Chapter 23
Treatment Strategies for Hyperpigmentation

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Dyschromia is an increasingly common disorder, especially among darker skinned ethnic groups [1]. Despite the arsenal of treatment options available for pigmentary disorders, treating hyperpigmentation remains a clinical challenge. There are no standardized protocols and few randomized controlled trials studying the efficacy and safety of treatments. In addition, although skin of color patients are at greatest risk for developing undesired treatment-related dyspigmentation, there exists no algorithm to predict which particular patient is more prone to side effects. Given the refractory nature of disease and the evolving population from increases in migration, hyperchromic complaints are likely to rise. Providing a treatment framework for hyperpigmentation would, therefore, be beneficial [2].

Evaluation of Hyperpigmentation

Ruling out an underlying cause for hyperpigmentation is vital when first evaluating a patient with dyschromia. Diffuse hyperpigmentation suggests a metabolic (i.e., Addison's disease), malignant, medication-related, or infectious etiology [3]. For medication-related hyperpigmentation (i.e., minocycline, amiodarone, oral contraceptives), the offending agent should be discontinued first and time permitted

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for natural pigmentation to return. For metabolic disorders, appropriate supplementation to correct the deficiency should be provided (i.e., vitamin B12, folic acid, levothyroxine) [3].

Localized disease suggests other etiologies, including post-inflammatory hyperpigmentation (PIH) or melasma, which are two of the most common causes of hyperpigmentation [3]. For PIH, underlying dermatoses, such as acne, should be treated first before pursuing post-inflammatory pigmentation therapeutics. Melasma is typically categorized into types depending on the pigmentation deposition: (i) epidermal—brown colored with basal or suprabasal pigment, (ii) dermal—blue-gray color with upper and deep dermal pigment, (iii) mixed—brown-gray color with epidermal and dermal pigment, and (iv) inapparent or indeterminate, which is seen more in darker skin types. Distinguishing pigment location is important as it informs likelihood of response to topical treatment, with dermal type being less likely to respond [4]. Under Wood's lamp, only the epidermal component intensifies, which can be useful in determining disease extent, although the utility of this is controversial as all subtypes will show some amount of increased pigment deposition in both dermal and epidermal layers of the skin [5].

Treatment of these most common acquired causes of hyperpigmentation is based on two key principles: photoprotection and the use of agents that both disrupt melanogenesis and remove melanin. Topical lightening agents, chemical peels, oral agents, microdermabrasion, microneedling, and laser therapy are all potential treatment modalities.

Topical Therapies

The induction of melanin production and, therefore, pigmentation has been demonstrated with ultraviolent (UV) in the UVA (290–320 nm), UVB (320–340 nm), and visible light (400–760 nm) spectrums. Sun-protective strategies, therefore, are crucial in the treatment and prevention regimen for hyperpigmentation disorders. The American Academy of Dermatology (AAD) recommends sunscreens with a sun protection factor (SPF) of 30 or higher, that offer broad-spectrum coverage, and are water resistant for 40 or 80 min [6]. In addition, patients should practice sun-protective behavior including seeking shade whenever possible, wearing sun-protective clothing (wide-brimmed hats, sunglasses with UV protection), avoiding indoor tanning beds, applying sunscreen 15–30 min before going outdoors, and reapplying every 2 hours [7]. Darker skinned ethnic groups may furthermore benefit from vitamin D supplementation as their higher melanin content inherently predisposes them to vitamin D deficiency [7, 8].

Most individuals apply sunscreen at a quarter to a half of the FDA-mandated amount of 2 mg/cm^2 used in SPF testing [6, 9]. SPF, a measure of UVB, is the ratio of the minimal erythema dose in sunscreen-protected skin over the minimal erythema dose in non-sunscreen-protected skin [10]. Consequently, to achieve a 10–15-fold protection, a sunscreen with SPF 30–50 should be applied [11].

