DOI: 10.66069/ojspub.27451028

Iatrogenic Hyperpigmentation: Pathogenesis, Risk Factors, and Advances in Prevention

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Abstract: ***Background:*** *Iatrogenic hyperpigmentation is an acquired pigmentary change associated with medications, dermatologic procedures, surgery, radiotherapy, and other medical interventions. Although many cases are benign, visible or persistent discoloration can impair quality of life, reduce treatment satisfaction, and occasionally complicate the management of an otherwise necessary therapy [42,43]. The term encompasses mechanistically distinct disorders, including post-inflammatory hyperpigmentation (PIH), drug-induced pigmentation, phototoxic pigmentation, and deposition of non-melanin pigments.* ***Objective:*** *To summarize current understanding of the mechanisms and risk factors of iatrogenic hyperpigmentation and critically review emerging preventive strategies, with emphasis on evidence published in recent years.* ***Methods:*** *This narrative review was developed using targeted searches of PubMed and reference lists of relevant reviews and clinical studies. Priority was given to literature published from 2022 through October 2026, while earlier mechanistic studies and clinical trials were retained when they remain important to the interpretation of current evidence. As this is a narrative rather than systematic review, no meta-analytic pooling or formal evidence grading was performed.* ***Results:*** *Major mechanisms include inflammation-driven melanogenesis, disruption of the dermoepidermal junction with pigment incontinence, altered melanosome transfer, ultraviolet- and visible-light-associated pigment induction, and direct tissue deposition of drugs or metabolites. Risk is influenced by baseline skin phototype and pigmentary history, active inflammation, medication exposure and cumulative dose, treatment energy and depth, anatomical site, and post-procedure care. Recent evidence supports individualized procedural planning and careful control of inflammation. A 2026 network meta-analysis of randomized trials suggested that selected interventions—including topical corticosteroids, tranexamic acid (TXA), vasoconstrictors, and epidermal cooling—may reduce laser-associated PIH, but the small and heterogeneous evidence base limits generalization. A 2024 randomized trial found a lower incidence of laser-induced PIH with pre-treatment isobutylamido thiazolyl resorcinol (ITR) used twice daily, whereas evidence for epidermal growth factor-containing products and systemic TXA remains inconsistent. Photoprotection is central to prevention but cannot prevent pigmentation caused predominantly by dermal drug deposition.* ***Conclusions:*** *Prevention should be mechanism-based rather than uniform. A practical approach combines pre-treatment risk assessment, treatment of active inflammation, conservative and indication-specific procedures, medication review, barrier-supportive aftercare, photoprotection, and structured follow-up. Better-designed prospective studies using standardized pigmentary outcomes are needed, particularly for drug-induced pigmentation and for patients with darker skin phototypes.*

Keywords: Iatrogenic hyperpigmentation, Drug-induced pigmentation, Post-inflammatory hyperpigmentation, Laser complications, Melanogenesis, Photoprotection, Risk stratification, Prevention.

1. Introduction

Pigmentary changes are common adverse effects of medical and dermatologic interventions. They may follow prescribed systemic or topical medications, laser and light-based procedures, chemical peels, surgery, radiotherapy, inflammatory reactions to dressings or antiseptics, and other forms of treatment-related skin injury. The resulting discoloration ranges from transient erythema-associated darkening to persistent brown, blue-gray, slate, or black pigmentation. In addition to cosmetic concerns, visible dyschromia can cause psychosocial distress, undermine confidence in treatment, and lead patients to discontinue necessary medication or avoid further care [1–5].

"Iatrogenic hyperpigmentation" is best understood as an umbrella term rather than a single diagnosis. Post-inflammatory hyperpigmentation (PIH) occurs when cutaneous inflammation increases melanin synthesis or disrupts the epidermal–dermal interface, allowing melanin to enter the dermis. Drug-induced pigmentation (DIP), by contrast, may reflect increased melanin, direct drug or metabolite deposition, iron-containing complexes, or mixed mechanisms. Phototoxic reactions may initiate a secondary PIH response, while radiotherapy and surgical procedures can cause pigmentary changes through inflammation, vascular injury, and tissue remodeling [1,2,6]. These categories overlap clinically but should not be assumed to share the same pathogenesis or preventive treatment.

The need for prevention is particularly relevant in patients with richly pigmented skin, those with a history of PIH or melasma, patients receiving potentially pigment-inducing medications, and individuals undergoing procedures that deliberately injure the epidermis or dermis. However, darker phototype is a risk modifier rather than a deterministic predictor: the procedure, inflammatory response, baseline disease, drug exposure, and post-treatment environment all contribute [3,4,7–9].

