

The Stepwise Approach to the Treatment of Melasma

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Melasma is a symmetric progressive hyperpigmentation of facial skin that occurs in all races but has a predilection for darker skin phenotypes. Melasma has been associated with hormonal imbalances, sun damage, and genetic predisposition. Clinically, melasma can be divided into centrofacial, malar, and mandibular according to the pigment distribution on the skin. On Wood light examination, the pigment can be found within the epidermis, where it will enhance, or within the dermis, where it will not enhance. Melasma can be classified as mild, moderate, or severe for evaluation and treatment purposes. In this article, we will discuss the objective evaluation of the patient with melasma, as well as the treatments based on disease severity. Further recommendations for maintenance in these patients also will be addressed.

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Melasma is a symmetric hyperpigmentation that develops and progresses slowly. It is often associated with hormonal changes, though exposure to UV light and heat and genetic factors are its principal causes. Most of this abnormal pigmentation occurs on facial skin; however, the exterior surface of the arms also may be involved.

Facial melasma is characterized by discoloration ranging from light brown to dark gray, depending on where the pigment resides on the skin. The location

of the pigment within the skin and the reflection of light determine the perception of color. Epidermal pigment is usually light to dark brown; dermal pigment is gray-blue. On Wood light examination, pigment that resides within the epidermis is accentuated, while dermal pigment is not enhanced. Fortunately, epidermal melasma is the most common form and also the most treatable.¹ Dermal melasma, however, is very difficult to treat because the pigment is entrapped in the dermis in the melanin granules within the melanophages. To date, very few treatments are effective for dermal melasma.

Clinically, facial melasma is described in accordance with the anatomic location of the discoloration.² The centrofacial area is the most commonly affected area, as seen in two thirds of patients with melasma; the malar area is the next most frequently affected area, occurring in 20% of patients; and the mandibular area is implicated in 16% of patients. Most patients with melasma are young and middle-aged women. All races are affected. However, certain racial and ethnic groups, such as Hispanics and Asians, are more susceptible to this condition.²

Higher levels of estrogen and progesterone are among the hormonal changes implicated in the development of melasma. For example, this pigmented disorder can affect 50% to 70% of pregnant women and is frequently seen with the use of oral contraceptives.³ Perez et al⁴ reported that fertile women who developed melasma without ever having been pregnant or ever having taken oral contraceptives might show a mild ovarian dysfunction consistent with polycystic ovarian disease. They concluded that estrogen receptor sensitivity at the melanocyte target site may play a role in the causation of melasma.⁴

Despite its association with hormonal changes and genetic predisposition, sun exposure remains

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the principal cause of melasma. Melanocyte activity is increased in melasma. The melanocytes of skin affected with melasma have been shown to be highly dendritic on electron microscopic evaluation, exhibit rapid increase of DNA synthesis with sun exposure, and multiply rapidly.¹ Indeed, patients with melasma often attest to how rapidly the condition recurs after even minimal sun exposure. It is known that chronic exposure to UVA radiation increases melanin production, resulting in epidermal and dermal cellular damage manifested as pigment disorders, such as lentigines, poikiloderma, mottled hyperpigmentation with hypopigmentation and telangiectasia, and melasma.⁵ Hence, the multifactorial etiology of melasma makes it a difficult dyschromia to treat.

Specifics of melasma treatment depend on the severity of the condition. The major factors that determine the severity of the condition as mild, moderate, or severe include the extent of surface area affected, intensity of pigmentation, and homogeneity of the affected area.

Surface Area—The greater the percentage of surface area affected, the more extensive the condition. On a scale of 1 to 4, with 4 being maximum involvement (both cheeks=2, chin=1, forehead=1), full-face melasma is considered severe; a patient with melasma affecting both cheeks and the chin or forehead will be a 3 (moderate); and a patient with melasma only on the maxillary area (both cheeks) or only on the chin and forehead will be a 2 (mild).

