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REVIEW

Melasma: A Step-by-Step Approach Towards a Multimodal Combination Therapy

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Abstract: Melasma is a common challenge in the field of pigmentary skin disorders, exerting a significant emotional and psychosocial burden on patients. The persistent and recurring nature of melasma complicates its management in routine clinical practice. This comprehensive review outlines a stepwise, practical approach encompassing diagnostic, preventive and therapeutic strategies for the management of melasma. A thorough exploration of aggravating and exacerbating factors, including sun exposure, hormonal imbalances, photosensitizing medication and cosmetics, is essential for a holistic assessment of the disease. With an emphasis on consistent and effective photoprotection, initial topical treatment modalities target the melanin production and/or the transfer of melanosomes to keratinocytes. Topical tyrosine inhibitors emerge as the first choice for reducing and preventing hyperpigmentation, with compounds such as thiamidol or tranexamic acid (TXA) being preferred for their safety profile over hydroquinone (HQ), kojic acid and arbutin. Combination with chemical peels can further enhance the therapeutic efficacy, even in cases with resistant melasma. In more severe cases, laser- and light-based interventions may be considered, but with the caveat of the likelihood of recurrence within 3–6 months. Assisted TXA delivery, via either fractional non-ablative laser or microneedling techniques, can further improve clinical outcomes. In conclusion, an optimal melasma management strategy is a multimodal approach, which includes effective photoprotection and a mix of different topical treatments targeting melanin synthesis, the anti-inflammatory environment, senescence and vascularity. Complementary procedures, such as chemical peels, and laser, light-based or microneedling procedures, with or without TXA, can further expedite melanin clearance in more severely affected instances. Individual discussions with patients regarding treatment expectations, recurrence likelihood and potential side effects are paramount to a comprehensive and successful therapeutic journey.

Keywords: melasma, chloasma, hyperpigmentation, melanosis

Introduction

Melasma (syn. chloasma) presents as distinct, symmetrically patterned, hyperpigmented patches or small spots that occur predominantly on sun-exposed areas of the face. While its predominant location is generally centrofacial, affecting 50–80% of cases, melasma can also manifest on malar and mandibular areas.[1,2] The prevalence of melasma exhibits striking variability across populations and ethnicities, with reported overall prevalence rates ranging from of 1% in the general population to as high as 9–50% in high-risk populations, particularly dark-skinned women (Fitzpatrick phototypes III–IV) in their third and fourth decades of life.[3]

Despite being a common and predominantly benign condition, melasma carries a considerable emotional and psychosocial burden, profoundly affecting the patient's self-esteem and overall quality of life.[4,5] Given its persistence and recurring nature, effectively managing patient expectations and implementing preventive and therapeutic interventions tailored to the severity and underlying pathophysiology are paramount. However, reviews providing a practical treatment pathway for the management of melasma are limited.

This comprehensive review outlines a stepwise, up-to-date practical approach encompassing diagnostic, preventive and therapeutic strategies for the management of melasma to facilitate its management in everyday clinical practice.

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Understanding Pathophysiology and Aggravating Factors

The pathogenesis of melasma is multifactorial and not yet fully understood; various internal and environmental factors can contribute to triggering, maintaining and the relapsing of lesions[6,7] (Table 1). Among these, the most important factors are genetic predisposition, sun exposure and hormonal imbalances, especially as they occur in the context of pregnancy ("mask of pregnancy") or when taking contraceptives. All of them can significantly increase tyrosinase activity. In addition, chronic inflammatory skin diseases, photosensitizing interventions, drugs or food, liver diseases, ovarian tumors, helminthiasis, and even increased stress can cause melasma.[8]

As a concomitant disease, melasma is more often diagnosed in patients with polycystic ovary syndrome, insulin resistance or thyroid dysfunction. Furthermore, 76% of patients report depressive or stress symptoms, which may, at least partially, be caused by hormonal imbalances as well.[3,9]