Sunscreens can be categorized into two types based on mechanism of action—physical (inorganic) versus chemical (organic). Chemical sunscreens absorb light and convert it to heat energy, while physical sunscreens (i.e., titanium dioxide, zinc oxide) reflect or scatter light [10]. Micronized forms of metal oxides, though often classified as physical sunscreens, actually act as chemical sunscreens by absorbing UV radiation and emitting it as longer-wave heat radiation [12]. Unfortunately, physical blockers are often less cosmetically acceptable, especially among darker skin types due to the white sheen they leave on the skin. Consequently, new physical blockers (i.e., iron oxide) have been developed that better simulate natural skin tones and can now be obtained as tinted products in different shades. Iron oxide also has the ability to block against visible light, which has been shown to be etiologic in melasma [13–15]. There are currently 17 FDA-approved active sunscreen ingredients (Table 23.1) [6, 10].

Aside from sunscreen, first-line treatment for hyperpigmentation disorders consists of topical lightening agents [16]. There are currently only a handful of prescription agents (i.e., hydroquinone (HQ), retinoids, and azelaic acid) in comparison to a plethora of over-the-counter lightening formulations (i.e., kojic acid, licorice extract, arbutin, ascorbic acid, soy, niacinamide, and *N*-acetyl glucosamine) (Table 23.2). The most commonly used agents are HQ, triple combination cream, azelaic acid, retinoids, and kojic acid. All other agents have demonstrated limited efficacy in clinical investigations but are used in practice with varying response.

Table 23.1 FDA-approved sunscreen ingredients (as of December 7, 2009)

UV spectrum coverage	Ingredient	
UVA1 (340–380 nm)	**Chemical**	**Physical**
	Avobenzone	Zinc oxide
	Ecamsule (terephthalydene dicamphor sulfonic acid)	
UVA2 (320–340 nm)	**Chemical**	**Physical**
	Oxybenzone	Titanium dioxide
	Sulisobenzone	
	Dioxybenzone	
	Meradimate (menthyl anthranilate)	
UVB (290–320 nm)	**Chemical**	**Physical**
	PABA	Zinc oxide
	Padimate O	Titanium dioxide
	Octinoxate (octyl methoxycinnamates)	
	Cinoxate	
	Octisalate (octyl salicylate)	
	Homosalate	
	Trolamine salicylate	
	Octylocrylene	
	Ensulizole (phenylbenzimidazole sulfonic acid)	

From Wang and Lim [6]

Table 23.2 Strengths and weaknesses of various topical hypopigmenting agents

Drug	Mechanism	Strengths	Weaknesses
Hydroquinone	• Inhibits tyrosinase [17] • Inhibits formation of melanosomes [18] • Promotes degradation of melanocytes [18] • Promotes necrosis of melanocytes [18]	• Long study record [19]	• Exogenous ochronosis [20] • Confetti leukoderma [21]
Retinoids Tretinoin Adapalene/tazarotene	• Inhibits tyrosinase [22] • Enhances epidermopoiesis [22]	• Can simultaneously treat comedonal acne [23] • Greater specificity for retinoic acid receptor compared to tretinoin [23] • Possibly fewer side effects compared to tretinoin [24]	• Retinoid dermatitis [25] • Requires long treatment period [26] • More expensive than tretinoin [27]
Triple topical therapy (hydroquinone, retinoid, corticosteroid)	• Inhibits tyrosinase [17] • Inhibits formation of melanosomes [18] • Promotes degradation of melanocytes [18] • Promotes necrosis of melanocytes [18] • Enhances epidermopoiesis [22]	• Safe and effective in dark-skinned ethnic groups [28, 29] • More efficacious than constituent agents alone [30]	• Skin atrophy [31] • Telangiectasia [31]
Azelaic acid	• Inhibits tyrosinase activity [32] • Interferes with DNA synthesis [32]	• Cytotoxic effect specific to abnormally hyperactive melanocytes [33]	• Pruritus [19] • Transient erythema [19] • Scaling [19]
Mequinol	• Inhibits tyrosinase [33]	• Less irritating than hydroquinone [34]	• Limited studies in post-inflammatory hyperpigmentation
Kojic acid	• Inhibits tyrosine kinase by chelating copper [35]	• Pharmaceutically stable [36]	• More irritating compared to other topical agents [36] • High frequency of contact sensitivity [37]
Licorice	• Inhibits tyrosinase [38] • Disperses melanin [39] • Removes epidermal melanin [39]	• Minimal side effects [40]	• Few studies

