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Balancing Efficacy and Safety: An In-Depth Review of Diclofenac-Associated Adverse Effects

Shamili Sree Billapati¹, Mounika Manepalli¹, Likhita S R T Satti¹, Meghana Suravaram¹, Satti Naga Santhosh Reddy², D Veerandra Kumar³, Devanaboyina Narendra⁴, Abhinav VKS Grandhi*⁵.

1. PharmD Scholar, Doctor of Pharmacy, VJ's College of Pharmacy, Diwancheruvu, Rajahmundry - 533296, Andhra Pradesh, India.
2. UG Scholar, Bachelor of Pharmacy, VJ's College of Pharmacy, Diwancheruvu, Rajahmundry - 533296, Andhra Pradesh, India.
3. Associate Professor, Department of Pharmacy Practice, VJ's College of Pharmacy, Diwancheruvu, Rajahmundry - 533296, Andhra Pradesh, India.
4. Principal and Professor, VJ's College of Pharmacy, Diwancheruvu, Rajahmundry - 533296, Andhra Pradesh, India.
5. Assistant Professor, Department of Pharmacy Practice, VJ's College of Pharmacy, Diwancheruvu, Rajahmundry - 533296, Andhra Pradesh, India.

ABSTRACT

Diclofenac, a widely prescribed nonsteroidal anti-inflammatory drug (NSAID), remains one of the most commonly used analgesics and anti-inflammatory medications worldwide. Despite its therapeutic efficacy, diclofenac is associated with a spectrum of adverse drug reactions (ADRs) ranging from common gastrointestinal and cardiovascular effects to rare but serious complications, including cutaneous hyperpigmentation and Nicolau syndrome. This comprehensive review examines the drug profile, mechanism of action, pharmacokinetics, and detailed analysis of reported ADRs. Special attention is given to uncommon but clinically significant reactions such as Nicolau syndrome following intramuscular administration and drug-induced hyperpigmentation. The review provides evidence-based management strategies, risk factor identification, and monitoring protocols essential for safe clinical practice. Through systematic analysis of clinical trials, case reports, and pharmacovigilance data, this review highlights the importance of appropriate patient selection, route optimization, and vigilant monitoring in minimizing diclofenac-associated morbidity.

Keywords Diclofenac, adverse drug reactions, Nicolau syndrome, hyperpigmentation, pharmacovigilance

*Corresponding Author Email: 2402abhinav@gmail.com

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INTRODUCTION

Diclofenac, synthesized in 1973, has become one of the most extensively prescribed NSAIDs globally, with worldwide clinical experience exceeding 7.6 million patient-years. As a non-selective cyclooxygenase inhibitor, diclofenac provides potent analgesic, anti-inflammatory, and antipyretic effects, making it a cornerstone therapy for various musculoskeletal and inflammatory conditions. However, its widespread use has revealed a complex safety profile encompassing both predictable, dose-dependent adverse effects and rare idiosyncratic reactions that can result in significant morbidity. [1-3]

The clinical significance of diclofenac-associated ADRs extends beyond individual patient outcomes to broader public health implications. Studies indicate that approximately 26% of patients receiving diclofenac experience some form of adverse reaction, with gastrointestinal complications representing the most frequent category. More concerning are the cardiovascular risks, which have led to regulatory restrictions and contraindications in patients with established heart disease. [4-6]

This comprehensive review synthesizes current evidence on diclofenac's adverse effect profile, with particular emphasis on rare but serious complications that require heightened clinical awareness. By examining the mechanistic basis of these reactions and providing practical management guidance, this review aims to enhance safe prescribing practices and optimize patient outcomes.

Drug profile

Generic Name: Diclofenac

Major Brand Names Globally:

United States: Voltaren, Cataflam, Cambia, Pennsaid, Zipsor, Zorvolex, Solaraze

India: Voveran, Dynapar, Diclowin, Dicloran, Diclomax, Fenac, Reactin

United Kingdom: Voltarol, Dicloflex, Econac, Motifene

European Union: Voltaren, Deffamat, Olfen, Diclac

Australia: Voltaren, Fenac

Diclofenac is available in multiple salt forms, including sodium, potassium, and diethylamine salts, each optimised for specific formulations and routes of administration.