Table 1 Factors Contributing to Melasma Pathogenesis and Diagnostic Work-Up

	Factors Contributing to Melasma Pathogenesis	Anamnesis/Diagnostic Work-Up
Genetic Predisposition	• Abnormal melanocyte activation • Excessive melanogenesis	Genetic testing is not possible, but typical signs of excessive melanogenesis can be seen in dermoscopy, Wood's lamp and/or reflectance confocal microscopy
Environmental Factors	• UV radiation	Sunlight exposure, LED screens, tanning beds, type of sunscreens used (UVA, UVB, etc)
	• Oxidative stress	
	• Solar elastosis and photoaging with extracellular matrix abnormalities	
	• Phototoxic medication	Phototoxic skin care or make-up products, phototoxic medication, eg St. John's wort products
	• Excessive consumption of certain food items	Copper-containing food, soy products, dairy products, high glycemic index products
Hormonal Factors	• Hormonal imbalances	Pregnancy test, sex hormone status, adrenocorticotropic hormone, cortisol, gynecologist consultation
	• Polycystic ovary syndrome, ovarian dysfunction and tumors, testicular dysfunction	
	• Thyroid disorders	Thyroid function test
	• Contraceptives and other hormonal therapies	Contraceptives, diethylstilbestrol, steroids, etc
Metabolic Disorders	• Hepatopathies • Diabetes mellitus	Liver function tests, glucose, HbA1c
Proinflammatory Factors	• Elevated mast cells • Increased vascularization	Blood count/hemogram, inflammatory skin disease
Procedural Factors	• Basement membrane damage	Waxing and/or other previous invasive cosmetic or laser skin treatments
Psychological/ Neurological Factors	• Depression, stress	Antiseizure drugs, hydantoin derivatives, chlorpromazine, antidepressants, anxiolytics
	• Antiseizure drugs/antidepressants	
Infections and Parasitic Infestations	• Malassezia	Skin culture
	• Helminthiasis	Stool examination

Note: Data from Pietowska et al (2022)[6] and Bagherani et al (2015).[7]
Abbreviations: HbA1c, glycosylated hemoglobin; UVA, ultraviolet A; UVB, ultraviolet B.

Diagnostic Work-Up

The diagnosis of melasma is primarily based on its clinical presentation; however, it is important to carefully investigate aggravating and triggering factors by obtaining a detailed history of the patient (Table 1) and to rule out other pigmentary disorders, which can mimic melasma.

Familial predisposition is the most important risk factor for melasma, and nearly 300 genes have been identified to be differentially expressed in the skin lesions of melasma. However, no Mendelian pattern of inheritance has been identified yet.[10] The clinical diagnosis can be further confirmed by dermatoscopic examination, showing typical pronounced hyperpigmentation in the pseudo-rete ridges of the skin,[11] or an accentuated, epidermal hyperpigmentation, when using Wood's lamp.[12] Reflectance confocal microscopy (RCM) is another non-invasive technique, showing activated melanocytes and melanophages as well as solar elastosis at a cellular level of resolution.[13,14] Dynamic optical coherence tomography (D-OCT) can be used to study changes in cutaneous blood vessels in melasma before or during treatment.[15] Based on the individual history of the patient, further laboratory tests, such as sex hormones, thyroid and liver function tests, adrenocorticotropic hormone, cortisol, complete hemogram and stool examination, may be conducted as well (Table 1).

The main differential diagnoses for melasma include ephelides, lentigines, post-inflammatory hyperpigmentation, phototoxic dermatitis, including phytophotodermatitis, and drug-induced pigmentation. In rare cases, lichen planus pigmentosus, discoid lupus erythematosus, erythema dyschromicum perstans, pigmented contact dermatitis, poikiloderma of Civatte, erythromelanosis follicularis faciei, ochronosis, Hori's nevus, argyria, nevus of Ota and macular amyloidosis can also mimic a melasma-like clinical picture.[7]

Management of Melasma: Practical Guidance

The therapeutic management of melasma is challenging because of its chronic and recurring nature. It includes topical, oral and procedural treatments targeting various aspects of the pathogenesis, including ultraviolet (UV) damage, hyperpigmentation, inflammation and vascularization (Figure 1, Table 2).[16–19]

