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Cutaneous adverse reactions caused by non-steroidal and steroidal anti-inflammatory drugs

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Abstract

Non-steroidal anti-inflammatory drugs (NSAIDs) and corticosteroids are among the most commonly prescribed and self-administered medications worldwide, owing to their analgesic, antipyretic, and anti-inflammatory properties. Despite their broad therapeutic utility, both drug classes are frequently associated with cutaneous adverse reactions, ranging from mild, self-limiting eruptions to severe, potentially life-threatening dermatoses. Cutaneous involvement represents one of the most common manifestations of drug intolerance and often serves as an early indicator of adverse drug reactions. This narrative review summarizes the mechanisms, clinical patterns, and diagnostic approaches to cutaneous reactions induced by NSAIDs and corticosteroids. NSAID-related cutaneous reactions arise through both immunologic and non-immunologic mechanisms, most commonly related to cyclooxygenase inhibition and subsequent alterations in arachidonic acid metabolism. These reactions include frequent phenotypes such as urticaria and maculopapular eruptions, as well as less common but severe manifestations, including Stevens–Johnson syndrome and toxic epidermal necrolysis. Recent advances in the classification of NSAID hypersensitivity have emphasized the distinction between pharmacological cross-reactivity and true immune-mediated hypersensitivity, as well as the recognition of overlapping clinical phenotypes. Cutaneous adverse effects of corticosteroids are predominantly driven by their pharmacologic impact on skin structure and immune function. Prolonged exposure, particularly to high-potency topical formulations, may result in skin atrophy, striae, telangiectasia, acneiform eruptions, and increased susceptibility to cutaneous infections. Although less common, immediate and delayed hypersensitivity reactions to corticosteroids—including allergic contact dermatitis—have been documented and may complicate diagnosis due to partial masking by their intrinsic anti-inflammatory effects. This review also addresses the potential exacerbation of pre-existing dermatologic conditions, the importance of chronological and morphological pattern analysis, and the principles of structured drug-related rash assessment. Accurate recognition of cutaneous drug reactions, combined with systematic diagnostic approaches, is essential to guide appropriate management, prevent severe outcomes, and optimize patient safety in clinical practice.

Keywords: cutaneous adverse drug reactions, NSAIDs, corticosteroids, drug hypersensitivity, skin toxicity, Stevens–Johnson syndrome

Introduction

Non-steroidal anti-inflammatory drugs (NSAIDs) and corticosteroids are among the most frequently prescribed and self-administered medications worldwide because of their analgesic, antipyretic, and anti-inflammatory properties [1, 2]. They are extensively used in the management of acute and chronic inflammatory conditions, autoimmune diseases, allergic disorders, and various pain syndromes [3]. Despite their well-established therapeutic efficacy, both classes of anti-inflammatory agents are associated with a broad spectrum of adverse effects, among which cutaneous reactions represent some of the most common and clinically significant manifestations [4].

Cutaneous adverse drug reactions range from mild, self-limiting manifestations—such as pruritus and maculopapular eruptions—to severe, potentially life-threatening conditions, including Stevens–Johnson syndrome, toxic epidermal necrolysis, and drug reaction with eosinophilia and systemic symptoms (DRESS) [5]. These reactions may substantially impair quality of life, necessitate treatment discontinuation, and, in severe cases, result in significant morbidity or mortality [6]. The skin frequently serves as an early indicator of drug intolerance or hypersensitivity [7], making prompt recognition of dermatologic manifestations essential in routine clinical practice.

NSAIDs are particularly well known for their association with hypersensitivity reactions mediated through both immunologic and non-immunologic mechanisms, often involving cyclooxygenase inhibition and subsequent alterations in arachidonic acid metabolism [8–11]. In contrast, corticosteroids may induce a wide range of cutaneous manifestations, including immediate hypersensitivity reactions such as urticaria and erythematous eruptions, as well as inflammatory dermatoses, photosensitivity reactions, and acneiform eruptions [12, 13]. With prolonged use or exposure to high-potency formulations—especially topical agents—local trophic effects become prominent, leading to skin atrophy, striae, telangiectasia, premature skin aging, hypertrichosis, and perioral dermatitis [14]. These manifestations reflect both allergic-type responses and the direct pharmacologic effects of corticosteroids on skin structure, collagen metabolism, and immune function [15].