(continued)

Table 23.2 (continued)

Drug	Mechanism	Strengths	Weaknesses
Arbutin	• Inhibits tyrosinase [41]	• Efficacious in light-skinned patients [41]	• May cause paradoxical hyperpigmentation [42] • Limited studies in darker Fitzpatrick skin types
Ascorbic acid	• Reduces oxidized dopaquinone [43] • Suppresses activation of NF-kβ and TNF-α [44] • Protects against phototoxic injury [45]	• 5% formulation has fewer side effects than 4% hydroquinone [46]	• Limited studies for PIH
Soy	• Blocks transfer of melanosomes to keratinocytes [47]	• Well-tolerated [48] • Efficacious in combination with other topicals [49]	• Few monotherapy studies
Niacinamide	• Decreases melanosome transfer to keratinocytes [50] • Interferes in cell-signaling pathway to decrease melanogenesis [50]	• Unaffected by light, moisture, acids, alkalis, oxidizers [43]	• Limited studies in darker skinned populations • Limited studies in post-inflammatory hyperpigmentation
N-acetyl glucosamine	• Inhibits tyrosinase glycosylation [51]	• Well-tolerated [51]	• Few studies among dark-skinned ethnic groups

Hydroquinone

HQ is one of the most popular agents given its efficacy. HQ blocks conversion of dihydroxyphenylalanine (DOPA) to melanin by inhibiting tyrosinase [17]. It also inhibits the formation of and promotes degradation of melanosomes, along with causing melanocyte necrosis [18]. HQ efficacy is proportional to its concentration, with lower concentrations having slower onset to action [52]. While over-the-counter preparations contain a maximum 2–3% concentration, depending on the formulation, higher concentrations can be obtained through prescription. HQ is efficacious when used as monotherapy or when used in conjunction with other topical agents [53, 54]. In a randomized, double-blind trial of 4% HQ and sunscreen versus sunscreen for 12 weeks (n = 45), Ennes et al. [53] demonstrated a significantly greater clearance rate of melasma among patients who used HQ compared to sunscreen alone (38% vs. 8%).

The most common acute side effect of HQ is irritant contact dermatitis, with up to 25% of users developing a pruritic eruption as evidenced by a single randomized study [21]. Other side effects include allergic contact dermatitis, PIH, and post-inflammatory hypopigmentation of surrounding skin—the "halo effect" [4, 21]. Fitzpatrick skin types (FST) V and VI are also more vulnerable to side effects including "confetti leukoderma," which refers to areas of focal depigmentation [21]. Long-term, rare side effects include ochronosis, nail discoloration, conjunctival melanosis, and corneal degeneration.

Exogenous ochronosis typically occurs in black patients and is secondary to the accumulation of homogentistic acid in the dermis. It presents as asymptomatic patches over bony prominences (i.e., face, neck, extensor surfaces) and sun-exposed sites coinciding with the application of topical lightening agents [20]. While it is more prevalent in Africa, where HQ is frequently combined with resorcinol or compounded in a hydroalcoholic lotion [20], many cases have been reported in the U.S., most often from patients using adulterated compounds from non-U.S. countries [55]. It is typically associated with the use of higher percentages of HQ; however, it has been reported with 2% formulations [56]. Clinicians should be prepared to recognize ochronosis as adulterated, and above FDA-recommended concentrations of hydroquinone are illicitly sold in ethnic stores and through websites [43, 55, 57]. Finally, although animal studies have shown an increased risk of cancer with the administration of high doses of oral HQ, there have been no human reports to date that show an increased risk of skin cancer or internal malignancies from topical application of HQ [33, 43, 58, 59].