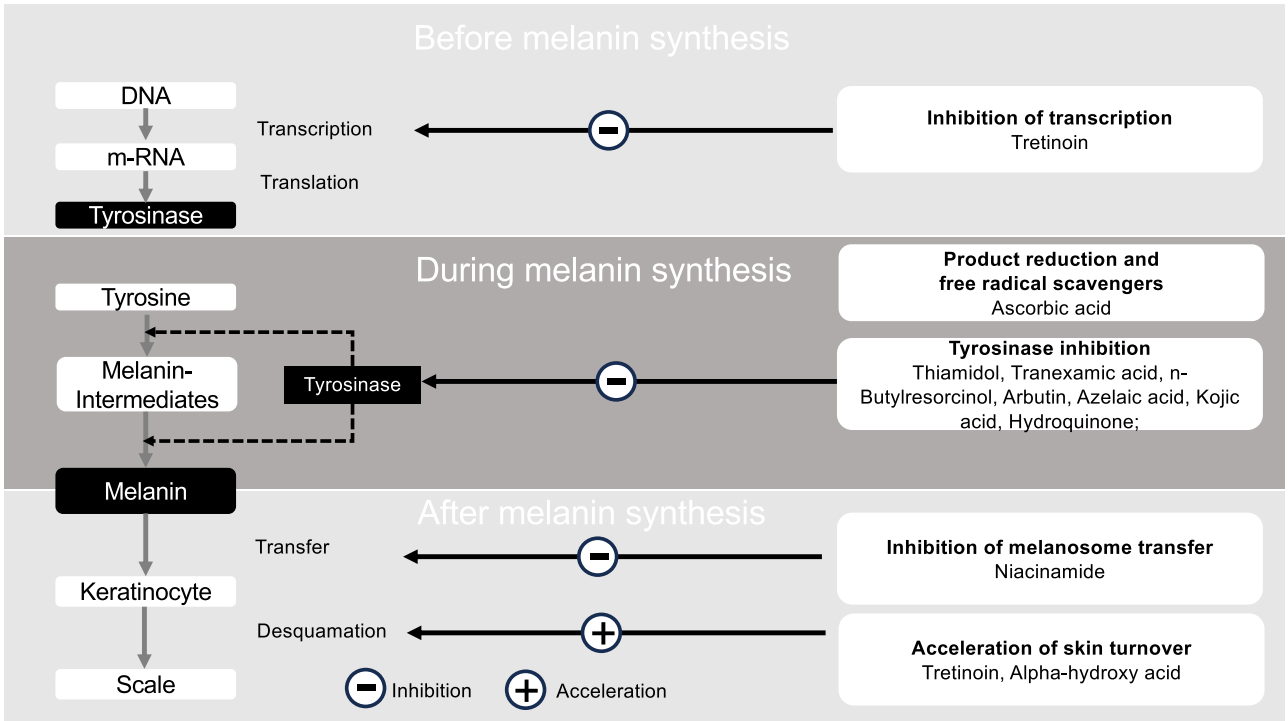

Figure 1 The main principles of topical melasma treatment include the inhibition of melanin synthesis pathways.
Abbreviations: AHA, alpha-hydroxy acid; DNA, deoxyribonucleic acid; m-RNA, messenger ribonucleic acid.

Table 2 Overview of Commonly Used Topical or Oral Therapies and Their Mode of Action in Melasma*