Intensity of Pigmentation Relative to Surrounding Skin—On a scale of 1 to 3, with increasing number illustrating increase in severity, 1 shade difference is considered mild, 2 shades' difference is considered moderate, and 3 or more shades' difference is considered severe.

Homogeneity of Lesions—More homogeneous lesions are considered more severe than heterogeneous ones on a scale of 1 to 3.

Based on these parameters, a score of 3 to 5 out of a possible 10 is classified as mild melasma, 6 to 8 is moderate melasma, and 9 to 10 is severe melasma. These parameters provide an objective method for clinical evaluation in patients with melasma.

Principles of Stepwise Treatment

Because melasma is a chronic, recurrent, photo-induced dyschromia of the skin seen in genetically predisposed individuals, the treatment requires consideration of the following 3 principles: protection from sun exposure is indispensable and mandatory for success, inhibition of melanocyte activity is necessary for successful treatment even after removal of the melanin, and

chronic and adjuvant treatment is necessary for successful results.

Step 1—In any regimen prescribed for the treatment of melasma, broad-spectrum sun protection against both UVA and UVB light is vital for success. If no recurrence of melasma is the goal, the use of sun protection in the patient with melasma is a lifetime commitment. Because the action spectrum of melanogenesis is considered to be within the longer wavelength UVA range, UVA protection is indispensable.

Step 2—After the patient accepts the commitment, the next step is to inhibit melanin synthesis and transportation of melanosomes to keratinocytes. This is accomplished by the use of skin-lightening agents such as hydroquinone (HQ). HQ is a phenol compound that lightens skin color by decreasing the production of melanocyte pigment through degradation by auto-oxidation, tyrosinase, and phenol oxidases into highly reactive oxygen radicals, semiquinones, and quinones.⁶ These reactive substances prevent melanin production within melanosomes and increase degradation of melanosome packages after transfer to adjacent keratinocytes. HQs, therefore, disrupt the function and proliferation of melanocytes. In this way, topical application of HQ produces a gradual reduction of dyschromia by total melanocyte down-regulation—from prevention of production of melanosomes to their transfer to keratinocytes.

HQ 4% is the standard therapy for melasma and has been used for more than 5 decades. Lower concentrations are generally clinically effective for a milder form of the condition.⁷ Higher concentrations of HQ (up to 10%) have been used effectively in the treatment of severe melasma. However, chronic use of topical HQs, even at lower concentrations (eg, 2%), can be associated with an increased risk for exogenous ochronosis,⁸ especially when used by dark-skinned blacks. Higher concentrations of HQs also are likely to induce both more irritation and induction of exogenous ochronosis.

The effectiveness of HQ 4% is seen after approximately 20 weeks of use, and efficacy seems to plateau after 6 months' use as monotherapy. Topical HQ is more effective when applied twice a day to affected areas. Because excessive lightening of non-melasma-affected skin has not been documented in patients treated with HQ, application to the entire facial area is recommended instead of spot treatment.⁹ More localized applications can lead to a "bull's-eye" area of discoloration. Although reversible, the effect is disconcerting.

Exfoliating and moisturizing agents, such as α -hydroxy acids (eg, glycolic acid),¹⁰ have increased

the penetration and effectiveness of HQ as a skin-lightening agent. Moreover, the combination of HQ 4% with tretinoin¹¹ or retinol,¹² which in the skin is transformed to tretinoin,¹³ has been shown to be effective for chronic photodamage of facial skin and the skin of the neck and chest.¹⁴ Because tretinoin and retinol have been shown to be effective in prevention and reversal of photodamage at the molecular level, combination products can treat melasma via 2 mechanisms: correcting both the pigmentary abnormality and the photodamage component.