This review summarizes the principal mechanisms of iatrogenic hyperpigmentation, examines patient- and treatment-related risk factors, and evaluates preventive strategies. Emphasis is placed on evidence from 2022–2026, while selected older studies are retained when they provide mechanistic foundations or controlled trial data that remain relevant. A central argument is that prevention should begin by identifying the likely pigmentary pathway and the modifiable component of risk.

2. Literature Approach and Scope

We conducted a narrative review using targeted PubMed searches and reference-list screening. Search terms covered

drug-induced pigmentation, iatrogenic hyperpigmentation, post-inflammatory hyperpigmentation (PIH), laser-related complications, photoprotection, and preventive interventions, including tranexamic acid and topical tyrosinase inhibitors. We prioritized publications from January 2022 to October 2026. Earlier studies were retained when they provided foundational mechanisms or evidence not adequately addressed by newer work.

The evidence is uneven. Recent systematic reviews address PIH treatment, and a network meta-analysis has examined prevention after laser and energy-based procedures. By contrast, prevention of drug-induced pigmentation (DIP) relies largely on drug-specific observations, mechanistic data, case series, and clinical judgment [1,6,7,24–33]. Available evidence varies in quality and directness, and recommendations throughout this review are framed accordingly; no formal GRADE rating was applied.

3. Definitions and Clinical Classification

3.1 Drug-induced Pigmentation

DIP refers to skin, mucosal, nail, hair, or other tissue discoloration temporally associated with medication exposure. More than 50 agents have been implicated, including selected antibiotics, antimalarials, antiretrovirals, antipsychotics, prostaglandin analogues, antiarrhythmics, heavy metals, and antineoplastic drugs [1]. Clinical patterns include localized blue-black macules at sites of prior inflammation, diffuse slate-gray discoloration, photodistributed brown pigmentation, mucosal pigmentation, and nail or hair changes. Some reactions are reversible after drug withdrawal; others resolve slowly or remain persistent because of dermal deposition or long-lasting tissue changes.

A temporal association alone does not establish causality. The evaluation should include the medication start date, dose and cumulative exposure, distribution of pigmentation, relevant organ dysfunction, concurrent drugs, previous inflammation, phototoxic symptoms, and improvement or progression after withdrawal where clinically feasible. Histopathology may be useful when the differential includes lichen planus pigmentosus, ochronosis, hemosiderin deposition, melanoma, or another pigmentary disorder.

3.2 Procedure-associated PIH

Procedure-associated PIH is an acquired increase in pigmentation after an inflammatory or traumatic insult, including laser treatment, intense pulsed light (IPL), chemical peeling, microneedling, surgery, cryotherapy, and other interventions. Lesions are usually brown to dark brown when epidermal melanin predominates and may appear slate or blue-gray when pigment is located deeper in the dermis. Dermal pigment may persist longer because melanophages clear more slowly than epidermal melanin is shed [2–5].

PIH can develop after procedures intended to remove pigmentation. This paradox is clinically important: a treatment directed at melanin may trigger enough inflammation or epidermal disruption to cause new pigment production, worsening the original problem. Patients should be counseled that a technically successful intervention can still produce delayed pigmentary complications, particularly when underlying inflammation, phototype, and procedural parameters are not adequately considered [4,5,24,25].

3.3 Phototoxic and Photo-aggravated Pigmentation

Some drugs increase cutaneous susceptibility to ultraviolet (UV) radiation. An acute phototoxic reaction may resemble exaggerated sunburn, followed by PIH. In other cases, pigmentation develops gradually in exposed sites during ongoing treatment. Photosensitivity-associated pigmentation should be differentiated from direct drug deposition because strict photoprotection can be more influential in the former than in the latter. Visible light may also exacerbate selected pigmentary conditions, particularly in darker phototypes, although direct evidence specific to every form of iatrogenic pigmentation is limited [16–22].

3.4 Other Pigmentary Complications

Radiotherapy, recurrent local inflammation, adhesive reactions, antiseptic-associated dermatitis, and topical irritant exposure can cause secondary pigmentation. Iron-containing pigments after bleeding or tissue injury may produce brown discoloration that is not simply a melanogenic response. Chronic use of depigmenting treatment can itself cause dyschromia, including exogenous ochronosis associated with prolonged hydroquinone exposure. Accurate classification is therefore a prerequisite for rational prevention and management [13–15,35–37].