Mode of Action	Substance	Application	Additional Effects	References
Inhibitors of tyrosinase transcription	Retinoids	Topical, oral	Inhibition of UVB-stimulated keratinocytes, reduction of melanosome transfer, increased keratinocyte turnover	[20–31]
Tyrosinase inhibitors	4-n-Butyl resorcinol (Rucinol)	Topical	Inhibitor of TRP-1	[32–39]
	Arbutin	Topical	Inhibitor of DHICA, inhibition of melanosome maturation	[40–42]
	Azelaic acid	Topical	Melanocyte inhibitor	[43–46]
	Cysteamine	Topical	Peroxidase inhibitor, iron and copper chelator; increase in intracellular glutathione; inhibitor of eumelanin synthesis	[47–49]
	Glycolic acid	Topical	Increase in keratinocyte turnover	[25,50–58]
	Hydroquinone	Topical	Peroxidase inhibitor, melanocyte inhibitor, destruction of melanocyte cell membranes	[43,44,46,59–64]
	Kojic acid	Topical		[62–67]
	Thiamidol	Topical		[68–71]
	Tranexamic acid (TXA)	Topical, intradermal, oral	Melanocyte inhibitor, mast cell downregulation, plasmin inhibitor (reducing the amount of arachidonic acid and MSH); reduction of solar elastosis; lowers VEGF and endothelin-1	[72–87]
	Triple combination cream (4% hydroquinone, 0.05% tretinoin and 0.01% fluocinolone acetonide)	Topical	Peroxidase and melanocyte inhibitor; destruction of melanocyte cell membranes, inhibition of UVB-stimulated keratinocytes, inhibition of tyrosinase transcription, reduction of melanosome transfer, increase in keratinocyte turnover; inhibition of recruitment and maturation of mast cells; anti-inflammatory effect	[88–94]
Tyrosinase inhibitor, anti-inflammatory, melanosome inhibitor	Licorice root extract	Topical	Glabridin inhibits tyrosinase, liquiritin reduces UV-induced erythema; anti-inflammatory, melanosome inhibitor	[95–99]
Antioxidants	Ascorbic acid	Topical, oral	Decreases dopaquinone and DHICA oxidation, tyrosinase inhibitor via copper ions, photoprotective	[100–108]
	Pycnogenol	Topical, oral	Anti-inflammatory effect	[109–111]
	Ferulic acid	Topical		[111–113]

Inhibitors of melanosome transfer	Dioic acid	Topical	Intranuclear PPAR agonist	[114]
	Niacinamide	Topical, oral, intravenous	Melanocyte inhibitor, reduction of solar elastosis, anti-inflammatory, anti-aging (stimulation of ceramide production), PAR-2 inhibitor	[115,116]
	Soybean	Topical	Melanosome transfer inhibitor, antioxidant by (isoflavones and serine proteases), pigment attenuating, photoprotective	[117–119]
Increase keratinocyte turnover	Trichloroacetic acid	Topical		[52,120–123]
	Linoleic, alpha-linolenic and oleic acid	Topical	Photoprotective effect	[124]
Inhibitors of recruitment and maturation of mast cells	Corticosteroids	Topical	Anti-inflammatory effect with non-selective inhibition of melanogenesis	[125,126]
Induction of mast cell apoptosis	Calcineurin inhibitors	Topical	Anti-inflammatory effect	[127]
Anti-hormonal substances	Estrogen antagonists or anti-androgenic substances, eg flutamide	Oral, topical	Reduction of the concentrations of MSH and cAMP	[128,129]

Notes: Data from Pietowska et al (2022)[6] and Searle et al[18] *Please see references and additional literature for potential side effects of the different substances. Besides skin irritation, which is common for many active ingredients, and other substance-specific side effects, some substances, eg hydroquinone, arbutin and kojic acid, are suspected of having cancer-promoting effects.

Abbreviations: cAMP, cyclic adenosine monophosphate; DHICA, 5,6-dihydroxyindole-2-carboxylic acid; MSH, melanocyte-stimulating hormone; PAR-2, protease-activated receptor 2; PPAR, peroxisome proliferator-activated receptor; TRP-1, tyrosinase-related protein 1; UVB, ultraviolet radiation B; VEGF, vascular endothelial growth factor.

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Tyrosinase Inhibitors

Tyrosinase inhibitors, such as hydroquinone, thiamidol, kojic acid, arbutin, n-butylresorcinol and azelaic acid, competitively inhibit the conversion of 1-3,4-dihydroxyphenylalanine to melanin and are the most targeted dermocosmetic solution to reduce and prevent hyperpigmentation (Table 2).

