Proven Strategies to Prevent

When hyperpigmentation brings patients to your office, be prepared to offer effective, efficient interventions.

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Dyschromia accounts for a significant number of dermatology visits by patients of color. Postinflammatory hyperpigmentation and melasma are among the most common presentations for which patients with darker skin seek dermatologic care; pigmented disorders account for the third most common dermatologic diagnosis in blacks, Hispanics, and Asians. Despite the relatively high incidence of hyperpigmentation disorders, treatment remains notoriously challenging. Effective options exist, but these may be associated with irritation, slow onset, and paradoxically in some cases risk of inflammation and subsequent pigmentary alteration. Dermatologists must work closely with patients to develop effective regimens, promote compliance, and encourage healthy patient behaviors, such as sun avoidance.

Understanding Causes
Postinflammatory hyperpigmentation frequently develops as a result of inflammatory cutaneous disorders or irritation associated with topical therapeutic interventions. Both topical retinoids and benzoyl peroxide may be associated with cutaneous irritation and subsequent development of hyperpigmentation. Interestingly, topical retinoids are also a potential treatment for hyperpigmentation. Postinflammatory hyperpigmentation is a normal biological response in human skin. It may develop as a response to papulosquamous diseases (such as allergic contact dermatitis, lichen planus, etc.), vesiculo-bullous diseases (such as bullous pemphigoid, herpes zoster, etc.), or inflammatory diseases, primarily acne. Post-inflammatory hyperpigmentation is a common sequela of acne vulgaris, particularly in patients of color. Many patients report greater distress over subsequent hyperpigmented macules than over acne lesions themselves.

Melanin production may remain unchanged in response to cutaneous trauma or inflammation, but in some cases, melanocytes can react with increased production. The actual pathogenesis of postinflammatory hyperpigmentation is unknown, although the actions of cytokines and inflammatory mediators from keratinocytes on melanocyte function are implicated.

Recent research suggests that heat could play a role in development of melasma. Ambient heat and subsequent increased cutaneous temperature may influence melanocyte function; further study is indicated. Meanwhile, dermatologists should counsel patients about the risk and urge avoidance of excessive heat (including standing over hot stoves, in front of fireplaces, etc.).

Diagnostic Tips
Postinflammatory hyperpigmentation develops due to an increase in melanin production, an abnormal distribution of melanin pigment, or both. Epidermal melanin appears brown in color, whereas dermal melanin tends to have a blue or bluish-gray appearance. Use of a Wood’s lamp may help distinguish between dermal and epidermal melanin deposition. The lamp shone on the skin will enhance the epidermal component while the dermal component will become unapparent. However, due to optical factors, the Wood’s lamp does not always prove useful in persons of color. Hyperpigmentation disorders in which the melanin is epidermal are easier to treat than those in which melanin is dermal. It is critical that physicians attempt to uncover underlying causes of hyperpigmentation and attempt to treat them. Eliminating contributory disease processes is the only way to prevent further development of dyschromia.

Skin Care and Sun Avoidance Basics
Sun avoidance and sun protection are critical elements of therapy for patients with hyperpigmentation. Use of a broad-spectrum sunscreen in conjunction with one of the phenolic or nonphenolic therapies discussed below is first-line therapy for hyperpigmentation. Failure to adhere to appropriate sun protection strategies can contribute to redevelopment of hyperpigmentation and reverse the therapeutic benefits of topical therapy. Given the potentially lengthy duration of therapy to diminish hyperpigmentation, neither patients nor physicians welcome the prospect of redevelopment of dyschromia.

Counsel patients to select a broad-spectrum (UVA/UVB) sunscreen product for daily use. Physical sunscreens provide more protection than chemical sunscreens, however, they are not as cosmetically elegant. They can leave an ashy residue that is more pronounced in darker skin. There are numerous sunscreen formulations available at various concentrations, formulations, and costs, providing patients ample opportunity to identify a product that fits their individual preferences, thus promoting compliance. Given the nature of potential con-
Phenolic hydroquinone has been the gold-standard of hyperpigmentation therapy for over half a century. It is available over-the-counter in 2% formulations and by prescription in 3-4% concentrations (Claripel, Stiefel; EpiQuinMicro, Skinmedica; Glyquin, Valeant; Lustra, Medicis; TriLuma, Galderma). Higher concentrations, from 5-10%, may be compounded. These higher strengths may be irritating and unstable, but they may be necessary to treat extremely dark postinflammatory hyperpigmentation or melasma. Gradual titration of hydroquinone to higher concentrations and/or incorporation of a topical corticosteroid can limit adverse reactions and improve tolerability of therapy for patients.