Retinoids

Through the stimulation of keratinocyte turnover and reduction of melanosome transfer, retinoids (i.e., retinoic acid, tretinoin, adapalene, tazarotene) promote the loss of melanin [22]. Tretinoin (0.01–0.1%) has been shown to inhibit tyrosinase transcription and enhance epidermopoiesis, thereby decreasing contact time between keratinocytes and melanocytes [19, 60]. In a randomized, double-blind, vehicle-controlled study of African American patients with melasma (n = 28), 0.1% tretinoin for 40 weeks resulted in a 32% improvement in the Melasma Area and Severity Index (MASI) score compared to 10% in the placebo group [61]. Similarly, when used to treat PIH, 0.1% tretinoin cream applied daily for 40 weeks resulted in a significant lightening of lesions (40% vs. 18%) compared to vehicle cream [25]. However, 50% of patients developed retinoid dermatitis [25]. To minimize this side effect, retinoids can be started at lower concentrations and titrated up [62]. While tretinoin demonstrates good efficacy, it generally requires a long 20–40 week treatment period for maximal benefit [26].

Adapalene (0.1–0.3%) and tazarotene (0.05–0.1%) are synthetic retinoids that can be used to treat PIH and melasma as well [63, 64]. Compared to 0.05% tretinoin cream, 0.1% adapalene gel demonstrated similar efficacy in treating melasma

among 30 Indian women. The adapalene gel was better tolerated as significantly more patients in the tretinoin group experienced pruritus, burning, dryness, erythema, and scaling compared to the adapalene group (63% vs. 8%) [24]. Tazarotene 0.1% cream similarly reduced severity and intensity of hyperpigmentation in a randomized, double-blind, vehicle-controlled study among 74 acne patients of darker skin types. Erythema, burning, and peeling occurred minimally in both treatment groups [65]. Retinoids are able to increase the epidermal penetration of other active ingredients and have, therefore, been found to be effective in combination products [29].

Combination Therapy

Hydroquinone is frequently combined with a retinoid, most commonly tretinoin, and a corticosteroid for synergistic effects. In addition to increasing keratinocyte proliferation, tretinoin increases pigment elimination by preventing oxidation of hydroquinone and improves epidermal penetration by causing mild irritation. Topical corticosteroids reduce irritation and inhibit melanin synthesis [4]. Combination therapy has been found to be more effective than any of its constituent agents alone [30]. The original Kligman's formula (5% hydroquinone, 0.1% tretinoin, 0.1% dexamethasone) was found to be effective in treating hyperpigmentation [19]. A subsequent formulation consisting of 4% hydroquinone, 0.05% tretinoin, and 0.01% fluocinolone acetonide has been shown to be safe and effective in dark-skinned ethnic groups. [28, 29] Two 8-week studies (n = 161, n = 1042) demonstrated good safety and efficacy for facial melasma across a wide range of FSTs with 75–77% of patients achieving "moderate or marked improvement," "almost clear," or "clear" results by week 8 [29, 66]. Two longer studies, a 12-month extension of a previous 8-week trial [31] (n = 569) and a 12-month multi-center study of patients with facial melasma (n = 228), demonstrated complete or nearly complete clearance of 80 and 90% of cases, respectively [31, 67]. Between the 2 long-term studies, 2 cases of skin atrophy and 29 cases of telangiectasia occurred [31]. These studies indicate that fixed triple combination agents are safe and effective [68].

Azelaic Acid

Azelaic acid is a dicarboxylic acid that inhibits tyrosinase activity and interferes with DNA synthesis. It is naturally found in *Malassezia furfur*, the etiologic agent for pityriasis versicolor [32]. Azelaic acid offers two advantages compared to other agents. First, azelaic acid's cytotoxic effect is specific to abnormally hyperactive melanocytes, and so normally pigmented skin does not become depigmented. Second, it has a good safety profile, with minimal side effects including pruritus,

transient erythema, and scaling. [19, 52, 69, 70] However, a long treatment duration is required and improvement is not noticeable for several months.