Mechanism of Action

Diclofenac exerts its therapeutic effects through non-selective inhibition of cyclooxygenase-1 (COX-1) and cyclooxygenase-2 (COX-2) enzymes, thereby blocking the synthesis of

prostaglandin G₂, the precursor to other prostaglandins. This inhibition disrupts multiple physiological pathways.[7]

Anti-inflammatory Effect:

By reducing prostaglandin E₂ (PGE₂) and prostacyclin (PGI₂) production, diclofenac diminishes vasodilation, vascular permeability, and leukocyte chemotaxis at inflammatory sites.[8]

Analgesic Effect:

modulates nociception through both peripheral and central mechanisms. Peripherally, it reduces PGE₂-mediated sensitization of nociceptors, while centrally it affects pain processing in the spinal cord dorsal horn.[9]

Antipyretic Effect:

The drug crosses the blood-brain barrier to inhibit PGE₂ synthesis in the hypothalamic thermoregulatory centres, thereby reducing fever responses.[10]

Indications

Diclofenac is FDA-approved for multiple inflammatory and pain conditions

Primary Indications:

- Osteoarthritis and rheumatoid arthritis
- Ankylosing spondylitis
- Acute pain management
- Primary dysmenorrhea
- Migraine (powder formulation)
- Actinic keratosis (topical gel)
- Postoperative ocular inflammation (ophthalmic formulation)
- Off-label Uses:
 - Biliary colic, corneal abrasions, fever, gout, myalgia, and post-episiotomy pain.

Pharmacokinetics and Pharmacodynamics**Absorption:**

Diclofenac exhibits complete oral absorption but undergoes significant first-pass metabolism, resulting in approximately 60% bioavailability for the unchanged drug. Peak plasma concentrations occur within 10-40 minutes for oral solutions, 1.5-2 hours for enteric-coated tablets, and are further delayed with sustained-release formulations.

Distribution:

The volume of distribution ranges from 5-10 L (0.1-0.2 L/kg), with extensive protein binding (>99.7%) primarily to albumin. Diclofenac accumulates in synovial fluid, reaching peak

concentrations 2-4 hours post-administration. Limited central nervous system penetration occurs, with cerebrospinal fluid concentrations reaching only 8.2% of plasma levels.

Metabolism:

Hepatic metabolism occurs primarily via CYP2C9, producing 4'-hydroxy diclofenac as the major metabolite (30-fold less active than the parent compound). Additional metabolites include 3'-hydroxy diclofenac and various conjugated products.

Elimination:

Approximately 60-70% of the administered dose is eliminated renally, with 30% via faecal excretion. The terminal half-life is approximately 2 hours, though the apparent half-life including metabolites extends to 25.8-33 hours.

Dosing and Formulations**Oral Formulations:**

- Osteoarthritis: 50 mg 2-3 times daily or 75 mg twice daily (maximum 150 mg/day)
- Rheumatoid Arthritis: 50 mg 3-4 times daily or 75 mg twice daily (maximum 225 mg/day)
- Ankylosing Spondylitis: 25 mg 4 times daily with an additional 25 mg at bedtime if needed
- Acute Pain: 50 mg 3 times daily or initial 100 mg followed by 50 mg doses
- Parenteral Administration:
 - Intramuscular: 75 mg for acute severe pain, may repeat after 30 minutes maximum 150 mg/day)
 - Intravenous: 75 mg over 15 seconds every 6 hours as needed

Topical Formulations:

Available as 1% gel, cream, and solution for localized musculoskeletal pain with reduced systemic exposure.

Diclofenac is available in multiple formulations, allowing flexible dosing options tailored to clinical needs. For acute pain management, oral administration typically involves 50 mg given three times daily, or an initial loading dose of 100 mg followed by 50 mg doses as needed to achieve effective analgesia.

Intramuscular administration can provide rapid relief with a dose of 75 mg, which may be repeated after 30 minutes if necessary, with a maximum daily dose of 150 mg to limit adverse effects. This route is especially useful in acute severe pain but carries risks such as Nicolau syndrome, warranting cautious use and preference for other routes when feasible.

Topical formulations, such as the 1% gel, offer localized pain control with reduced systemic exposure. The gel is typically applied in 2-4 g amounts to the affected area three to four times

daily, not exceeding 32 g per day. This route is preferred when inflammation is localized to minimize systemic risks.