4. Pathogenesis

4.1 Inflammation-driven Melanogenesis

The most common pathway underlying procedure-associated PIH is inflammation-driven melanogenesis. Cutaneous injury activates keratinocytes, fibroblasts, mast cells, macrophages, and other immune or stromal cells. These cells release cytokines, growth factors, eicosanoids, and reactive oxygen species that can modify melanocyte activity. Prostaglandins, leukotrienes, endothelin-related signaling, stem-cell factor, and other mediators have been implicated in the communication between injured epidermis and melanocytes [2–5,9]. Their relative contributions vary with the initiating disease, injury depth, and individual biology.

Melanogenesis is regulated through several converging pathways. Activation of melanocortin-related signaling and cyclic adenosine monophosphate (cAMP) can stimulate protein kinase A and cAMP response element-binding protein, increasing microphthalmia-associated transcription factor (MITF) activity. MITF regulates tyrosinase and other melanogenic proteins required for melanin synthesis. Inflammation can influence these pathways directly or indirectly through paracrine signals from keratinocytes and dermal cells [2,3,9]. Although this model provides a useful framework, the exact molecular signature of PIH in humans is not completely defined, and the importance of individual mediators may differ across inflammatory conditions.

Reducing initial inflammation is central to prevention.

Depigmenting agents target downstream melanogenesis, whereas wound care and injury limitation block the upstream signal. Neither alone is universally sufficient, as post-procedural inflammation is unavoidable and drug-deposition pigmentation resists melanogenesis inhibition.

4.2 Dermoepidermal Junction Injury and Pigment Incontinence

Inflammation can damage basal keratinocytes and the dermoepidermal junction. Melanin and melanosomes may then enter the papillary dermis and be engulfed by macrophages, producing melanophages. This process — pigment incontinence—helps explain why some post-inflammatory lesions acquire a gray-brown or blue-gray hue and persist after the initiating inflammation has resolved [3–5]. Deeper pigment is generally more difficult to clear than predominantly epidermal pigment, and aggressive additional procedures may aggravate the process.

Injury depth determines whether pigmentation is epidermal or dermal. Severe injury disrupting the basement membrane favors dermal deposition, justifying conservative procedures in high-risk patients, though no universal injury threshold exists.

4.3 Melanosome Production, Transfer, and Distribution

Visible pigmentation is determined not only by the quantity of melanin produced but also by melanosome maturation, transfer to keratinocytes, intracellular distribution, and epidermal turnover. Keratinocyte-derived growth factors can influence melanocyte dendricity and melanosome transfer. PIH may therefore reflect several coordinated changes rather than a simple increase in tyrosinase activity [2,9].

This distinction matters for topical prophylaxis: tyrosinase inhibitors block new melanin formation yet fail to quickly eliminate epidermal melanosomes or dermal melanophages. Efficacy differs by timing, so trials must separate preventive and treatment outcomes.

4.4. Oxidative stress and environmental light

Oxidative stress may amplify inflammatory signaling, modify melanocyte function, and impair tissue repair. UVB can initiate erythema and delayed pigmentation, whereas UVA penetrates more deeply and can contribute to immediate or persistent pigmentary changes. Visible light is also capable of inducing pigmentation in melanocompetent skin, with larger responses generally observed in darker phototypes in experimental studies [16–19,23,50]. The magnitude of these effects depends on wavelength, dose, baseline pigmentation, and the endpoint measured.

The preventive importance of visible light is best established in melasma and selected pigmentary disorders, rather than in all forms of DIP. Nevertheless, broad-spectrum UV protection remains essential after procedures that induce inflammation, and tinted formulations with iron oxides may be considered when visible-light-associated pigmentation is a concern. Such advice should be presented as an adjunct to—not a substitute for—physical shade, protective clothing, and adherence to post-procedure care [16–22].

4.5 Direct drug or Metabolite Deposition

Some drugs cause pigmentation through pathways that do not primarily depend on inflammation-induced melanin synthesis. A drug or metabolite may bind to tissue components, form insoluble complexes, chelate metals, or accumulate in macrophages. The resulting pigment can contain drug-related material, melanin, iron, or combinations of these substances. Minocycline is a well-described example with multiple clinical patterns, including pigment associated with pre-existing inflammation, pigmentation on otherwise normal skin, and diffuse pigmentation in sun-exposed sites [10–12].

The 2024 review by Tisack and Mohammad emphasizes the diversity of drug-induced pigmentary adverse reactions and the importance of distinguishing mechanisms rather than treating all cases as conventional PIH [1]. This distinction has direct preventive consequences. Medication review, early recognition, dose or agent modification when appropriate, and site-specific monitoring may be more effective than routine use of a topical bleaching agent. Some forms of drug-associated pigmentation may persist despite discontinuation because the pigment is deposited in the dermis or other tissues.