Historically, hydroquinone (HQ) 4% as monotherapy, but also in combination with tretinoin and topical steroids ("triple cream"), has been an established topical, first-line treatment over years, but concerns about its side effects (permanent depigmentation, ochronosis, potential risk of cancer due to its metabolites) have prompted the use of potentially safer alternatives and the withdrawal of HQ in many countries.[53,54] Notably, most of the "older" tyrosinase inhibitors were previously tested using an in vitro mushroom tyrosinase model, but showed only limited efficacy in inhibiting the human tyrosinase, while thiamidol 0.2% was identified as being the most effective inhibitor of the human tyrosinase, corresponding to its good clinical efficacy[68–71] (Figure 2).

Besides the inhibition of tyrosinase activity, tranexamic acid (TXA) has additional anti-pigmentary, anti-inflammatory and anti-vascularization properties. It prevents plasminogen binding to keratinocytes, reduces melanocyte-stimulating hormone (MSH), reduces the concentration of arachidonic acid, prostaglandins and leukotrienes in keratinocytes, and is one of the very few methods that inhibits angiogenesis, through the suppression of vascular endothelial growth factor (VEGF) and endothelin-1 (EDN1). TXA can be used orally, topically or via an injection as part of mesotherapy or microneedling.[72–87] Whereas topical TXA 5% was well tolerated in clinical studies, several side effects, including oligomenorrhea, gastrointestinal discomfort, headache and transient skin irritation, were reported with oral TXA; in addition, a possible increased risk of thromboembolism needs to be considered.[6] Therefore, owing to the limited amount of data on the safety of oral TXA, topical or delivery-assisted TXA application should be preferred in melasma patients.

Retinoids

Topical retinoids, including tretinoin 0.05–0.1%, adapalene, tazarotene, isotretinoin and retinol, regulate the differentiation, proliferation and apoptosis of cells by binding to nuclear receptors (Table 2). They inhibit the transcription of tyrosinase and melanin synthesis and reduce oxidative stress by inhibiting the activation of the matrix metalloproteinase. In addition, they reduce the transfer of melanosomes to keratinocytes and accelerate melanin loss as a result of an

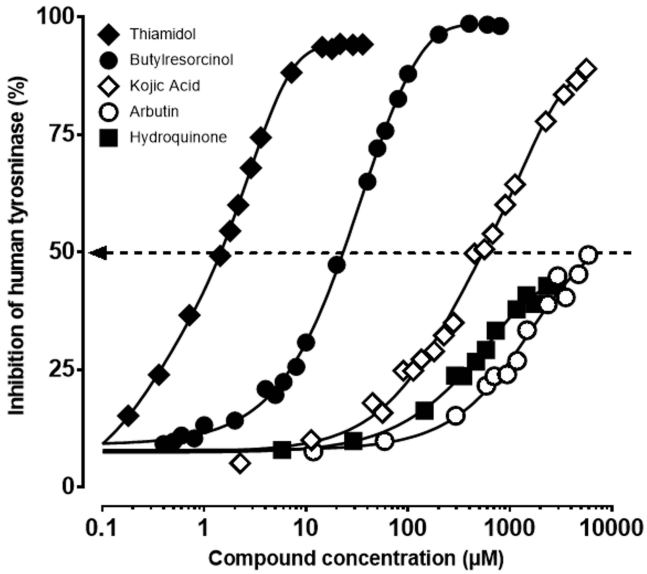

Figure 2 Inhibition of human tyrosinase by various concentrations of thiamidol, 4-butylresorcinol, kojic acid, arbutin and hydroquinone using an in vitro assay with purified human tyrosinase.

Notes: Adapted from Arrowitz C, Schoelermann AM, Mann T, Jiang LI, Weber T, Kolbe L. Effective tyrosinase inhibition by thiamidol results in significant improvement of mild to moderate melasma. *J Invest Dermatol*. 2019;139(8):1691–1698.e6 © 2019, Creative Commons.[69]

increased turnover of keratinocytes and their exfoliative properties. When used in combination, they may enhance the transepidermal penetration of other topical medications.[6,20–31,130–133] However, retinoids are known to be slow-acting substances, and it may take up to 24 weeks to see clinical benefits in melasma.[20] In addition, the risk of secondary hyperpigmentation due to retinoid-induced irritation needs to be considered in melasma.

