clinical Journal of the American Society of Nephrology, 16(6), pp. 898–907. Available at: https://doi.org/10.2215/CJN.18501120