In fact, combination therapy with HQ and tretinoin is an effective form of treatment for facial dyschromias.¹⁵ Now, newer formulations of HQ 4% with antioxidants, such as ascorbyl palmitate and tocopherol, were found to contribute significantly to overall reductions in melanin readings in both light-skinned and dark-skinned individuals.^{16,17} In addition, the substitution of tretinoin for retinol has made the therapy more tolerable for individuals with sensitive skin, without decreasing effectiveness.¹⁸ Thus, the newer formulations are preferred for the general therapy of melasma in all skin types. Moreover, the beneficial effect of the additional active ingredients contained in the newer skin-lightening formulations is intended for full-facial improvement. Therefore, full-facial application, not spot treatment, is recommended.

Step 3—In addition to optimal medical treatment of melasma, there are chemical and surgical therapies that can be used adjunctively. While a patient is using one of the topical skin-lightening formulations appropriate for his or her condition, chemical and physical peels can be administered concomitantly on a regular basis. In particular, salicylic acid peels (20%–30%),¹⁹ glycolic acid peels (10%–70% nonbuffered),¹⁰ and microdermabrasion or Parisian peels (physical peels)²⁰ have been shown to be efficacious in the treatment of melasma and other forms of photodamage. Microdermabrasion has the least potential for complications. However, these peels should not be administered at the expense of optimal medical therapy, which is the cornerstone therapeutic regimen to be followed on a chronic basis.

Another important consideration when administering such chemical treatments to patients with melasma is to avoid any inflammation. Inflammation inflicted on darker skin types or in patients with a tendency to hyperpigmentation is translated into dyschromias that are then more difficult to remove. The same principles apply with any ablative procedure in patients with dyschromia.²¹ For physicians who frequently treat patients with skin

of color, sun protection and pretreatment with skin-lightening agents are mandatory before the procedure is performed, and should be resumed shortly after re-epithelialization of the ablated skin for prevention and treatment of expected postinflammatory pigmentation.²²

An Individualized Approach

My approach to the treatment of melasma is listed in the Table. Most importantly, all patients with melasma should use a sunblock on a daily basis with a sun protection factor of 30 and with physical and hypoallergenic chemical ingredients effective against UVA and UVB light. Patients should reapply every 2 hours when spending prolonged periods outdoors. For patients with melasma, the use of 6-inch rim hats should be mandatory for outdoor activities, and exposure to peak hours of UVB light (10 AM–3 PM) should be avoided. Sunbathing should be strongly discouraged.

In patients with mild melasma, the use of formulations containing HQ 4% or HQ 4%/retinol is recommended twice a day for 6 months. With further improvement of the condition, the HQ 4% or HQ 4%/retinol treatment is continued once-a-day with the application of tretinoin cream every night for 6 months. After one year with no recurrence, maintenance is reduced to the application of tretinoin cream every night, as tolerated. If melasma recurs, resume previous HQ 4% or HQ 4%/retinol treatment.

Patients with moderate melasma are recommended to use a HQ 4% product or a HQ 4%/retinol combination in the morning and tretinoin cream in the evening for 3 months to determine effectiveness. If the patient has no improvement after 3 months, a HQ 4%/tretinoin/corticosteroid triple combination cream alone may be used once a day for 2 months. Treatment is continued with once-a-day application of HQ 4% or HQ 4%/retinol cream and the application of tretinoin cream at night, as tolerated, for 6 months. After one year with no recurrence, maintenance should be reduced to the application of tretinoin cream at night. If melasma recurs, the patient should resume the original therapeutic regimen.

Patients with severe melasma should apply the triple combination cream at night for 2 months and should be monitored very closely. Although the tretinoin cream has some steroid-sparing benefit, a clinical study²³ and experience have shown that at 8 weeks of therapy, steroid-related side effects, such as telangiectasia and steroid acne, can begin to appear. If the condition has not cleared, continuation of the triple combination cream is