In a study among FST IV-VI (n = 52), 20% azelaic acid cream significantly decreased the intensity of facial hyperpigmentation [71]. When compared to hydroquinone, results are mixed [72, 73]. A South American randomized, double-blind, multicenter study of melasma patients (n = 243) treated with 4% hydroquinone cream twice daily versus 20% azelaic acid cream twice daily yielded equivocal differences at 24 weeks [72]. In another randomized double-blind trial of melasma patients (n = 155) with FST III-V, 20% azelaic acid was more efficacious at decreasing lesion size and intensity compared to 2% hydroquinone at 24 weeks (73% vs. 19%) [73].

Mequinol

Mequinol (4-hydroxyanisole) is a derivative of hydroquinone and is postulated to induce depigmentation by inhibiting tyrosinase [33]. Although it is not as effective as hydroquinone, it is thought to be less irritating [34]. It is typically combined with 0.01% tretinoin, which can enhance penetration. Draelos et al. [74] demonstrated that 2% mequinol combined with 0.01% tretinoin can effectively treat solar lentigines in patients with FST II–V, with minimal adverse effects. However, few studies among dark-skinned ethnic groups have been conducted, and studies on its efficacy for PIH are still lacking.

Kojic Acid

Kojic acid, a fungal metabolite, inhibits tyrosine kinase by chelating copper [35]. It is available in gel or cream formulation with concentrations ranging from 1 to 4%. Kojic acid has marginal efficacy and can be irritating [30, 36]. It is typically used in combination products with studies showing mixed results. When combined with other lightening agents, 2% hydroquinone and 10% glycolic acid (GA), pigmentation was not significantly reduced with the addition of kojic acid (n = 40) [75]. Similarly, in a split-face study where a 4% HQ/5% GA gel was compared to 2% kojic acid/5% GA gel, there was no significant difference in pigmentation reduction between the two treatment arms [36]. Furthermore, kojic acid is highly sensitizing and is associated with a high frequency of contact sensitivity [37].

Licorice

Licorice extract contains glabridin, licochalcone A, and liquiritin, which exert skin-lightening effects [38, 39]. In a study of 20 Egyptian women with melasma,

topical liquiritin cream decreased pigment intensity and lesion size in 70 and 60% of patients, respectively [40]. Side effects were minimal (i.e., mild irritation) and resolved with continuation of treatment [40].

Arbutin

Arbutin is a plant-derived derivative of hydroquinone that causes depigmentation by inhibiting tyrosinase activity and melanosome maturation. The more potent synthetic derivative, deoxyarbutin, has been effective in treating solar lentigines among light-skinned patients in a 3% formulation (n = 34) but not in dark-skinned populations (n = 16) [41]. It should be used with caution as higher concentrations may cause paradoxical hyperpigmentation [42].

Ascorbic Acid

Ascorbic acid exerts lightening effects through three mechanisms: reducing oxidized dopaquinone (a substrate in the melanin synthesis pathway), suppressing activation of NF-kβ and TNF-α (anti-inflammation), and protecting against UVA- and UVB-induced phototoxic injury (photoprotection) [44, 45]. As it is frequently combined with other lightening agents, few studies have examined its efficacy as monotherapy. In a small split-face study (n = 16) in a Latino population comparing 5% ascorbic acid cream versus 4% hydroquinone, there was no significant objective difference in improvement between the two treatment arms. However, there were fewer side effects among those treated with ascorbic acid. [46] When magnesium-L-ascorbyl-2-phosphage (a derivative of ascorbic acid) was used to treat chloasma or senile freckles in an Asian population, 56% of patients (n = 34) experienced “effective” or “fairly effective” improvement [76].

Soy

Soy blocks the transfer of melanosomes to nearby keratinocytes by inhibiting protease-activated receptor 2 (PAR-2) expressed on keratinocytes [47]. Few studies have examined the effect of soy extract alone in improving hyperpigmentation. However, in a 16-week study among FST III-V patients, soy combined with salicylic acid and retinol significantly improved PIH compared to placebo [49]. Soy is relatively well-tolerated, but more studies are needed to evaluate its efficacy among dark-skinned ethnic groups [43, 48].

