Despite the availability of multiple treatments for the condition, hyperpigmentation continues to prevent clinical management challenges for dermatologists. Difficulty may be traced to physician or patient reluctance to use certain agents or interventions, failure to identify and avoid contributing factors, and insufficient attention paid to the psychosocial aspects of the disease. The following review, focused specifically on melasma and hyperpigmentation, will address current understanding of these aspects of care and provide a guide to efficient management of hyperpigmentation.

**EVALUATION OF HYPERPIGMENTATION**

Hyperpigmentation may be localized, as in the case of post-inflammatory hyperpigmentation or melasma, or more diffuse in its presentation. Diffuse hyperpigmentation, on the other hand, tends to be associated with metabolic causes, certain medications, malignancy, or autoimmune or infectious etiologies (Table 1). Since diffuse hyperpigmentation may be associated with malignancy or may be improved through treatment of the underlying disease process or insufficiency or elimination of the causative medication, it is important to identify the cause.

Both localized and diffuse hyperpigmentation share the same basic pathogenesis, which, though not yet fully elucidated, is generally understood to involve inflammatory mediators, such as prostaglandins (including PGE2), and leukotrienes (including LTC4 and LTD4). These have been shown to stimulate epidermal melanocytes, which in turn produces a disruption in the skin’s basal layer. This leads to dermal deposition of melanin and subsequent macrophage activation.

**TREATMENT OPTIONS FOR LOCALIZED PIGMENTATION**

First and foremost, it is essential to identify and treat any underlying dermatoses and stress the importance of sun protection. Patients must use sunscreens—preferably containing physical blockers like titanium dioxide or zinc oxide—on all sun-exposed skin on a daily basis. Additionally, patients should practice UV avoidance through the use of physical barriers like hats and clothing that will reduce exposure.

In the case of melasma or PIH, topical treatment options include retinoids, azelaic acid, hydroquinone, chemical peels, and cosmeceuticals. Reassurance and time are also essential.
elements of the treatment regimen that are sometimes overlooked by the physician and the patient.

The selection of a particular retinoid may depend on the preference of the prescriber or patient. Recent research suggests that tazarotene 0.1% cream may offer better efficacy than adapalene 0.3% gel for the management of post-inflammatory hyperpigmentation. Findings come from a controlled, blinded trial involving 180 subjects with PIH related to acne. Investigators evaluated improvement of both PIH and acne among subjects, who included African-Americans, Asians, and Hispanics. While 20 percent of patients in the tazarotene 0.1% cream group had complete resolution at week 16, only seven percent of patients in the adapalene 0.3% gel group achieved complete resolution at this point.

Hydroquinone remains a workhorse of melasma management, despite recent controversy. The supervised use of prescription topical hydroquinone had no more than a theoretical risk of malignancy, developing ochronosis, or of the long-term safety side effects. There is no substantial evidence to prove carcinogenicity. Importantly, unsupervised use of hydroquinone and use of unapproved formulations is reportedly linked to ochronosis and unwanted side effects. Therefore, patient education is crucial. Take time to assure patients of the safety of the prescription agent you recommend—when used as you direct—and describe clearly the intended duration of therapy. Ideally, patients will not fear the use of hydroquinone, but they will have a healthy respect for the agent, reducing the risk for abuse and misuse.

Another topical treatment option is azelaic acid (AzA), which may offer optimal benefit when combined with a topical corticosteroid. In a prospective, single blinded, right/left comparison study, 40 Indian patients with melasma were instructed to apply AzA cream 20% to one half of the face for 24 weeks and to apply clobetasol 0.05% for eight weeks followed by AzA cream 20% for next 16 weeks. Sequential therapy was associated with more significant improvement than monotherapy (p<0.01).

Triple combination fixed therapy (fluocinolone acetonide 0.01%, hydroquinone 4%, tretinoin 0.05%) has become a standard intervention, as well, with evidence suggesting that the combination is more effective than hydroquinone monotherapy. In a multicenter randomized control trial of Southeast Asian subjects (n=260) patients, 129 individuals were assigned to the triple combination group, and 131 were assigned to treatment with hydroquinone alone. During the eight-week study, assessments of Melasma GSS, MASI, and patient satisfaction were made. Triple combination therapy offered superior efficacy to monotherapy in GSS and other variables, although it was associated with more adverse effects.

Numerous case reports and studies have been performed over the last decade highlighting the use of products such as zinc, arbutin, kojic acid, vitamin C based compounds, and green tea extracts, as newer therapies for treating our melasma patients. One example of a novel therapy for melasma that has recently appeared in the literature demonstrates the effects of topical methimazole. Topical methimazole is a potent peroxidase inhibitor under investigation for the management of hyperpigmentation. Peroxidase is important in the final steps of melanogenesis and in some tyrosinase free cells. Even at high concentrations, methimazole is not melanocytotoxic. Kasraee et al showed 20 patients with no TSH, free thyroxine, or free iodothyronine levels. The drug is odorless and very well tolerated. Though more randomized, controlled large cohort trials are needed to further elucidate the role of products such as methimazole, zinc, arbutin, and others, these recent studies give some hope to our patients suffering from melasma for more novel therapies in our armamentarium against this often devastating condition.