Niacinamide

Niacinamide (4%), alone or in combination with retinoic acids, inhibits melanosome transfer to keratinocytes and has been shown to decrease pigmentation in melasma within a period of 8 weeks[115,116,155] (Table 2).

Antioxidants

Ascorbic acid protects the skin from oxidative stress by neutralizing free radicals, as it is a potent electron donor. In addition, it interacts with the copper ions at the active site of the tyrosinase enzyme and reduces its activity.[100–108] Topical application of ascorbic acid and zinc has been shown to improve skin lesions in melasma, with only very few side effects.[134] Other topical natural antioxidants, such as Korean red ginseng, ferulic acid, and orchid or parsley plant extracts, can improve melasma, as can orally taken antioxidants, such as pycnogenol[111–113,135,136] (Table 2).

Chemical Peels

Chemical peels are typically used as a second-line treatment procedure in the management of melasma.[19,137–139] Chemical peels can improve melasma by reducing melanin and melanosome transfer owing to their exfoliative properties and by inducing the phagocytosis of melanin. When used in combination with local treatment or laser therapy, they can enhance and accelerate the therapeutic effects, even in the case of resistant melasma.[19,137] However, they should be used with caution, especially in people with darker skin types, because of the risk of post-inflammatory hyperpigmentation.[138,139]

Laser, Light-Based and Microneedling Techniques

Laser- and light-based therapies, such as intense pulsed light (IPL), Q-switched low-fluency lasers, non-ablative fractional lasers (NAFLs) or picosecond lasers, can accelerate the removal of melanin and lead to more rapid improvement in patients. However, all of these methods are not causative, as they do not have any direct or indirect effect on melanin synthesis. The risk of recurrence and, with some techniques, the risk of post-inflammatory hyperpigmentation or hypopigmentation has to be considered and explicitly explained to patients.[6]

NAFLs may provide a more effective and sustained response, with recurrence after 3–6 months, whereas in IPL or Q-switched laser treatments skin lesions appear usually within 3 months after the procedure. The 1927nm wavelength allows practitioners to treat Fitzpatrick skin types III–VI as well, which is not the case for IPL and Q-switched lasers. Combination with a topical tyrosinase inhibitor, applied before and after the NAFL, can further enhance long-term improvement.[139–144]

Picosecond lasers generate pulses in the picosecond domain, which leads to a mainly photoacoustic-driven melanin fragmentation without causing thermal damage to the surrounding tissues, which may enhance the efficacy and safety properties of this method in treating melasma. The use of picosecond lasers with diffractive lens arrays may, in addition, alleviate related photoaging characteristics, and the effects may be maintained for a longer time.[145–149]

Microneedle radiofrequency (RF) creates microscopic channels to the required depths of the dermis, so that thermal energy can stimulate the production of collagen and elastin. As a result of this controlled skin injury, keratinocyte turnover is accelerated, which leads to increased melanin removal as well as to decreased blood vessel proliferation and restoration of the basement membrane. Owing to its additional benefits on solar elastosis and skin aging, combined with an excellent safety profile, microneedle RF may be beneficial as adjunct melasma therapy.[150]

Topical TXA, alone or in combination with either a fractional CO_2 laser or microneedling, achieved better results than when used alone, but there was no difference between the laser and microneedling techniques.[151,152] Hence, a combination of microneedling or a fractional CO_2 laser with topical TXA 5% may be another treatment alternative for melasma, resulting in better treatment outcomes than the single use of substances or procedures.[151]

Prevention by Photoprotection

Visible light, especially high-energy visible light (HEVL), and UVA (UVA1) radiation are the main causative triggers for melasma,[148] and the avoidance of and protection against UV radiation and visible light are critical for the sustained control of melasma. Therefore, the use of a broad-spectrum UVA/UVB sunscreen with a high sun protection factor (SPF 30+) and high protection against UVA1 and HEVL all year round should be recommended to all melasma patients. In choosing suitable sunscreen, the combination of broad-spectrum UVA and UVB filters with visible light blockers, such as iron oxide, should be favored, as such combinations showed better results in prevention of melasma flares compared to broad-spectrum UV filters alone.[19,153–155]