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Hydroquinone exerts its effect by inhibiting the enzyme tyrosinase, reducing the conversion of dihydroxyphenylalanine (DOPA) to melanin. Additional proposed but unproven mechanisms include destruction of melanocytes, degradation of melanosomes, and inhibition of DNA and RNA synthesis. Although lower OTC concentrations demonstrate efficacy, the onset of action is generally significantly delayed compared to that of hydroquinone 3% or higher.

Co-administration of vitamin C, retinoids, or alpha-hydroxy acids topically can enhance the efficacy of hydroquinone by increasing penetration of the agent. Certain formulations of hydroquinone, such as Lustra and Glyquin, incorporate AHAs and antioxidants into the formulation. Exercise caution, as retinoids and AHAs may also be associated with development of cutaneous irritation.

Adverse reactions to hydroquinone include irritant and allergic contact dermatitis, which may result in postinflammatory hyperpigmentation, and nail discoloration. Hypopigmentation of normal skin surrounding treatment areas may also develop. These side effects usually resolve with discontinuation of therapy.

Exogenous ochronosis may result from exposure to hydroquinone, but only 45 cases have been reported in North America despite a significant history of use of the agent. However, in South Africa, where women often use very high concentrations of hydroquinone over large surface areas, reports are more common.

Arbutin. A plant-derived compound, arbutin is the B-D-glucopyranoside derivative of hydroquinone, effective in managing hyperpigmentation characterized by hyperactive melanocytes. The agent is available in a range of non-prescription products in a 3% concentration. Studies demonstrate a dose-dependent reduction in tyrosinase activity and melanin content in melanocytes. Higher concentrations demonstrate greater efficacy than lower concentrations, but the former may paradoxically produce hyperpigmentation. Arbutin and kojic acid (discussed below) are indicated in those patients who develop allergic reactions to hydroquinone or those who have been using hydroquinones for an extended period of time to help diminish the risk of developing exogenous ochronosis.

Kojic Acid. A naturally-occurring hydrophilic fungal derivative used in the treatment of hyperpigmentation disorders, kojic acid is also available in a range of over-the-counter skin care products in concentrations from 1-4%. It inhibits tyrosinase with efficacy similar to hydroquinone.

Initial excitement for kojic acid focused heavily on the lack of any sensitizing activity associated with the agent. In fact, kojic acid is widely used in skin care products in Japan. However, recent long-term data from Japan show that kojic acid may produce contact dermatitis and erythema.

Azelaic Acid. This naturally occurring, non-phenolic agent originally developed for treatment of acne inhibits tyrosinase and subsequently improves hyperpigmentation. Azelaic acid 20% (Azelex, Allergan) is approved in the US for treatment of acne but is widely used off-label for post-inflammatory hyperpigmentation. Many clinicians include azelaic acid as an element of the first-line topical treatment regimen for acne in patients of color or those with a history of post-inflammatory hyperpigmentation. Azelaic acid reduces production of free radicals, which studies implicate in development of post-inflammatory hyperpigmentation. Additionally, by inhibiting DNA synthesis and mitochondrial enzymes, it is cytotoxic to melanocytes.

Whereas one study found azelaic acid 20% equivalent to 2% hydroquinone in management of melasma, another showed the 20% concentration is better. It has also been used in management of lentigo maligna and other hyperpigmentation disorders. Azelaic acid will not depigment normally pigmented skin, freckles, senile lentigines, and nevi. This may reflect the fact that the agent selectively acts on abnormal melanocytes.

Topical Retinoids. The mechanism of action of topical
tretinoin (Retin-A, Ortho-Neutrogena; Avita, Bertek) in hyperpigmentation is poorly understood, but possible inhibition of tyrosinase and subsequent reduction in epidermal melanin are suspected.\textsuperscript{16} Topical tretinoin 0.05-0.1\% as monotherapy demonstrates efficacy in the management of postinflammatory hyperpigmentation and melasma; however, longer treatment periods, lasting 20-40 weeks, may be necessary.

After 40 weeks of therapy, black subjects treated with tretinoin in one study had significantly lighter post-inflammatory lesions compared to controls. Epidermal melanin content of lesions had decreased 23 percent in the treated group compared to three percent in controls.\textsuperscript{17}

Forty weeks of tretinoin monotherapy yielded a 32 percent improvement in the Melasma Area and Severity Index score in black patients compared to 10 percent improvement in the control group. Sixty-seven percent of treated patients experienced moderate side effects of desquamation and erythema.\textsuperscript{18,19} Darker skinned patients who develop a dermatitis from tretinoin therapy risk developing hyperpigmentation as a response to the dermatitis. This is often called retinoid hyperpigmentation.\textsuperscript{20}

The retinoid analogue, adapalene (Differin, Galderma), is an alternative to tretinoin. In one study comparing adapalene 0.1\% to tretinoin 0.05\% cream in management of melasma, adapalene demonstrated similar efficacy with fewer side effects and greater patient acceptability. Because retinoids are effective for postinflammatory hyperpigmentation, they are a good medication to use to simultaneously treat both acne and post-inflammatory hyperpigmentation from acne.