**PROCEDURES**

Superficial chemical peels are generally effective for the management of PIH and melasma when properly applied. Standard options include glycolic acid 20-70%, salicylic acid 20-30%, TCA 10-25%, or Jessner’s solution. Pre-treatment with a course of hydroquinone 4% topically (if available) is thought to improve outcomes. Any patient using topical retinoids should discontinue their use for seven days prior to the peel. They may continue to use a non-comedogenic, SPF moisturizer.

Support for the use of glycolic acid peels comes from a study that involved 19 subjects randomized to apply a twice-daily regimen of 2% hydroquinone/10% glycolic acid gel, along with tretinoin 0.05% cream nightly or to undergo six consecutive glycolic acid peels (up to 68%) with no additional topical therapy. Overall, patients treated with peels alone showed a trend for more rapid and greater improvement.

Salicylic acid peels have been shown useful in PIH, including for patients with darker skin types. In an open-label trial, 25 patients were treated with five salicylic acid peels (20-30% concentration) provided at two-week intervals. Patients underwent two weeks of pre-treatment with hydroquinone 4%. Four of five patients with Fitzpatrick type V or VI had greater than 75 percent improvement in pigmentation.

Laser therapy can be effective for hyperpigmentation with durable improvement. In one study of 27 female subjects,

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**TABLE 2. RISK FACTORS FOR HYPERPIGMENTATION**

<table>
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<td>Sunlight</td>
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<td>Endocrine issues</td>
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<td>Genetic predisposition</td>
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<td>Thyroid dysfunction</td>
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<tr>
<td>Hormonal contraceptives</td>
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<td>Never forget medications</td>
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*Never forget medications*
phototypes II–V, with mixed-type melasma refractory to previous therapies, low-fluence QS Nd:YAG laser treatment was provided at 1.6–2 J/cm² with 5 or 6 mm spot immediately following microdermabrasion. Daily application of a broad-spectrum sunscreen began immediately post-procedure. Additionally, subjects used a topical skin care regimen of hydroquinone with tretinoin or vitamin C. Treatments were repeated at four-week intervals. Most subjects showed >50 percent clearance of melasma one month after the first treatment. Side effects were limited to mild post-treatment erythema, which developed after the microdermabrasion and lasted approximately 30–60 minutes. Four subjects noted temporary exacerbation of melasma after inadvertent sun exposure, but this resolved within several weeks of resuming the topical skin care regime. Remission lasted at least six months.

**GENERAL GUIDELINES**

In order to identify any underlying causes of hyperpigmentation or identify any factors that may hinder treatment, it is essential to obtain a detailed medication history for all patients. It is also important to assess any family history and/or personal history of melasma. If the patient has been treated for melasma in the past, ascertain what therapies were used and how the patient responded. Allergic reactions to cosmetics and/or fragrance-based products may contribute to post-inflammatory hyperpigmentation. Consider patch-testing when there is suspicion for allergy. Serial photography is essential in the clinical management of hyperpigmentation. Take good baseline photos and track response throughout the treatment process. Establish protocols for image capture to ensure quality over time. Use a simple, dark background that is non-distracting. These images can be especially helpful when patients think treatment is not working. Convey to patients that you empathize with them, which will increase your credibility and rapport dramatically. Biopsy may be indicated if there is any question about the diagnosis: a 2mm punch will elucidate dermal vs. epidermal vs. other processes.

**MORE TO LEARN**

Pigmentary disorders continue to be a large part of a busy medical dermatology practice, effecting patients of all skin types. Treatment can be challenging, and slow response can lead to patient frustration. More randomized, controlled trials are needed to evaluate the efficacy of up and coming treatments in the diagnosis, management and treatment of conditions, such as melasma and vitiligo.

In addition to implementing effective therapies, physicians must dedicate time to patient education and always emphasize sun avoidance. Always take a step back and try to establish the underlying pathology and address any factors that may be contributing to pigmentary irregularity.

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**TABLE 3. DR. DESAI’S TREATMENT ALGORITHM**

- Topical triple combination therapy
- *My own compound containing HQ, kojic acid, triamcinolone, and tretinoin in special base*
- Add on chemical peels
  - Start with salicylic acid to help concomitant acne
  - Otherwise, studies favor glycolic acid
- Increase the percentage strength of hydroquinone if needed
- Consider dermabrasion for special cases
- ALWAYS EMPHASIZE UV PROTECTION

**TABLE 4. GENERAL TREATMENT GUIDELINES**

- First-line therapy
  Topicals with triple combination
  - Should patients develop irritation/allergy to triple combination therapy, dual combinations can be used
- Second-line therapy
  Chemical peels in combination with topicals

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