The availability of diverse administration routes underscores diclofenac's versatility, allowing clinicians to tailor therapy according to the severity, urgency of pain relief needed, patient comorbidities, and risk factors. [55-58]

Known/Expected Side Effects from Clinical Trials

Clinical trials demonstrate that approximately 12% of patients experience adverse effects with diclofenac, leading to discontinuation in 1.5-2% of cases. [11]

The most frequent adverse effects include: Gastrointestinal (Most Common):

- Nausea, dyspepsia, abdominal pain (occurring in 2-10% of patients)
- Diarrhoea, constipation, flatulence
- Peptic ulceration (0.009% incidence in large studies) [12]

Central Nervous System:

Headache, dizziness, drowsiness

Less frequent: confusion, depression, tinnitus

Dermatological:

- Rash, pruritus (0.8% incidence in pediatric studies) [13]
- Photosensitivity reactions

Cardiovascular:

- Hypertension, oedema
- Risk of thrombotic events increases with dose and duration [14]

ADR overview

Reported ADRs

Comprehensive pharmacovigilance data from multiple sources reveal the breadth of diclofenac-associated adverse reactions. A prospective study in orthopaedic patients found that 19 of 65 patients (29%) receiving diclofenac developed ADRs, with 14 experiencing gastrointestinal symptoms, 3 dermatological reactions, and 2 non-specific symptoms.[15]

Major Categories of Reported ADRs:

Gastrointestinal System (Most Frequent):

- Peptic ulceration and bleeding
- Gastritis, dyspepsia, nausea
- Hepatotoxicity including fulminant hepatitis [15]

Cardiovascular System:

- Myocardial infarction, stroke risk elevation
- Hypertension, congestive heart failure exacerbation
- Thrombotic events [15]

Dermatological System:

- Fixed drug eruption, Stevens-Johnson syndrome
- Allergic contact dermatitis
- Hyperpigmentation (rare but clinically significant) [16]

Injection Site Reactions:

- Nicolau syndrome (embolia cutis medicamentosa)
- Local tissue necrosis and scarring [16]

Classification of ADRs

Diclofenac-associated ADRs can be classified using the standard ADR classification system:

Type A (Augmented) - Dose-dependent, Predictable:

- Gastrointestinal ulceration and bleeding
- Cardiovascular thrombotic events
- Renal dysfunction
- Hypertension

Type B (Bizarre) - Dose-independent, Unpredictable:

- Anaphylaxis and severe allergic reactions [17]
- Stevens-Johnson syndrome/Toxic epidermal necrolysis [18]
- Fixed drug eruption[19]
- Nicolau syndrome[20]

Type C (Chronic) - Related to Long-term Use:

- Progressive renal impairment
- Cardiovascular disease progression
- Chronic hepatic dysfunction

Type D (Delayed) - Occurs After Delay:

- Some hepatotoxic reactions may manifest weeks to months after initiation [21]

Incidence and Frequency

Overall ADR Incidence:

- General population: 12% experience any adverse effect[22]
- Orthopaedic patients: 29% develop ADRs (primarily gastrointestinal)[23]

- Community pharmacy setting: 33.3% report suspected ADRs[23]

Specific ADR Frequencies:

- Serious gastrointestinal events: 0.009% (peptic ulceration)[24]
- Dermatological reactions: 0.8% in children[24]
- Anaphylaxis: Very rare (<0.1%)[25]
- Nicolau syndrome: Extremely rare, estimated <0.001%[26]
- Hyperpigmentation: Rare, precise incidence unknown[27]

Age-Related Variations:

- Elderly patients show higher susceptibility to serious gastrointestinal and cardiovascular events[28]
- Pediatric patients demonstrate similar ADR patterns to adults but with lower serious event rates (<0.8%). [29]

Case Studies

Case Study 1: Nicolau Syndrome Following Intramuscular Diclofenac

A 65-year-old female received a single intramuscular injection of diclofenac sodium (75 mg) in her left buttock for back pain. Within hours, she developed severe localized pain followed by bluish discoloration and eventual tissue necrosis characteristic of Nicolau syndrome. Treatment required surgical debridement, drain insertion, and prolonged wound care, with complete healing occurring over several weeks with scarring.[30]