A comprehensive understanding of the types, mechanisms, and clinical presentations of cutaneous reactions associated with NSAIDs and corticosteroids is essential for early diagnosis, appropriate management, and prevention of severe outcomes. The first section of this review outlines the underlying pathophysiologic mechanisms involving the development of these adverse reactions. This is followed by a detailed discussion of the cutaneous manifestations associated with NSAIDs and corticosteroids. Finally, the review addresses the assessment of drug imputability in cutaneous reactions, emphasizing its role in establishing causality and guiding clinical decision-making.

Mechanisms of action of nsaids and corticosteroids in cutaneous adverse reactions

NSAID-related cutaneous adverse reactions arise through both immunologic and non-immunologic mechanisms [16]. Immunologic reactions are less common and most frequently reflect delayed type IV hypersensitivity responses occurring after prior sensitization, characterized by T-cell–mediated inflammation and onset typically several days after drug exposure [17]. These reactions are usually selective for a single NSAID and generally do not exhibit cross-reactivity with structurally unrelated agents [18]. Clinical manifestations include maculopapular eruptions, fixed drug eruptions, and severe cutaneous adverse reactions (SCARs), such as drug reaction with eosinophilia and systemic symptoms (DRESS), Stevens–Johnson syndrome, and toxic epidermal necrolysis [19].

In contrast, the majority of NSAID-associated cutaneous manifestations are pharmacologically mediated and result from cyclooxygenase inhibition with subsequent disruption of prostaglandin homeostasis. This imbalance may promote leukotriene overproduction, mast cell activation, increased vascular permeability, and amplification of inflammatory signaling pathways [20, 21]. Additional contributing factors include direct local toxicity, irritant effects of formulation components, photosensitivity reactions, and drug accumulation in cutaneous tissues. These mechanisms help explain the heterogeneity of clinical presentations observed following both topical and systemic exposure [22].

Cutaneous adverse effects of corticosteroids are predominantly driven by their pharmacologic impact on skin architecture and immune regulation [12]. By inhibiting fibroblast proliferation and suppressing collagen and extracellular matrix synthesis, corticosteroids induce epidermal thinning and reduced dermal structural support. Clinically, this results in skin atrophy, striae, telangiectasia, purpura, and impaired wound healing, particularly with prolonged use or high-potency formulations [23]. Local immunosuppression further increases susceptibility to cutaneous infections and contributes to acneiform eruptions [24]. Although uncommon, immunologic reactions to corticosteroids do occur and most often manifest

as allergic contact dermatitis mediated by delayed type IV hypersensitivity, directed against either the corticosteroid molecule itself or formulation excipients [15, 25]. Structural similarities among corticosteroid classes may lead to cross-reactivity, thereby complicating diagnosis and therapeutic management.

Precipitation and exacerbation of dermatologic diseases

In addition to inducing primary cutaneous adverse reactions, both NSAIDs and corticosteroids may exacerbate or unmask pre-existing dermatologic diseases, a phenomenon that warrants separate consideration [26].

Beyond inducing *de novo* reactions, NSAIDs may worsen or precipitate flares of pre-existing dermatologic conditions, including chronic urticaria, dermatitis herpetiformis, chronic benign bullous epidermolysis, and psoriasis [27]. These effects are generally pharmacologic rather than immunologic and may occur even upon first exposure. Altered arachidonic acid metabolism and amplification of pro-inflammatory pathways appear to play a central role [28]. Topical NSAIDs may further aggravate disease through local irritant effects, particularly when applied to compromised skin [29]. Such reactions are often dose-dependent and may demonstrate cross-reactivity among different NSAIDs [30].