Niacinamide

Niacinamide, the physiologically active form of niacin, decreases the transfer of melanosomes to keratinocytes [50]. In a study among 18 Asians, 5% niacinamide in a facial moisturizer compared to facial moisturizer alone significantly increased skin lightness at 4 weeks. Afterward, the effect plateaued, similar to other lightening agents (i.e., retinoids) [50]. The advantages of niacinamide are that it is generally well-tolerated and is unaffected by light, acids, alkalis, and oxidizers [77]. However, further studies are needed to evaluate its effect on disorders of hyperpigmentation.

N-Acetyl Glucosamine

N-acetyl glucosamine (NAG) is a precursor to hyaluronic acid and inhibits tyrosinase glycosylation—a step in the melanogenesis pathway [51]. When used as monotherapy for 8 weeks to treat hyperpigmentation in a Japanese population ($n = 50$), 2% NAG reduced the appearance of pigmentation, though not significantly. [51] When combined with 4% niacinamide, the improvement in hyperpigmentation was significantly greater, as demonstrated in 2 studies among Caucasian participants [51, 78]. The difference may be attributable to inhibiting 2 separate steps in the melanogenesis pathway [51]. Like niacinamide, NAG was well-tolerated in all studies [51]. However, few studies have evaluated its effect in dark-skinned ethnic groups.

Emerging Topical Agents

New promising agents include aloesin, linoleic acid, ellagic acid, resveratrol, 4-*n*-butylresorcinol, methimazole, and metformin. In a study among 7 Korean patients, aloesin, an inhibitor of tyrosinase, exerted an inhibitory effect on pigmentation after UV radiation in a dose-dependent manner [79, 80]. In a study using guinea pigs, linoleic acid demonstrated a lightening effect on UV-stimulated hyperpigmented skin by suppressing melanin production and promoting desquamation of pigment from the epidermis [81]. Ellagic acid, an inhibitor of melanin synthesis, demonstrated comparable efficacy to 4% hydroquinone when combined with 0.1% salicylic acid when treating hyperpigmentation in a multi-ethnic population ($n = 54$) [82]. The cosmetic use of resveratrol, another tyrosinase inhibitor, has been limited so far due to chemical instability [79]. However, Ryu et al. recently demonstrated that resveratrol triacetate (prodrug of resveratrol) decreases intensity of hyperpigmentation among FSTs III-IV without inducing skin irritation [83]. Similarly, 4-*n*-butylresorcinol, an inhibitor of tyrosinase and tyrosinase-related protein-1, has been shown to be efficacious in reducing melasma pigmentation after 8 weeks of

use [84]. Topical methimazole cream was shown to inhibit melanin synthesis and significantly improve hyperpigmentation in two hydroquinone-resistant melasma patients [85]. Finally, topical metformin induced tail whitening in animal studies and exerted an anti-melanogenic effect on reconstituted human epidermis and human skin biopsies [86].

Chemical Peels

Chemical peels are an increasingly popular method to disperse unwanted pigment among those with more darkly pigmented skin tones [87]. They may be used as monotherapy or as an adjunct to topical agents. Superficial (epidermis to upper papillary dermis) and medium-depth (epidermis to upper reticular dermis) are the primary peels used in dark-skinned ethnic groups. Superficial peels include 30–50% glycolic acid (GA), 20–30% salicylic acid (SA), 10–35% trichloroacetic acid (TCA), and Jessner's solution [88]. Medium-depth peels include 50% TCA and 70% GA [87]. Deep peels are avoided in dark-skinned ethnic groups, due to the higher risk of hypopigmentation, hyperpigmentation, scarring, and keloid and milia formation [19, 89]. More details on patient selection, pre-and post-treatment care, and types of peels can be found in the chemical peels chapter.

Microdermabrasion

Microdermabrasion is a superficial skin resurfacing procedure that removes the stratum corneum. A negative pressure system pulls the skin into a handpiece connected to a vacuum pump that blows chemically inert crystals (usually aluminum oxide), which cause mechanical skin abrasion. Used crystals and abraded material are then suctioned off into a waste receptacle [90]. Alternative machines use less harsh sodium chloride and sodium bicarbonate crystals, and some employ diamond wand systems that are crystal-free [91].