Topical Corticosteroids. Hypopigmentation is a well-documented side effect of long-term topical corticosteroid use. However, reliably influencing pigmentation with topical corticosteroids may be somewhat difficult. Nonetheless, topical corticosteroids have been used alone or in combination with other topical agents to improve hyperpigmentation. These agents demonstrate variable effect when used as monotherapy to treat post-inflammatory hyperpigmentation or when used as monotherapy or combination therapy for melasma.

Combination Therapy

Combination regimens designed to balance the relative strengths and weaknesses of the various available agents may yield optimal results by allowing for more rapid clearance and enhancing outcomes. The first published study of combination therapy used tretinoin 0.1\%, hydroquinone 5\%, and dexamethasone 0.1\% for postinflammatory hyperpigmentation.\textsuperscript{21} Tretinoin reduced the atrophy of the corticosteroid and enhanced penetration of the hydroquinone, while the corticosteroid helped diminish tretinoin-induced irritation. Now, a similar FDA-approved combination formulation is available in the US (Tri-Luma). It incorporates fluocinolone acetonide, hydroquinone 4\%, and tretinoin 0.05\%. In studies, 78 percent of patients treated with the formulation for melasma demonstrated near or complete clearing after eight weeks of therapy. A 12-month study demonstrated similar efficacy and safety.\textsuperscript{22}

Some dermatologists compound similar tretinoin/corticosteroid/hydroquinone formulations with higher concentrations of hydroquinone. Alternatively, if compounding is unavailable, physicians may develop therapeutic regimens that include use of a topical hydroquinone cream plus a layering application of a separate topical retinoid or topical corticosteroid on top of the first cream.

Linea Nigra: A Unique Presentation

The linea alba is a pale line that normally appears to extend from the xyphoid process over the abdomen through the umbilicus to the symphysis pubis. During pregnancy, when the line darkens, it is called the linea nigra.\textsuperscript{23,24} Similar darkening may appear around the nipples, areola, perineum, vulva, and inner thighs.\textsuperscript{25} Though the exact mechanism of this benign and common condition is unclear, hormonal mechanisms are likely at play.

Up to 90 percent of pregnant women may develop linea nigra; pigmentation is usually more intense in women of color. This gestational pigment darkening usually resolves naturally within several months post-partum.\textsuperscript{26}

Agents in Development

- **NCAP (N-acetyl-4-cysteaminylphenol).** This phenolic agent currently in development but not yet available in the US demonstrates efficacy in the management of melasma. In a retrospective study of 12 melasma patients treated with NCAP, 66 percent showed marked improvement and eight percent had complete clearance. The agent began to demonstrate efficacy within two to four weeks.\textsuperscript{27,28}

- **Licorice extract.** With a mechanism of action similar to that of kojic acid, licorice extract is used across the world. Its primary component, glabridin, demonstrates the ability to inhibit tyrosinase activity, blocking melanogenesis and inflammation. But the agent does not appear to affect DNA synthesis.\textsuperscript{1}
Beware of Medication Abuse

Contrary to FDA regulation, some prescription-strength corticosteroid and hydroquinone products may be available to patients over-the-counter. This is particularly true in larger urban centers, such as Washington, DC, New York City, Los Angeles, and Miami, where ethnic stores often carry these "skin care" products. Available corticosteroids may be high-potency (class 1 and 2), while hydroquinone products are generally available in a range of strengths.

While cases of exogenous ochronosis have remained low despite a very high rate of use of hydroquinone in the US, the rate of adverse events may increase significantly as greater numbers of patients obtain and use high-strength hydroquinone without physician supervision.

Consider Adjunct Measures

Use of microdermabrasion in conjunction with topical therapy is common in management of hyperpigmentation. Chemical peels may also prove beneficial as additive measures in hyperpigmentation treatment. Superficial chemical peels, such as beta-hydroxy acids (salicylic acid), are very effective in treating post-inflammatory hyperpigmentation from acne and may improve acne itself.

In melasma, chemical peels are useful as part of a maintenance regimen in combination with daily use of bleaching agents. However, chemical peels must be done on a regular basis to provide notable benefit in melasma. Microdermabrasion is effective for postinflammatory hyperpigmentation from acne but is not very helpful for melasma. Lasers have not demonstrated significant efficacy in management of melasma, but they may be effective for nevus of Ota or postinflammatory hyperpigmentation.

The 694 nm Q-switched ruby laser, in particular, has demonstrated benefit.

However, all of these modalities have potential side effects, including pigmentary alteration, when used in skin of color. Therefore, use them judiciously and only when you are comfortable doing so.

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