Corticosteroids may also contribute to disease exacerbation, particularly when used topically and for prolonged periods [31]. By suppressing local immune responses and altering epidermal barrier function, corticosteroids can worsen or mask conditions such as acne, rosacea, perioral dermatitis, and cutaneous infections [32]. Abrupt withdrawal after chronic use may provoke rebound flares or withdrawal reactions [32]. In patients with allergic contact dermatitis to corticosteroids, continued application may paradoxically intensify inflammation at the site of treatment, thereby mimicking disease progression [33].

Principles of cutaneous adverse drug reaction diagnosis

Determining whether an NSAID is responsible for a cutaneous adverse drug reaction is central to diagnosis and management and requires integration of chronological, clinical, and biological data. Chronological analysis focuses on the time interval between drug exposure and lesion onset, any association with dose or treatment modifications, and the occurrence of recurrence upon re-exposure [34]. This assessment is particularly relevant given that NSAID hypersensitivity is relatively common in patients receiving chronic therapy, especially those with comorbid conditions such as asthma or chronic urticaria, thereby warranting heightened clinical suspicion [35]. Delayed allergic reactions, including maculopapular eruptions, fixed drug eruptions, and DRESS, typically develop 1–3 days after drug intake but may appear as late as 2–6 weeks after exposure. In contrast, pharmacologic reactions such as urticaria, angioedema, or bronchospasm generally occur within minutes to hours [36–38].

Although these principles apply broadly to both drug classes, the temporal patterns and clinical evolution of corticosteroid-related reactions differ in important respects. Corticosteroid-induced cutaneous reactions are most often delayed and may develop days to weeks after exposure, particularly in the context of prolonged topical use [15, 39]. Allergic contact dermatitis mediated by delayed type IV hypersensitivity may present as progressive or paradoxical worsening at the site of application, sometimes partially obscured by the intrinsic anti-inflammatory effects of the drug itself [33, 40]. In addition, abrupt discontinuation after chronic use may result in rebound flares or withdrawal reactions rather than true recurrence upon re-exposure, underscoring the importance of considering both ongoing treatment and recent cessation when evaluating suspected corticosteroid-related skin reactions [32].

Cutaneous manifestations associated with nsaids use

Cutaneous adverse reactions to non-steroidal anti-inflammatory drugs (NSAIDs) present a broad clinical spectrum, ranging from mild, self-limited eruptions to severe, life-threatening dermatoses [41]. In recent years, most notably with the 2025 World Allergy Organization (WAO) update, these manifestations have been redefined and reclassified within an expanded framework of NSAID hypersensitivity reactions, emphasizing the distinction between immediate and delayed immune-mediated mechanisms and recognizing overlapping (“mixed” or “blended”) phenotypes [42]. Despite advances in classification, skin involvement remains one of the most common and clinically relevant presentations of NSAID-related adverse reactions.

Overview of frequent presentations

The most frequently observed cutaneous reactions to NSAIDs include maculopapular eruptions and urticaria [43]. Maculopapular eruptions typically present as symmetric erythematous macules and papules, whereas urticaria manifests as transient pruritic wheals and occurs more commonly in atopic individuals or in patients with a prior history of urticaria [44, 45]. Photosensitivity

reactions have also been reported following NSAID exposure [46].

1. Bullous dermatoses

Among the most severe cutaneous manifestations associated with NSAID exposure are bullous dermatoses, including erythema multiforme, Stevens–Johnson syndrome, and toxic epidermal necrolysis. These entities are grouped together because of shared pathophysiologic mechanisms and their potential progression toward extensive epidermal necrolysis [47, 48].

Erythema multiforme represents the mildest end of this spectrum and is characterized by target-like lesions that may involve the skin and mucous membranes [49]. Although many drugs may act as triggers, pyrazolone and oxicam derivatives are disproportionately implicated among NSAIDs [50, 51]. Stevens–Johnson syndrome is considered a severe variant within this spectrum and is characterized by fever and widespread mucocutaneous involvement affecting multiple orifices, sometimes accompanied by systemic symptoms [52].

Toxic epidermal necrolysis, also known as Lyell syndrome, is the most severe NSAID-associated cutaneous adverse reaction. It is defined by epidermal detachment involving more than 30% of the body surface area and carries high morbidity and mortality [53]. Immediate withdrawal of the offending drug and management in specialized intensive care units are essential. NSAIDs, particularly pyrazolone derivatives and certain oxicams, are recognized pharmacologic triggers and have been associated with extensive epidermal detachment and prominent mucosal involvement [54].