Treatment Algorithm for Melasma*

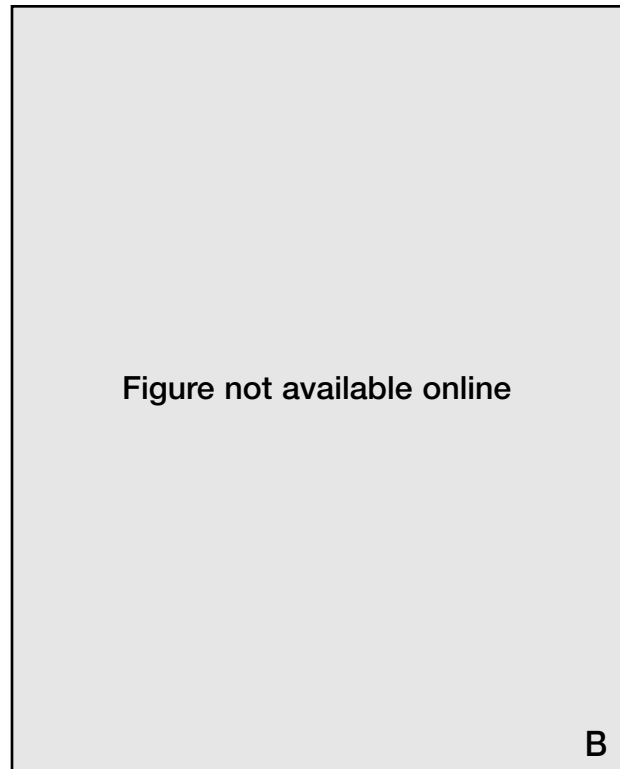
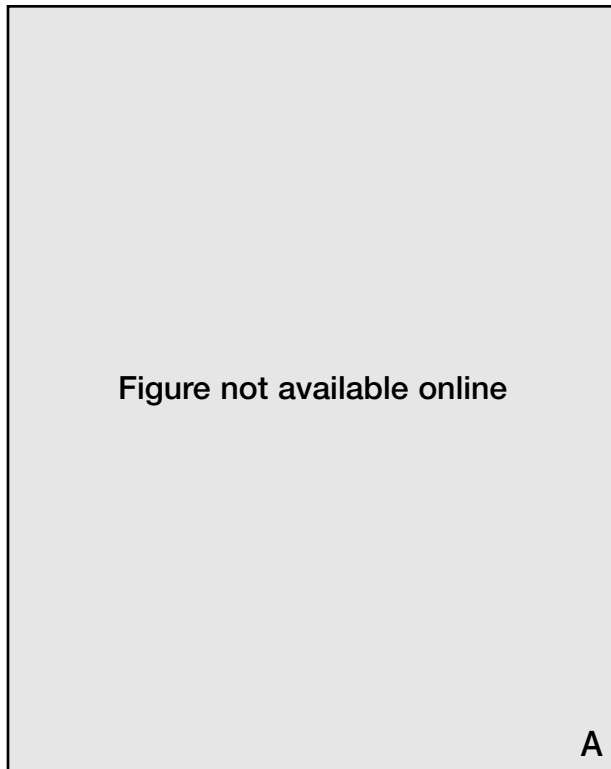
	Mild	Moderate	Severe	Resistant or Dermal	With Sensitive Skin
Basic	Physical sunblock—UVA and UVB protection				
Primary therapy					
1	HQ 4% bid or HQ 4%/retinol bid for 6 mo	HQ 4% qam or HQ 4%/retinol qam and tretinoin cream qpm for 3 mo	Triple combination cream qpm for 2 mo	Triple combination cream for 2 or 3 mo, then HQ 4%/retinol qam for 12 wk	HQ 4%/retinol bid for 6–12 mo
2		If inadequate response, triple combination cream qd for 2 mo qam	If inadequate response, triple combination cream qpm with HQ 4%/retinol for 2–3 mo	Medium-depth chemical peels	
3		HQ 4% qd or HQ 4%/retinol qd and tretinoin cream qpm for 6 mo	HQ 4%/retinol bid for 6 mo	HQ 4%/retinol bid for 6 wk. If inadequate response, triple combination cream qpm for 2–3 mo	
Maintenance therapy	Tretinoin cream qpm	Tretinoin cream qpm	Tretinoin cream qpm	Tretinoin cream qpm	Retinol qd or HQ 4%/retinol qd
Adjunctive therapy throughout treatment process	Salicylic acid peel, glycolic acid peel, or microdermabrasion	Salicylic acid peel, glycolic acid peel, or microdermabrasion	Salicylic acid peel, glycolic acid peel, or microdermabrasion	Salicylic acid peel, glycolic acid peel, or microdermabrasion	Salicylic acid peel, glycolic acid peel, or microdermabrasion