4.6 Medication-induced photosensitivity and secondary PIH

A drug can contribute to pigmentation through more than one mechanism. Photosensitizing drugs may provoke a phototoxic inflammatory response that is followed by PIH; other drugs may produce pigment deposition while also increasing susceptibility to sunlight. A patient's pigmentation may therefore reflect both a primary drug-related process and a secondary response to light exposure. Exposure pattern, preceding burning or erythema, and the color and distribution of lesions may help distinguish these components [1,10–12].

For photosensitivity-associated pigmentation, strict photoprotection and review of the implicated drug may meaningfully reduce ongoing stimulation. For pigment arising primarily from deposition, these measures may limit aggravation but cannot be expected to fully prevent or reverse existing discoloration. This is another reason a mechanistic assessment should precede selection of a preventive regimen.

4.7 Other Non-melanin Pigments and Iatrogenic Dyschromia from Treatment Itself

Not every dark lesion after treatment represents melanin overproduction. Hemosiderin after bleeding or vascular injury, exogenous material, and hydroquinone-associated ochronosis may produce clinically important brown, blue-gray, or black discoloration. Exogenous ochronosis has been associated particularly with long-term hydroquinone use, often at higher concentrations or in unsupervised regimens. Recent mechanistic work and a review of hydroquinone safety reinforce the need for carefully supervised use [45,46]. A 2022 systematic review of reported cases identified prolonged exposure as a recurring feature and described blue-black or gray-blue facial macules with characteristic histopathological

findings [13,14].

This creates a prevention paradox: treatments intended to lighten pigmentation may themselves cause new or worsening discoloration when used for too long, at inappropriate concentrations, or without follow-up. Prescribing should specify treatment duration, monitoring, and a plan for discontinuation or reassessment when improvement is insufficient. Unregulated multi-ingredient lightening products are particularly problematic because their contents and concentrations may be uncertain [13–15,47].

5. Risk Factors

5.1 Baseline Skin Pigmentation and Phototype

Darker skin phototypes are more likely to develop clinically prominent and persistent PIH after inflammatory or traumatic insults. Higher epidermal melanin content, differences in melanosome properties and distribution, and the visible contrast between background skin and a new lesion may contribute to the clinical burden [3,4,7,9,41,48,49]. However, the Fitzpatrick phototype scale was developed primarily to describe burning and tanning responses to UV exposure; it should not be treated as a complete biological measure of pigmentation risk. Race or ethnicity alone is also an imprecise substitute for direct skin assessment.

Risk assessment should therefore combine phototype with measured or documented baseline pigmentation, previous PIH after minor trauma or procedures, history of melasma or lichen planus pigmentosus, and the nature of the planned intervention. In trials, stratification by phototype and objective baseline pigmentation is preferable to broad racial categories alone [4,7,17–21].

5.2 Previous PIH and Pigmentary Disease

A history of prolonged post-acne pigmentation, PIH after shaving or minor injury, or worsening pigmentation after previous procedures suggests susceptibility to future dyschromia. Active melasma or other pigmentary disorders can complicate the interpretation of post-treatment changes and may be aggravated by inflammation and light exposure. Prior PIH should prompt more conservative treatment planning, careful counseling, and documentation of baseline lesions. It does not necessarily mean a procedure is contraindicated; instead, it shifts the benefit–risk balance and the level of monitoring required [3–8,24].

5.3 Active Inflammation and Barrier Dysfunction

Active acne, eczema, contact dermatitis, infection, folliculitis, and other inflammatory conditions increase the likelihood that an elective intervention will add to an existing inflammatory burden. Barrier impairment can increase irritancy from topical products and may prolong recovery. When feasible, the underlying condition should be controlled before an elective peel, laser, microneedling session, or other nonessential procedure. When treatment cannot be delayed, the plan should minimize additional inflammation and avoid unnecessary topical irritants [4,5,8,37–40].

5.4 Drug, Dose, Duration, and Comedication

Medication-related risk depends on the drug class, cumulative dose, duration, photosensitizing potential, renal or hepatic function where relevant, co-administered agents, and the patient's indication. Minocycline-associated pigmentation has been described more often with prolonged exposure and higher cumulative doses, although it may occur earlier or at lower doses [10–12]. Antimalarials and selected antineoplastic, antiarrhythmic, psychotropic, and other drugs are also implicated [1].

Medication screening should include prescriptions, OTC drugs, supplements, topicals and lightening cosmetics. Suspected offending agents need substitution assessment; essential medications must not be stopped abruptly without specialty consultation.