2. Maculopapular eruptions

Maculopapular (morbilliform or exanthematous) eruptions are among the most common delayed cutaneous adverse drug reactions, and NSAIDs are a well-recognized trigger [37]. In NSAID hypersensitivity, these eruptions typically reflect a T-cell–mediated (type IV) delayed reaction, often appearing days after initiation of the drug. They present with widespread erythematous macules and papules, usually without mucosal involvement, and improve after drug discontinuation [55]. Management consists primarily of prompt cessation of the culprit NSAID, symptomatic therapy (*e.g.*, topical corticosteroids, oral antihistamines), and careful evaluation for warning signs of severe cutaneous adverse reactions [26, 56]. In a clinical series focused on NSAID-related skin reactions, maculopapular eruption was a frequent phenotype, underscoring that clinicians should consider NSAIDs (including selective COX-2 inhibitors, as reported in some studies) in the differential diagnosis when a new morbilliform rash develops after use of analgesic or anti-inflammatory drugs [41].

3. Urticaria

Urticaria is among the most frequent cutaneous reactions observed following NSAID administration and typically presents with rapidly developing pruritic, erythematous, edematous wheals arising within hours of drug ingestion [57]. Individuals with a personal history of urticaria, allergic rhinitis, or atopy appear to be at higher risk, and NSAIDs may either trigger acute urticaria or exacerbate pre-existing chronic spontaneous urticaria [58].

Available evidence indicates that the severity of the reaction does not consistently correlate with the dose or the specific NSAID used and that the underlying mechanism is generally not IgE-mediated [59]. Instead, NSAID-induced urticaria is thought to result primarily from cyclooxygenase-1 inhibition, which diverts arachidonic acid metabolism toward the lipoxygenase pathway, leading to increased leukotriene production. Excess leukotrienes are believed to play a central role in the development of urticarial lesions [60]. In many patients, reactions occur with multiple chemically unrelated NSAIDs, supporting a mechanism of pharmacologic cross-reactivity rather than a drug-specific allergic response. However, cross-reactivity is not universal, and some individuals may react to a single NSAID while tolerating others, reflecting individual susceptibility [61]. NSAID-induced urticaria has most frequently been associated with arylpropionic acid derivatives such as ibuprofen and ketoprofen, as well as aceclofenac, naproxen, pyrazolones, and oxicams, with symptoms typically developing within 1–4 hours after ingestion [62].

4. Photodermatoses induced by NSAIDs

NSAIDs are well-recognized causes of drug-induced photodermatoses and may provoke both phototoxic and photoallergic reactions [63]. Phototoxic reactions do not require prior sensitization and occur shortly after ultraviolet exposure, presenting as exaggerated sunburn-like erythema that may be accompanied by blistering [64]. These reactions have most commonly been reported with NSAIDs such as piroxicam, ketoprofen, fenoprofen, ibuprofen, and diclofenac [65].

Experimental studies have demonstrated that diclofenac absorbs ultraviolet radiation and undergoes photodegradation under UVA and UVB exposure, generating reactive photoproducts and reactive oxygen species [66]. These processes lead to keratinocyte damage, DNA injury, and activation of apoptotic pathways, providing a molecular basis for NSAID-induced phototoxic skin injury [67, 68].

In contrast, photoallergic reactions are immune-mediated, require prior sensitization, and typically develop 24–48 hours after sun exposure [69, 70]. Clinically, they present as eczematous lesions confined to photo-exposed areas and have

most frequently been associated with piroxicam [70]. NSAIDs have also been implicated in photocontact dermatitis and pseudoporphyria, a blistering photodermatosis that clinically resembles porphyria cutanea tarda but lacks abnormalities of porphyrin metabolism [71].