Case Study 2: Anaphylactic Reaction to Intravenous Diclofenac

A 40-year-old male developed acute anaphylaxis within 10 minutes of intravenous diclofenac administration for abdominal pain. Clinical presentation included severe respiratory distress (oxygen saturation 67%), hypotension (80/60 mmHg), tachycardia (150 bpm), and generalized urticaria. Laboratory confirmation showed elevated serum tryptase (25 ng/ml) and urinary methylhistamine (136 ng/ μ mol). Emergency treatment with epinephrine, antihistamines, and corticosteroids resulted in complete recovery.[32]

Case Study 3: Extensive Fixed Drug Eruption

A patient developed extensive fixed drug eruption covering >50% body surface area following oral diclofenac therapy. The reaction presented as sharply demarcated, darkly pigmented patches with surrounding erythema, primarily affecting the trunk and extremities. Patch testing confirmed diclofenac as the causative agent, and lesions resolved with drug discontinuation and topical corticosteroid therapy.[33]

Case Study 4: Diclofenac-Induced Allergic Contact Dermatitis

Four cases of topical diclofenac-induced allergic contact dermatitis were documented, presenting as intensely pruritic eczematous lesions at application sites. Patch testing with the European standard battery and diclofenac sodium 1% in petrolatum confirmed the diagnosis. All cases were resolved within 2 weeks of drug discontinuation and topical corticosteroid application.[34]

Skin Pigmentation Mechanism

Diclofenac-induced hyperpigmentation represents a complex, multifactorial process involving several potential mechanisms:

Melanocyte Activity Modulation:

- Direct inhibition of the tyrosinase enzyme, paradoxically leading to compensatory melanin production
- Alteration of melanocyte function through prostaglandin pathway disruption
- Possible interference with normal melanin synthesis regulation.
- Dermal Pigment Deposition:
 - Migration of melanin from epidermis to dermis (pigmentary incontinence)
 - Phagocytosis of melanin by dermal macrophages
 - Potential deposition of iron or other pigments in dermal layers.
- Inflammatory Mediation:
 - Despite anti-inflammatory properties, diclofenac may trigger localized inflammatory responses.
 - Inflammation-induced melanocyte stimulation
 - Photosensitivity reactions leading to post-inflammatory hyperpigmentation

Nicolau Syndrome Mechanism

Nicolau syndrome following diclofenac injection results from a cascade of vascular and tissue events:

Vascular Compromise:

- Prostaglandin synthesis inhibition leading to vasoconstriction
- Reduced prostacyclin (PGI₂) production, eliminating vasodilatory effects
- Potential direct arterial injection or perivascular infiltration [35]

Sympathetic Nerve Stimulation:

- Injection trauma activates sympathetic pathways
- Enhanced vasoconstriction through adrenergic mechanisms
- Compound vascular compromise beyond prostaglandin effects.

Ischemic Cascade:

- Progressive tissue hypoxia from vascular compromise
- Cellular metabolism disruption and ATP depletion
- Inflammatory mediator release perpetuates tissue damage.
- Ultimate progression to necrosis without intervention.[36]

Risk Factors

Patient-Related Risk Factors:

Age-Related Vulnerabilities:

- Elderly (≥ 65 years): Increased cardiovascular and gastrointestinal complications, altered drug metabolism, and higher baseline risk factors.[37]
- Children: Potential for respiratory complications in asthmatic patients, though generally lower serious ADR rates.[38]
- Comorbidity-Associated Risks:
 - Cardiovascular Disease: A History of myocardial infarction, stroke, and heart failure significantly increases thrombotic event risk. [38]
 - Gastrointestinal Disorders: Peptic ulcer disease, inflammatory bowel disease, bleeding disorders, and elevated hemorrhagic complications. [24]
 - Renal Impairment: Reduced drug clearance, increased nephrotoxicity risk, and fluid retention potential. [24]
 - Hepatic Dysfunction: Impaired metabolism, increased hepatotoxicity susceptibility. [24]
- Genetic Factors:
 - Polymorphisms in UGT2B7, CYP2C8, and ABCC2 genes associated with increased hepatotoxicity risk
 - Variable drug metabolism affects systemic exposure and toxicity potential.
- Treatment-Related Risk Factors:
 - Route of Administration: Intramuscular injection carries Nicolau syndrome risk; the intravenous route increases anaphylaxis potential.
 - Dose and Duration: Higher doses and prolonged therapy increase all ADR categories.
 - Concomitant Medications: Anticoagulants, corticosteroids, and other NSAIDs amplify bleeding and cardiovascular risks.