5.5 Procedure Type, Wavelength, Depth, and Energy

The risk of procedure-associated PIH varies across devices and interventions. Ablative resurfacing produces barrier disruption and thermal injury, whereas nonablative fractional devices create microscopic thermal zones. Pigment-targeting lasers intentionally interact with melanin and may cause inflammation even when epidermal injury appears limited. IPL and vascular devices can also provoke PIH through thermal or inflammatory effects under certain conditions. Chemical peels vary according to agent, concentration, pH, contact time, application technique, and depth [24,25,34–38].

Adjustable laser parameters cover fluence, pulse width, density, overlap, passes, cooling and intervals. Poor indication, device choice, treating inflamed skin or early retreatment also trigger pigment complications. Therapy should be tailored to indication, target, skin features and planned injury.

5.6 Anatomic Site, Exposure, and Aftercare

Anatomical sites differ in baseline pigmentation, epidermal thickness, vascularity, sebaceous activity, hair distribution, friction, and exposure to sunlight. Face and neck lesions are particularly noticeable, whereas exposed extremities may receive greater cumulative UV exposure. Friction, picking, shaving, tight dressings, and irritant aftercare may maintain inflammation and extend the period during which pigmentation can develop. Evidence directly comparing every body site is limited, so these considerations should be treated as clinical modifiers rather than validated independent predictors [3–5,17–22].

5.7 Patient Adherence and Access to Follow-up

Prevention depends on whether patients can follow instructions, obtain suitable photoprotection, recognize early complications, and return for reassessment. Tinted sunscreen may not be acceptable to every patient because of shade mismatch, residue, or cosmetic feel. Complex regimens can increase irritation and decrease adherence. Instructions should therefore be feasible, clearly prioritized, and matched to the procedure and the patient's routine. A simpler regimen that is

followed consistently may be more effective than a complex plan that is poorly tolerated [17–22].

6. Prevention: Current clinical strategies

6.1 Establish the Indication and Baseline Before Treatment

The first preventive intervention is appropriate patient and procedure selection. Clinicians should confirm the diagnosis, identify whether the target pigment is epidermal, dermal, vascular, or mixed, and assess whether a procedure is likely to help the underlying problem. A procedure that induces additional inflammation may be counterproductive when the diagnosis is uncertain or when the lesion is a dermal pigment disorder that responds poorly to the proposed device [24,25,34–36].

Baseline documentation should include standardized photographs under consistent lighting, the distribution and color of existing lesions, relevant medication exposure, phototype, previous PIH, current inflammatory disease, and expected downtime. When available, objective measures such as melanin index or colorimetry can increase sensitivity to change, but their limitations should be acknowledged. Measurements can be influenced by erythema, ambient light, device positioning, hydration, and baseline skin tone; a change in instrument readout is not automatically equivalent to a change in melanin alone [3,4,6,7].

6.2 Control Active Inflammatory Disease

Elective procedures should generally be deferred until active dermatitis, infection, or severe inflammatory acne is adequately controlled. This reduces the chance that the procedure will compound an ongoing melanogenic stimulus. For acne-associated pigmentation, early control of active lesions is central because each new inflammatory lesion can produce additional PIH. A 2023 Delphi consensus and literature review supported early, effective acne treatment, commonly including topical retinoid and benzoyl peroxide therapy where appropriate, with adjunctive pigment-directed treatment selected according to tolerance and patient factors [38].

For patients receiving repeated procedures, the interval between sessions should allow adequate resolution of erythema, edema, crusting, and barrier disruption. Persistent erythema or pain should trigger reassessment rather than automatic continuation of the planned schedule. Preventing repeated or sustained inflammation is likely to be particularly important for patients with a history of severe PIH, although the ideal recovery interval differs by procedure and is not defined by a single universal rule.

6.3 Optimize Energy-based Treatment

Device selection should reflect the diagnosis, target chromophore, skin phototype, anatomical site, and available operator experience. For patients at higher risk of PIH, reasonable risk-reduction measures include a test spot when appropriate, conservative initial parameters, avoidance of unnecessary overlap and excessive density, effective cooling where indicated, and careful observation of the tissue endpoint. These measures are grounded in established procedural principles and cumulative clinical experience, though large head-to-head trials focused specifically on prevention remain scarce [24,25,34–36].

The 2023 review by Sowash and Alster concluded that laser therapy for PIH in skin of color should generally remain an adjunct for selected refractory cases because response is variable and treatment may worsen pigmentation if parameters are poorly chosen [24]. Reviews of dermal hyperpigmentation likewise emphasize accurate diagnosis and matching the device to the pigment depth and clinical disorder [36]. These recommendations concern the treatment of existing pigmentation, but the safety principles are also relevant when considering the risk of inducing additional PIH.