Introducing a Step-by-Step Multimodal Treatment Approach for Melasma

Single treatment approaches are, in general, of limited efficacy for the long-term management of melasma. Hence, a step-by-step, multimodal approach, which includes a mix of treatments and procedures targeting the melanin synthesis pathways, the anti-inflammatory environment, senescence and vascularity, should be used, along with avoidance of exacerbating factors such as UV light and hormonal contraception (Figure 3).[16,17]

In addition to consistent and effective photoprotection, topical treatments that inhibit the melanin synthesis pathway should be considered as first-line therapies for melasma.[6,18] The use of effective and potentially safer topical tyrosinase inhibitors, such as thiamidol or TXA, should be preferred (Figure 4). HQ, arbutin and kojic acid-containing topicals are no longer recommended because of the risk of side effects and the availability of safer alternatives. Combination with topical retinoids and/or niacinamide could be considered to target tyrosinase transcription, melanin synthesis, vascularization and oxidative stress. This can be further enhanced by antioxidants or mesotherapy as adjunct treatment.

Combining topical treatments with chemical peels may further enhance and accelerate therapeutic effects, even in resistant melasma.[19] In more severe and refractory cases, lasers and light-based therapies may be suggested, but patients must be prepared for a high recurrence rate. The combination of fractional CO_2 laser or microneedling techniques with TXA may further improve clinical outcomes.[152]

This comprehensive review is limited by its narrative methodology. It summarizes recent developments in melasma treatment for developing a step-by-step treatment approach for use in everyday clinical practice. It does not replace a systematic review, with a structured assessment and weighting of the individual studies and treatment strategies, and may lack completeness. Recent systematic reviews, however, were considered when available. National and international treatment recommendations are needed to further improve and standardize the management of such a common disease as melasma.

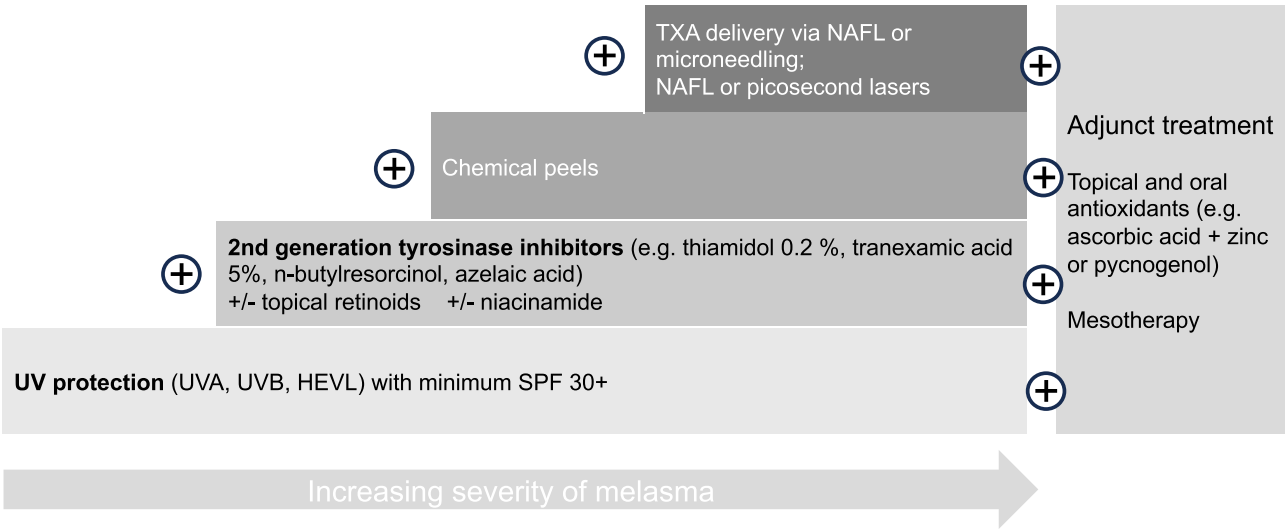

Figure 3 Management of melasma: a practical approach for a stepwise combination therapy.
Abbreviations: TXA, tranexamic acid; NAFL, non-ablative fractional laser; UV, ultraviolet; HEVL, high-energy visible light; SPF, sun protection factor.