5. Other cutaneous manifestations

In addition to the more common presentations, NSAID exposure has been associated with a variety of less frequent but clinically significant cutaneous reactions. These include isolated pruritus without visible lesions, purpura related to vascular involvement, exfoliative dermatitis with generalized erythema and scaling, and cutaneous small-vessel vasculitis [72–76]. Rare cases of IgA-mediated hypersensitivity vasculitis have been reported following NSAID administration, occasionally progressing to severe necrotic or purpura fulminans–like presentations [72].

Cutaneous manifestations of corticosteroids

Corticosteroids, whether administered topically or systemically, are widely used in clinical practice but can induce a broad spectrum of cutaneous adverse effects that are frequently underestimated. Topical corticosteroids may lead to prominent local skin changes, most notably cutaneous atrophy, discussed in detail below. Prolonged use may also result in striae, purpura due to dermal fragility, and delayed wound healing, reflecting impaired tissue regeneration [77]. In addition to these structural alterations, local immunosuppression predisposes to bacterial, fungal, and viral overgrowth, including bacterial folliculitis, furunculosis, recurrent herpes simplex or herpes zoster infections, and candidiasis [78]. Other well-recognized dermatologic complications of topical corticosteroid use include steroid-induced acne, exacerbation of rosacea, perioral dermatitis—particularly with fluorinated corticosteroids—hypertrichosis, infantile gluteal granuloma, pigmentary alterations, and local hypersensitivity reactions such as allergic contact dermatitis [79]. Systemic corticosteroid exposure, whether through excessive dosing or prolonged topical absorption, may additionally result in generalized cutaneous and systemic manifestations, including cushingoid fat redistribution, muscle wasting with thin extremities, acneiform eruptions, edema, purpura, and hirsutism, as well as iatrogenic hypercorticism with suppression of the hypothalamic–pituitary–adrenal axis [80, 81]. The likelihood and severity of these effects are closely related to the dose, potency, duration of therapy, and treated surface area, underscoring the importance of limiting corticosteroid use and reassessing treatment if therapy extends beyond three weeks [13].

1. Immediate hypersensitivity reactions

Corticosteroids can provoke true IgE-mediated or non-IgE immediate reactions that appear within minutes to an hour after exposure. Clinically, these present as urticaria, angio-edema, or a generalized erythematous rash, and may progress to anaphylaxis in severe cases [82, 83]. The reactions are rare but are reported across oral, injectable, and topical preparations, and are more common in patients receiving repeated high-dose courses. Diagnosis relies on a detailed drug history and, when feasible, skin-prick or intradermal testing with the suspected preparation [15, 82–84].

2. Dermatitis and rashes

Both acute irritant and delayed-type allergic contact dermatitis have been described with corticosteroids [33]. Patients develop erythema, papules, vesicles, or scaling lesions at the site of application, often accompanied by itching. Cross-reactivity among different steroid classes is frequent, making patch testing essential for identifying the culprit and guiding selection of an alternative agent. Systemic exposure can also trigger generalized maculopapular rashes, especially in individuals with prior sensitization [85–87].

3. Skin atrophy

Skin atrophy is a recognized cutaneous unwanted effect associated with the prolonged use of steroidal anti-inflammatory drugs, especially with topical or systemic administration. Glucocorticoids bind the cytoplasmic glucocorticoid receptor, translocate to the nucleus, and modify gene transcription, resulting in reduced collagen synthesis and disrupted stratum-corneum lipid production, which compromises barrier integrity. Clinically, this manifests as fragile skin, easy bruising, telangiectasia, and other atrophic changes. In addition, the catabolic milieu created by sustained cortisol excess can produce wide, purplish striae, characteristics of hypercorticism. Corticosteroids may also paradoxically provoke other skin side-effects, such as acneiform eruptions and delayed wound healing [88–90].