6.4 Immediate Postoperative Care and Inflammation Control

After procedures that disrupt the barrier, care should prioritize wound healing and prevention of avoidable irritant or infectious complications. Bland emollients or petrolatum, gentle cleansing, and procedure-specific wound care may be appropriate; patients should avoid scrubbing, picking crusts, or adding multiple irritating active ingredients before re-epithelialization. The exact regimen should be tailored to whether the intervention is ablative, nonablative, superficial, or deeper.

Topical anti-inflammatory therapy has some clinical evidence in selected contexts. In a split-face study of Asian patients undergoing ablative fractional CO_2 resurfacing, a short course of clobetasol propionate followed by petrolatum was associated with a lower incidence and intensity of PIH than petrolatum alone [27]. A smaller trial after Q-switched Nd:YAG treatment of Hori nevus also observed a tendency toward lower pigmentation with a combination containing a topical corticosteroid, although differences were not statistically significant [28]. These studies do not justify routine corticosteroid use after all procedures. Potency, application duration, infection risk, atrophy, and the wound-healing context must be considered, and use should follow appropriate clinical judgment.

6.5 Topical Melanogenesis Inhibitors Before or after Procedures

Topical agents that suppress melanogenesis are biologically plausible preventive adjuncts when the principal risk is melanin overproduction. These include hydroquinone, azelaic acid, retinoids, selected resorcinol derivatives, and other ingredients targeting tyrosinase or melanosome-related pathways. However, evidence supporting a universal pre-treatment regimen is limited, and irritant dermatitis caused by these agents can paradoxically increase PIH risk [3,5,7,39,40].

Hydroquinone remains a well-established depigmenting agent for selected disorders, but it requires proper prescribing, time-limited use, monitoring, and consideration of local regulation. Prolonged or unsupervised use can lead to irritant dermatitis and, rarely, exogenous ochronosis, a paradoxical

blue-gray or black pigmentation [13–15]. Consequently, hydroquinone should not be considered an innocuous default preventive product for every patient or every procedure.

A randomized, evaluator-blinded study published in 2024 assessed isobutylamido thiazolyl resorcinol (ITR) before Q-switched 532-nm Nd:YAG treatment of solar lentigines. In 24 patients, twice-daily ITR for two weeks before treatment was associated with a lower PIH incidence at week 4 compared with no pre-treatment (20.8% versus 50.0%; p=0.028); once-daily application did not show the same statistically significant result, and several objective pigment outcomes did not differ significantly between groups [30]. This is a promising but small trial. Replication in larger populations, varied phototypes, and different procedures is needed before ITR can be recommended as a universal preventive standard.

6.6 Tranexamic Acid: Promising but not Definitive

Tranexamic acid (TXA) has been investigated because it may influence plasmin-related signaling and melanogenesis. Studies have examined oral, topical, intradermal, and laser-assisted delivery. These routes are not interchangeable: efficacy, exposure, and potential adverse effects differ, and results from melasma treatment cannot be assumed to apply to procedural PIH prevention [29,33].

A prospective randomized controlled study of 40 patients receiving Q-switched 532-nm Nd:YAG laser for solar lentigines found that oral TXA started after treatment did not significantly reduce PIH incidence or improve several primary pigment outcomes compared with placebo, although dermoscopic pigmented granules were less frequent in the TXA group at selected follow-up visits [29]. A small split-area study examined laser-assisted delivery of TXA for established post-traumatic PIH, but its treatment setting differs from primary prophylaxis after a procedure [33]. Oral TXA also requires assessment of thromboembolic risk and contraindications; it should not be routinely prescribed solely to prevent PIH without an individualized clinical rationale.

A 2026 systematic review and network meta-analysis examined prevention of PIH after laser or other energy-based procedures. Fourteen randomized trials were included in the review and 11 in the network analysis. Intradermal tranexamic acid (TXA), topical corticosteroids, topical vasoconstrictors, oral TXA, and epidermal cooling were statistically favored over sunscreen alone in the network, with intradermal TXA ranked highest. Whitening agents and epidermal growth factor-containing products did not show a statistically significant advantage over sunscreen [26]. These rankings are interesting, but the estimates were often imprecise and the evidence base was small. They should not be read as a universal treatment hierarchy.