Immediate Management Strategies

Nicolau Syndrome Management:

Acute Phase (First 24-48 hours):

- Immediate injection cessation and wound assessment
- Pain control with systemic analgesics (avoid additional NSAIDs)
- Photographic documentation for monitoring progression
- Vascular assessment through imaging is performed if extensive involvement is suspected. [39]

Medical Interventions:

- Corticosteroids: Prednisolone 1 mg/kg daily to reduce acute inflammatory response
- Vasodilators: Pentoxifylline 400 mg three times daily to improve microcirculation
- Anticoagulation: Low-molecular-weight heparin if thrombosis is suspected
- Hyperbaric oxygen: Consider in severe cases with extensive necrosis

Surgical Management:

- Early debridement: Remove necrotic tissue to prevent secondary infection
- Wound care: Daily sterile dressings with appropriate topical agents
- Reconstructive procedures: Skin grafting may be required for extensive defects. [40]

Anaphylaxis Management:

- Immediate epinephrine: 0.3-0.5 mg intramuscularly, may repeat every 5-15 minutes
- Airway support: Oxygen therapy, intubation if severe respiratory compromise
- Volume resuscitation: Intravenous fluids for hypotension
- Antihistamines: H1 and H2 receptor antagonists for symptom control
- Corticosteroids: High-dose methylprednisolone for severe reactions. [41]

Monitoring Protocols**Cardiovascular Monitoring:**

- Baseline Assessment: Blood pressure, cardiac history, risk factor evaluation
- Ongoing Surveillance: Regular blood pressure monitoring, symptom assessment for chest pain, dyspnea, or neurological changes
- High-Risk Patients: Consider cardiology consultation before initiation. [42]
- Hepatic Monitoring:
 - Baseline: Liver function tests (ALT, AST, bilirubin) before therapy initiation
 - Follow-up: Repeat liver enzymes within 4-8 weeks of starting treatment
 - Long-term: Periodic monitoring every 3-6 months for chronic therapy
- Warning Signs: Patient education on jaundice, dark urine, abdominal pain, and fatigue. [43]

- Renal Function Monitoring:
- Baseline: Serum creatinine, estimated GFR, urinalysis
- Risk Factors: More frequent monitoring in elderly, dehydrated, or comorbid patients
- Signs of Dysfunction: Reduced urine output, oedema, elevated creatinine. [25]

Gastrointestinal Surveillance:

- High-Risk Identification: Age >65, history of ulcers, concomitant anticoagulants
- Symptom Monitoring: Abdominal pain, dyspepsia, signs of bleeding (melena, hematemesis)
- Prophylactic Measures: Proton pump inhibitors in high-risk patients. [44]

Prevention Strategies

Route Selection Optimization:

- Prefer Topical Formulations: When appropriate for localized conditions to minimize systemic exposure
- Avoid Intramuscular Route: Use oral or topical alternatives, when possible, to prevent Nicolau syndrome.
- Injection Technique: If parenteral is necessary, ensure proper anatomical landmarks, aspiration before injection, and avoid cold compress application. [45]
- Patient Selection Criteria:
- Cardiovascular Screening: Avoid in established heart disease, carefully evaluate risk factors
- Gastrointestinal Assessment: Consider alternative agents in ulcer history
- Renal Function: Avoid in moderate-severe impairment. [46]
- Education and Awareness:
- Healthcare Provider Training: Recognition of early ADR signs, proper injection techniques
- Patient Education: Warning signs requiring immediate medical attention
- Pharmacovigilance Participation: Encourage ADR reporting to national systems.

DISCUSSION

Diclofenac's extensive clinical use has established it as a cornerstone NSAID therapy, yet its safety profile demands careful consideration and proactive management. The drug's dual COX-1/COX-2 inhibition, while providing effective anti-inflammatory and analgesic effects, creates a complex risk-benefit profile that varies significantly across patient populations and clinical scenarios.

