

CLINICAL MANAGEMENT RECOMMENDATIONS

How to Manage Melasma

Seemal R Desai, MD¹, Maureen Ezekor, BS²

¹Department of Dermatology, University of Texas Southwestern Medical Center, Dallas, TX

²University of Texas Medical Branch, Galveston, TX

Melasma, previously known as chloasma, is a commonly acquired hypermelanosis characterized by symmetric, reticulated, hyperpigmentations of sun-exposed areas of the skin, particularly the face. Melasma has a higher prevalence in women and patients of darker skin tones, although it can occur in all skin types. The dyspigmentation caused by melasma often has a negative psychosocial impact on those affected with the condition as demonstrated by patient-reported anhedonia, decreased self-esteem, dissatisfactory mood, and impairment in social and occupational functioning.¹

The pathogenesis of melasma is still unclear, however various factors have been implicated and well supported such as ultraviolet radiation exposure, genetic predisposition, and hormonal influences.² Due to the incomplete understanding of its pathogenesis and the high recurrence rate, melasma remains a difficult disorder to manage resulting in physician frustration and patient dissatisfaction. Nevertheless, several topical, oral, and procedural treatment options are available with varying mechanisms of action addressing the multifactorial nature of the disorder. The purpose of this article is to provide a framework for dermatologists to use to approach and clinically manage this

common, yet therapeutically challenging, condition.

WHAT TOPICAL THERAPIES ARE AVAILABLE?

Evidence-based studies recommend that first line therapies for melasma incorporate topical agents, including photoprotection.³ Hydroquinone is historically the gold standard treatment for melasma and remains one of the most effective monotherapies. It works by inhibiting tyrosinase, thereby preventing the conversion of DOPA into melanin. Hydroquinone can cause skin irritation and very rarely lead to ochronosis with prolonged or highly concentrated applications.⁴ It should be avoided in pregnant and breastfeeding women. Although hydroquinone is the cornerstone of topical therapy, multiple studies have demonstrated superiority of topical combination therapies over monotherapy.²

Triple combination therapy (TCT) combines hydroquinone with a retinoid and a topical corticosteroid in varying concentrations.⁴ The corticosteroid serves as an anti-inflammatory agent while the retinoid is hypothesized to increase keratinocyte turnover.² Although more effective, TCT has been associated

with increased erythema and skin irritation.³ Other topical tyrosinase inhibitors such as azelaic acid, kojic acid, and ascorbic acid, for example, may also be used but have demonstrated inferiority to hydroquinone as monotherapies.² Last but not least, daily photoprotection is a critical component in the treatment of melasma. Broad spectrum sunscreens that combine UVA and UVB filters with visible light blockers, such as iron oxide, are preferable to broad-spectrum UV filters alone, with the former group showing greater improvement and reduced relapses.^{2,4}

WHAT IS THE ROLE OF ORAL THERAPY?

Oral therapies have emerged as effective treatment options for melasma, and often as an adjunctive to topical therapies. The hemostatic agent tranexamic acid (TA) is arising as a promising oral therapy to treat this disorder, as shown by recent studies.^{5,6} TA is a synthetic derivative of lysine and functions by blocking the conversion of plasminogen into plasmin, leading to a downstream effect of reduced production of melanocyte-stimulating hormone (MSH).⁴

TA is gaining attention for melasma because studies have shown effectiveness with frequently minimal side effects.^{5,6} The side effect profile for oral TA can include gastrointestinal irritation, headache, tinnitus, changes in menstrual cycle, and rarely deep vein thrombosis (DVT).^{2,5} Due to the serious, though rare, side effect of DVT, patients must be screened for risk of thrombosis prior to initiating this treatment.