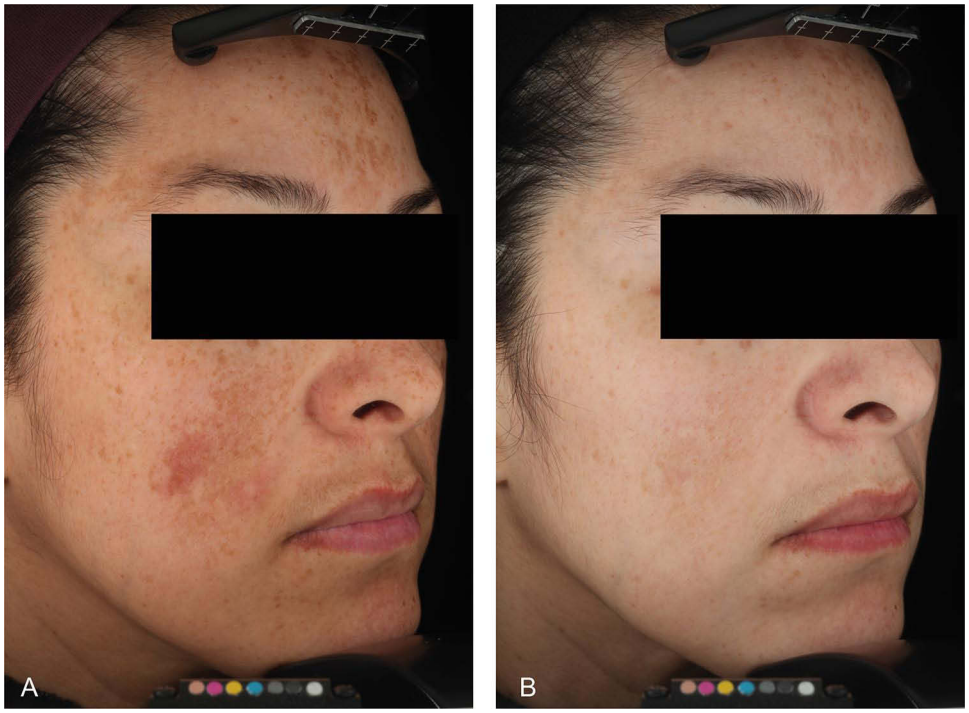

Figure 4 Melasma at baseline (**A**) and after 12 weeks (**B**) of treatment with the topical tyrosinase inhibitor thiamidol and subsequent sunscreen use.
Notes: Adapted from Philipp-Dormston WG, Vila Echagüe A, Pérez Damonte SH, Riedel J, Filbry A, Warnke K, Lofrano C, Roggenkamp D, Nippel G. Thiamidol containing treatment regimens in facial hyperpigmentation: An international multi-centre approach consisting of a double-blind, controlled, split-face study and of an open-label, real-world study. *Int J Cosmet Sci*. 2020;42(4):377–387. © 2020 Beiersdorf AG. International Journal of Cosmetic Science, published by John Wiley & Sons Ltd on behalf of the Society of Cosmetic Scientists and Société Française de Cosmétologie.[71]

Conclusion

The treatment of melasma remains challenging owing to its chronic and recurrent nature. Its multifactorial etiology implies the use of a multimodal approach that includes a mix of different topical treatments targeting the melanin synthesis pathways, the anti-inflammatory environment, senescence and vascularity, along with avoidance of exacerbating factors, such as UV light and hormonal contraception. Complementary procedures, including chemical peels, lasers, light-based or microneedling procedures, with or without TXA, can further expedite melanin clearance in more severely affected instances. This comprehensive review outlines a step-by-step clinical approach based on recent evidence encompassing diagnostic, preventive and therapeutic strategies for the management of melasma to facilitate its management in everyday clinical practice. Individual discussions with patients regarding treatment expectations, recurrence likelihood and potential side effects are paramount to a successful therapeutic journey.

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