The cardiovascular risks associated with diclofenac have emerged as a primary safety concern, with meta-analyses demonstrating thrombotic event rates comparable to selective COX-2 inhibitors. The European Medicines Agency's decision to contraindicate diclofenac in patients with established cardiovascular disease reflects the mounting evidence of elevated myocardial infarction and stroke risks, particularly with higher doses and prolonged therapy. This regulatory response highlights the importance of individualized risk assessment and the need for alternative therapeutic strategies in high-risk populations.[47]

Gastrointestinal toxicity, while historically the most recognized NSAID-associated risk, continues to represent a significant clinical challenge. The 0.009% incidence of peptic ulceration reported in large-scale studies, though seemingly low, translates to substantial absolute numbers given diclofenac's widespread use. The development of combination formulations with gastroprotective agents like misoprostol represents one approach to risk mitigation, though these strategies require careful patient selection and monitoring.[27]

The rare but serious complications of Nicolau syndrome and drug-induced hyperpigmentation underscore the importance of route-specific risk assessment. Nicolau syndrome, occurring predominantly with intramuscular administration, represents a preventable iatrogenic complication that can result in significant morbidity and disfigurement. The mechanistic understanding of prostaglandin-mediated vasoconstriction leading to tissue ischemia provides a rational basis for prevention strategies, including route selection and injection technique optimization.[48]

Hyperpigmentation, while cosmetically concerning rather than life-threatening, illustrates the complexity of drug-induced cutaneous reactions. The multifactorial mechanisms involving melanocyte dysfunction, inflammatory responses, and photosensitivity highlight the need for comprehensive dermatological assessment in patients experiencing unexplained pigmentary changes during diclofenac therapy.[49]

The emerging role of pharmacogenomics in predicting diclofenac-associated hepatotoxicity represents a promising avenue for personalized medicine approaches. Genetic polymorphisms affecting drug metabolism and transport may eventually enable pre-treatment risk stratification, though clinical implementation remains limited by testing availability and cost considerations.[50]

From a pharmacovigilance perspective, the community pharmacy studies revealing 33.3% suspected ADR rates suggest potential underreporting in traditional surveillance systems. Enhanced collaboration between healthcare providers, patients, and regulatory agencies is essential for comprehensive safety monitoring and signal detection. [51-54]

CONCLUSION

Diclofenac remains a valuable therapeutic agent when used judiciously with appropriate patient selection, route optimization, and vigilant monitoring. The comprehensive ADR profile, ranging from common gastrointestinal effects to rare complications like Nicolau syndrome and hyperpigmentation, necessitates a nuanced approach to prescribing and patient management.

Key principles for safe diclofenac use include: systematic cardiovascular and gastrointestinal risk assessment before therapy initiation; preference for topical formulations when clinically appropriate; avoidance of intramuscular administration when alternative routes are feasible; implementation of structured monitoring protocols for hepatic, renal, and cardiovascular function; and patient education regarding warning signs requiring immediate medical attention.

The evolving understanding of diclofenac's safety profile, particularly regarding cardiovascular risks and rare complications, underscores the dynamic nature of pharmacovigilance and the importance of continuous safety surveillance. Future research directions should focus on developing predictive biomarkers for serious ADRs, optimizing combination strategies with gastroprotective agents, and establishing standardized monitoring protocols across different clinical settings.

Healthcare providers must balance diclofenac's proven therapeutic efficacy against its well-characterized risk profile, ensuring that treatment decisions are informed by current evidence and individualized to patient-specific factors. Through such approaches, the clinical benefits of diclofenac can be maximized while minimizing the potential for adverse outcomes.

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Authors Contributions:

S.S.B., M.M., L.S.R.T.S., and M.S. conducted the literature review, performed data collection, and contributed to drafting the manuscript. S.N.S.R. assisted with reference compilation, formatting, and preliminary revisions. D.V.K. and D.N. provided critical academic guidance, supervision, and validation of the clinical content. A.V.K.S.G. conceptualized the study, coordinated the review

process, finalized the manuscript, and ensured its overall intellectual integrity. All authors read, reviewed, and approved the final version of the manuscript.

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