6.7 Epidermal Growth Factor-containing Products

Epidermal growth factor (EGF)-containing topical products have been proposed to improve recovery and potentially reduce PIH after laser procedures. A 2024 systematic review and meta-analysis included seven randomized controlled trials with 169 participants. PIH incidence was numerically lower with EGF-containing products, but the pooled difference was not statistically significant (odds ratio 0.64, 95% confidence interval 0.33–1.25; p=0.19). A lower melanin index was observed at one month but not consistently at other time points, and the authors highlighted small sample size and heterogeneity [32].

EGF should consequently be described as an adjunct under investigation rather than an established preventive therapy. Improved early recovery, subjective satisfaction, pigmentary outcomes, and durable prevention are distinct endpoints. Future studies should report these outcomes separately and compare the active product against an appropriate standardized wound-care regimen.

6.8 Triple-combination Creams and Delayed Intervention

Kang and colleagues evaluated postoperative risk assessment and delayed prevention after 532-nm Q-switched Nd:YAG laser treatment of solar lentigines in a randomized controlled study [31]. This work is relevant because pigmentary responses do not always emerge immediately and the timing of preventive intervention may affect outcomes. However, findings from a specific laser, indication, and patient population should not be generalized to every ablative or nonablative procedure.

6.9 Chemical Peeling and Microneedling

Chemical peels induce controlled chemical injury, and the risk of PIH increases when the depth or intensity exceeds what is appropriate for the patient and indication. In darker skin, superficial or carefully selected medium-depth approaches are generally favored over unnecessarily deep injury, and pre-treatment control of active inflammation is important. Patient selection should consider phototype, previous PIH, active acne or dermatitis, history of abnormal healing, and the specific agent and technique [37,38].

Microneedling and related procedures also produce controlled tissue injury. Their PIH risk is not zero, particularly when performed too aggressively or in the presence of active inflammation. The number of passes, needle depth, pressure, and aftercare should be selected according to the indication, and additional active ingredients should not be applied through a disrupted barrier unless the delivery method and formulation are clinically appropriate. Comparative prevention data across device types remain limited.

6.10 Photoprotection after Treatment

Photoprotection is one of the most broadly applicable preventive strategies because UV exposure can directly stimulate melanogenesis and aggravate post-inflammatory changes. Patients should receive instructions that include broad-spectrum sunscreen, appropriate reapplication, protective clothing, shade, and avoidance of intense exposure during recovery. The duration should reflect the anticipated course of inflammation and pigmentary risk, not simply the first few days after treatment [16–22].

For patients with pigmentary disorders or darker skin phototypes, visible-light protection may be relevant. Tinted

sunscreens containing iron oxides can attenuate visible light in addition to UV when the formulation provides adequate protection and is acceptable to the patient. In a randomized study of melasma, an iron-oxide-containing sunscreen used with hydroquinone produced greater improvement than UV-only sunscreen; however, that trial addressed melasma and should not be interpreted as direct evidence for preventing all procedure-related PIH [21].

Photoprotection cannot eliminate all forms of iatrogenic pigmentation. It is unlikely to prevent direct drug deposition, iron-containing pigment accumulation, or pigmentation due to ongoing inflammation in the absence of light exposure. Therefore, photoprotection should be positioned as a core adjunct rather than a complete standalone intervention.

6.11 Prevention of Drug-induced Pigmentation

DIP prevention starts with medication selection, informed prescribing, and early recognition. When a medication is known to cause pigmentation, clinicians should discuss the possibility before prolonged treatment, particularly when cumulative dose or duration is relevant. Where clinically appropriate, alternative agents may be considered, but an essential treatment should not be withdrawn without balancing the risks and benefits. A decision may involve the prescribing specialist, dermatologist, and patient [1,10–12].

For potentially pigment-inducing medications, useful measures include documenting baseline skin and mucosal findings, explaining the early signs of pigmentation, reviewing cumulative exposure, considering photoprotection for photosensitizing drugs, and reassessing new changes promptly. If pigmentation develops, the evaluation should determine whether it reflects direct deposition, phototoxicity, inflammation, or another diagnosis. The 2024 DIP review provides a useful contemporary framework for recognizing the breadth of implicated drug classes and mechanisms [1].

6.12 Avoidance of Iatrogenic Dyschromia from Depigmenting Products

Prevention also requires avoiding harm from the preventive treatment itself. Hydroquinone, retinoids, acids, and other topical agents may cause irritant dermatitis, especially when combined or used too frequently. In susceptible skin, irritation can trigger the very PIH the treatment was intended to prevent. Unsupervised use of potent topical corticosteroids or products of uncertain composition can lead to atrophy, telangiectasia, acneiform eruptions, infection, and other adverse effects [13–15,37].