Clinical pattern, differential diagnosis, and evolution

In NSAIDs-induced cutaneous adverse reactions, lesion morphology often reflects the underlying mechanism. Urticarial wheals and angioedema typically indicate a non-allergic, cyclooxygenase-1–mediated pharmacologic reaction, whereas fixed drug eruptions suggest a drug-specific delayed hypersensitivity [35]. Photosensitivity reactions point to involvement of specific NSAIDs molecules, and bullous lesions raise concern for severe cutaneous adverse reactions

such as Stevens–Johnson syndrome or toxic epidermal necrolysis [52, 69]. Overlapping patterns may occur, as illustrated by rare cases of fixed urticaria with recurrent localized wheals after NSAID exposure [91, 92]. Differential diagnosis should exclude viral exanthems, exacerbation of pre-existing dermatoses, and sun- or irritant-related reactions. Clinical evolution after drug withdrawal is informative: urticaria usually resolves within 24–48 hours, maculopapular eruptions within 5–10 days, whereas severe reactions may continue to progress despite discontinuation [92].

In corticosteroid-related cutaneous reactions, clinical patterns differ and are often related to prolonged exposure or hypersensitivity. Immediate urticaria or angioedema suggests rare acute hypersensitivity, whereas eczematous lesions at application sites are more consistent with allergic contact dermatitis. Chronic changes such as skin atrophy, telangiectasia, striae, and purpura reflect direct pharmacologic effects on skin structure. Differential diagnosis should include rebound flares after abrupt withdrawal, masked cutaneous infections due to local immunosuppression, and worsening of underlying dermatoses. Corticosteroid-induced reactions typically evolve over days to weeks and may persist after discontinuation [12, 22, 37].

Cessation of the medication involved in the cutaneous reaction is vital for the therapeutic approach and for a favorable outcome in both situations, for NSAIDs as well as for corticosteroids [37]. Symptomatic treatment is most often indicated, and in the case of cutaneous reactions caused by NSAIDs, the prescription of topical or even systemic corticosteroids may be required [93].

Laboratory evaluation and drug imputability assessment

There are no specific biomarkers for most NSAIDs-induced cutaneous adverse reactions, although laboratory abnormalities such as eosinophilia, elevated liver enzymes, or cytopenias may support a diagnosis of DRESS, and a skin biopsy can help distinguish reaction patterns [94, 95]. Drug provocation tests are rarely justified because of the potential risk. Ultimately, drug imputability is considered strong when a clear chronological relationship exists, the clinical presentation is consistent with the suspected drug, symptoms improve after withdrawal, and recurrence occurs upon re-exposure when historical data are available. In the setting of severe cutaneous adverse reactions such as Stevens–Johnson syndrome or toxic epidermal necrolysis, structured causality assessment tools such as the Algorithm for Drug Causality in Epidermal Necrolysis (ALDEN) may be particularly useful, especially in high-risk populations. Formal drug imputability scoring systems, such as the WHO–Uppsala criteria, may assist in evaluation, but the final diagnosis remains predominantly clinical [96–98].

Conclusions

Cutaneous adverse reactions to NSAIDs and corticosteroids constitute a clinically significant and highly heterogeneous group of conditions, ranging from mild, self-limited eruptions to severe, life-threatening dermatoses. As illustrated throughout this review, NSAIDs are among the most frequent causes of drug-induced skin reactions, with manifestations that span common phenotypes such as urticaria and maculopapular eruptions to rare but devastating entities including Stevens–Johnson syndrome and toxic epidermal necrolysis. Corticosteroids, although often employed in the treatment of inflammatory and allergic skin diseases, may themselves induce a broad spectrum of cutaneous complications, particularly with prolonged or inappropriate use. Advances in the classification of NSAID hypersensitivity, most notably reflected in recent updates, have emphasized the importance of distinguishing pharmacologic cross-reactivity from true immunologic hypersensitivity and recognizing overlapping or blended reaction patterns. A mechanistic understanding of these reactions, especially the role of cyclooxygenase inhibition, eicosanoid imbalance, and delayed T-cell–mediated hypersensitivity, is essential for accurate diagnosis and risk stratification. Ultimately, careful assessment of drug imputability based on chronology, clinical morphology, evolution after drug withdrawal, and selective use of diagnostic tools remains the cornerstone of management. Improved awareness of these cutaneous adverse reactions and adherence to structured diagnostic approaches are critical to minimizing morbidity, optimizing therapeutic decisions, and ensuring patient safety in everyday clinical practice.

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Conflicts of interest

The authors declare no conflicts of interest.

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