*HQ indicates hydroquinone; bid, twice a day; qam, every morning; qpm, each evening; qd, once a day.

recommended at night, with HQ 4%/retinol cream added in the morning for 2 to 3 additional months for maximal clearing (Figure). After this is accomplished, these patients should continue the HQ 4%/retinol cream twice a day for an additional 6 months, followed by maintenance therapy with tretinoin cream at night, as tolerated. If melasma

recurs, the patient should resume the previous therapeutic regimen that proved effective.

Topical treatment for resistant or dermal melasma is initiated with triple combination cream for 2 or 3 months, followed by a HQ 4%/retinol combination cream (for the triple combination's corticosteroid effect to wash out) every morning for



Patient with severe melasma before (A) and after (B) 4 months of treatment: first with triple combination cream at night for 2 months, then with hydroquinone 4%/retinol added in the morning for 2 additional months. The patient was instructed to use a physical sunblock with a sun protection factor of 30, to wear a 6-inch rim hat, and to not sunbathe.

12 weeks before the chemical peel is indicated. This is followed by a medium-depth chemical peel. This chemical peel consists of 70% glycolic acid for 3 to 4 minutes followed by a 35% trichloroacetic acid peel until frost occurs, as described in the literature.²¹ After the skin recovers, the patient is to return to the HQ 4%/retinol preparation twice a day for 6 weeks. If response is inadequate, then triple combination cream may be reinstated, as in the treatment of severe melasma. Maintenance therapy consists of tretinoin cream every evening. In patients with resistant disease or dermal melasma, more aggressive therapy is necessary. The use of medium-depth chemical peels is recommended for some of these patients (skin types IV and V, never on skin type VI). However, experience in treating darker skin types (IV and V) is necessary for success and prevention of complications. When treating these darker skin tones, the physician must anticipate hyperpigmentation before it occurs. For this reason, skin-lightening therapy should be instituted before hyperpigmentation develops.

Patients with melasma with sensitive skin can use HQ 4%/retinol combination cream twice a day for 6 to 12 months. Subsequently, application of a retinol cream or a HQ 4%/retinol cream is

recommended once a day for maintenance. If melasma recurs, the patient should resume the previous therapeutic regimen.

Lastly, all patients with melasma should be treated with either salicylic acid peels, glycolic acid peels, or microdermabrasion at the beginning of treatment and as maintenance. In patients with oily skin and a tendency to acne, salicylic acid peels are preferred. Patients are started at the lowest strength 4 weeks after topical therapy is initiated. The potency is increased on a monthly basis, as tolerated. In patients with dry skin, glycolic acid peels are recommended on a monthly basis and with increasing strength, as tolerated. These chemical peels penetrate only superficially but can accelerate improvement as adjuvant therapy and can prevent recurrence. Microdermabrasion also can be used as maintenance treatment for most patients. Deeper forms of chemical peels generally are not recommended as adjuvant therapy in patients with melasma.

Just as treatment varies with initial severity, so must it change as the melasma improves and becomes lighter with treatment; recommendations for the milder form of melasma should ultimately be adopted.

In addition, other conditions that may interfere with treatment have to be considered if therapy is to be successful. For example, patients with severe melasma and acne have to be treated differently than those with only severe melasma. The use of triple combination therapy in these patients may aggravate the acne, further contributing to post-inflammatory hyperpigmentation and more severe dyschromia. These patients are better treated as moderate melasma with the use of additional acne treatment that also can include a mild skin-lightening agent, such as azelaic acid.

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