When a depigmenting agent is used, patients should receive clear instructions about concentration, application site, frequency, treatment duration, expected irritation, and when to stop and seek review. Persistent or paradoxical darkening during treatment warrants reassessment for irritant dermatitis, allergic contact dermatitis, exogenous ochronosis, or an incorrect original diagnosis. Long-term unsupervised bleaching regimens should be discouraged.

7. Evidence Summary and Clinical Implications

Preventive strategy	Evidence base	Interpretation for practice
Individualized risk assessment and conservative procedure planning	Reviews, observational evidence, procedural consensus [3–5,24,25,34–38]	Strong clinical rationale; exact risk-prediction models remain unvalidated
Barrier-supportive wound care and control of avoidable inflammation	Clinical trials in selected ablative procedures plus biologic rationale [27,28]	Useful, but regimens must be procedure-specific
Short-course topical corticosteroid after selected laser procedures	Small randomized trials; favored in 2026 network meta-analysis [26–28]	Potentially beneficial in carefully selected cases; not a universal routine due to steroid-related risks
Tranexamic acid	Mixed results across routes and settings; network meta-analysis suggests possible benefit in selected laser protocols [26,29,33]	Promising but not definitive; systemic safety and route-specific evidence must be considered
ITR before Q-switched laser	Small randomized controlled trial [30]	Preliminary signal of reduced incidence; needs replication
EGF-containing products	Meta-analysis of seven small RCTs; incidence reduction not statistically significant [32]	Insufficient evidence for routine prophylaxis
UV and visible-light photoprotection	Consensus, reviews, and trials mainly in pigmentary disorders such as melasma [16–22]	Core adjunct; direct prevention evidence differs by condition, and it cannot prevent direct drug deposition
Medication review and early recognition for DIP	Drug review and medication-specific evidence [1,10–15]	Essential, mechanism-dependent, and often more important than topical prophylaxis

A key limitation deserves emphasis: the recent network meta-analysis combines studies that differ substantially in laser or energy device, treatment indication, skin phototype, and co-interventions. Such heterogeneity weakens the clinical meaning of indirect comparisons. The results are useful for generating hypotheses, but their value for choosing a preventive regimen for an individual patient remains limited [26].

8. Emerging Directions

Future iatrogenic pigmentation research should stratify cases by pathogenic pathway and use standardized, objective outcome metrics with predefined clinical cutoffs to avoid confounding by erythema and inconsistent imaging. Longer follow-up is needed to detect delayed PIH, recurrence and patient-centered outcomes. New tyrosinase inhibitor formulations require balanced assessment of efficacy and cutaneous risks. Studies should include diverse skin phototypes; pragmatic trials evaluate PIH preventive packages, whereas registries and safety cohorts are optimal for drug-induced pigmentation.

9. Limitations of the Current Evidence

This review is narrative rather than systematic, so relevant studies may have been missed despite targeted searching and citation chasing. The included literature also covers different clinical entities and interventions; results should not be interpreted as if they estimate a single common effect. Many preventive studies are small, single-center, and procedure-specific. Studies of skin of color use variable definitions of phototype, race, and ethnicity, which may not capture the diversity of pigmentation biology. Finally, a recent publication is not necessarily high-certainty evidence: a network meta-analysis can still be constrained by a small and heterogeneous set of primary trials [6,7,26,32].

10. Conclusion

Iatrogenic hyperpigmentation encompasses clinically similar but biologically diverse disorders arising after medications, procedures, and other medical interventions. Inflammation-driven melanogenesis and pigment incontinence are central to procedure-associated PIH, whereas direct drug or metabolite deposition and other non-melanin pigments require different preventive priorities. Risk reflects the combined effects of baseline pigmentation, prior PIH, active inflammation, medication exposure, procedure-related injury, and environmental light.

The most defensible preventive approach is individualized and mechanism-based. Clinicians should confirm the diagnosis, assess baseline risk, control active inflammation, select appropriate treatment parameters, provide barrier-supportive aftercare, recommend suitable photoprotection, review potential pigment-inducing drugs, and arrange follow-up capable of detecting delayed changes. Recent trials and meta-analyses suggest possible benefit from selected interventions, including topical corticosteroids in specific postoperative settings, TXA in selected protocols, and pre-treatment ITR, but the evidence does not support one universal prophylactic regimen. Larger prospective studies with standardized pigmentary outcomes and adequate representation of darker skin phototypes are needed. Until then, minimizing avoidable injury and tailoring prevention to the dominant mechanism remain the most reliable clinical principles.

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