A very comprehensive detailed history and physical examination are recommended for dermatologists prescribing this oral therapy. Patients must be screened for smoking, use

of oral contraceptives, history of miscarriages, plans of future pregnancy, and other important historical clues. If any the above, and/or other pertinent details are elucidated, then the patient would not be considered a candidate for TA. In addition to the oral form, TA has been used in other delivery routes including topical, intradermal, and microinjection.⁶ Clinical trials have demonstrated similar efficacy of topical TA to hydroquinone-based formulations.⁴

Other oral agents such as *Polypodium leucotomos* (PL), and even glutathione, have been discussed in the literature as possible adjunctive treatments for melasma and work by inhibiting reactive oxygen species. PL, a species of fern, protects against UV-induced damage, and oral ingestion has shown improvement in melasma with minimal to no side effects.⁸

Recently glutathione has been used as a depigmenting agent and is postulated to have this effect by inactivating melanocyte tyrosine kinase and promoting pheomelanin production from eumelanin.⁷ Treatment with oral glutathione is well tolerated with only few, mild reported side effects of flatulence, pruritus, erythema, and fatigue.⁸ However, the low oral bioavailability of glutathione leads to reduced plasma concentration and thus questionable overall effectiveness. This has led to a dramatic increase in intravenous usage of glutathione in many parts of the world, and has led to significant controversy due to safety issues. The US Food & Drug Administration, in fact, has a warning about the usage of intravenous glutathione (<https://www.fda.gov/ForConsumers/ConsumerUpdates/ucm460788>).

WHAT PROCEDURES HAVE DEMONSTRATED IMPROVEMENT?

In recent reports of literature, procedures such as chemical peels, microneedling, and lasers have been used as adjunctive and maintenance therapies for melasma. Chemical peels may be helpful in the epidermal variant of melasma through its superficial effects of helping remove melanin from keratinocytes and arresting melanosome transfer to keratinocytes.⁹ Priming with a topical agent such as hydroquinone or retinoids for at least four weeks is required in order to reduce complications and promote uniform penetration.⁹ Moreover, studies illustrate faster and better results when used in combination with topical therapy.⁹

Another procedural treatment is microneedling. In mesotherapy, small needles are used to create punctures in the skin to deliver drugs intradermally. The exact mechanism that stimulates skin lightening is unknown, nevertheless the procedure has demonstrated improvement in cases of recalcitrant melasma.¹⁰ Finally, lasers and other light treatments have been used to treat melasma with varying degrees of success. They should only be considered after a patient has failed treatment with topical therapies and chemical peels.¹¹ Although there is an array of lasers and light therapies available, it is important that patients are advised on the probability of recurrence and post inflammatory or rebound pigmentation.¹¹

OTHER EMERGING THERAPIES

Other new oral and topical treatments include melatonin, cysteamine, methimazole, flutamide, and pigment-correcting serum.⁴ While these agents have produced positive

results, additional well-designed clinical trials are needed to substantiate their safety and efficacy.

HOW TO DISCUSS MELASMA WITH PATIENTS

Although melasma is a difficult condition to treat, there are several available treatment options. To determine the proper treatment, dermatologists should consider the patient's melasma-specific medical history, skin type, and other concomitant dermatologic and medical conditions. For example, numerous reports of thyroid dysfunction associated with refractory melasma have also been found in the literature. Furthermore, it is essential to establish rapport with patients in order to build a therapeutic alliance with reasonable goals and expectations. Given this, we suggest the following approach when discussing melasma with patients:

- Melasma is a common chronic and relapsing acquired hyperpigmentation that is difficult to treat and has a negative psychosocial impact on the lives of affected patients.
- Topical therapy, particularly combination therapy with hydroquinone, is the mainstay of treatment and should be used as the first-line option.
- Daily photoprotection with broad-spectrum sunscreen is key to the management and should be incorporated into every treatment regimen.
- Oral therapies and procedural treatments can be used as adjunctive therapies to topical treatments after topical treatments have failed.
- A multimodality approach addressing the multifactorial nature of the disorder is optimal.

- UV and visible light should be avoided to prevent flares and exacerbation of melasma.
- Several new therapies are emerging as promising agents to treat melasma, but further clinical studies are warranted to investigate their efficacy.

Conflict of Interest Disclosures: None.

Funding: None.

Corresponding Author:

Seemal R Desai, MD
 University of Texas Southwestern Medical Center
 Dallas, TX
seemald@yahoo.com

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