Most studies have reported mild to moderate improvement (5–41%) in melasma after 6–8 weekly sessions [91, 92]. Compared to pre-treatment skin biopsies, post-treatment biopsies demonstrated decreased melanization and regular distribution of melanosomes in the epidermis [91, 93]. Of note, improvement can be enhanced when microdermabrasion sessions are combined with topical retinoid treatment (40% vs. 15% improvement) [92]. Similarly, Kauvar et al. demonstrated that a combination of microdermabrasion followed immediately by Q-switched neodymium-doped yttrium aluminium garnet (QS Nd:YAG) laser treatment yielded even higher improvement rates with 81% of participants achieving >75% clearance (n = 27) [94]. While there has been concern about potential adverse neurologic effects of aluminum oxide, there has been inconclusive evidence to date that long-term exposure to aluminum may be associated with cognitive impairment.

These findings have mainly been found in aluminum miners or factory workers and are specific to aluminum and not aluminum oxide [90].

In general, microdermabrasion is considered to be safe in all skin types with few side effects. Petechiae and purpura may develop depending on ablation speed and vacuum pressure, but lesions typically resolve by 3 days. Rarer side effects include acne and recurrent herpes simplex outbreaks. It should be performed with caution in darker skin types (i.e., III–VI) due to the risk of PIH, and those with rosacea as telangiectasias and erythema may be permanently worsened [92].

Microneedling

Microneedling is accomplished by rolling an instrument studded with rows of microneedles over the skin multiple times. The microneedles penetrate through the epidermis and into the upper dermis (0.5 mm), inducing a wound-healing response. For hyperpigmentary disorders, microneedling has been explored as a means of augmenting transepidermal drug delivery [95]. Fabbrocini et al. [95] conducted a split-face study among women with melasma (n = 20, FST III–V) wherein a serum containing rucinol and sophora-alpha was applied to skin with and without prior microneedling. Compared to the serum alone group, the MASI score decreased significantly more in the combination group (7.1 vs. 10.1 points). Lima Ede reported similar improvement with a combination of microneedling and triple combination cream (0.05% tretinoin, 4% hydroquinone, 1% fluocinolone acetonide), with preserved results at 2 years follow-up [96]. In a prospective randomized trial, microinjections of tranexamic acid with and without microneedling were administered among patients with melasma (n = 60, FST IV–V). After the third treatment session, there was greater improvement in the microneedling group compared to the microinjection alone group (44.41% vs. 35.72%). Furthermore, 41% of patients in the microneedling group showed >50% improvement [97]. Based on these studies, the augmented response to treatment with microneedling may be attributable to deeper and more uniform penetration of medication.

Microneedling is generally well-tolerated with no adverse effects reported in most studies [95–97]. Furthermore, as the epidermis remains largely intact, risks of scarring and infection are limited [98].

Lasers

Lasers are typically used as third-line agents for disorders of hyperpigmentation, as data is still limited, and there is an increased risk of scarring and dyspigmentation. Lasers that have been extensively explored in the treatment of pigmented disease,

albeit with variable success include Q-switched Ruby (695 nm), Q-switched Alexandrite (755 nm), QS Nd:YAG (1064 nm), intense pulsed light, pulsed dye laser, and fractional photothermolysis. For pigmentary disorders, the target chromophore is melanin (630–1100 nm), so ideally lasers with wavelengths within this range are used [99]. Lasers that produce pulses of light shorter than the thermal relaxation time (time necessary for the target tissue to lose 50% of its initial heated temperature) of melanosomes (250–1000 ns) must be used in order to selectively destroy melanin. Consequently, the QS Nd:YAG 1064 nm laser which emits long wavelengths in ultra short pulse durations is most commonly used [100]. Further details on patient selection, pre-and post-treatment care, and types of lasers can be found in the laser chapter.

Oral Agents

Oral agents are generally considered third-line agents for treatment of dyschromia after topical agents and/or chemical peels have failed. However, some authors use it as second-line agents [101].

Tranexamic Acid

Originally marketed as a fibrinolytic agent, tranexamic acid has recently demonstrated efficacious off-market use in treating melasma [102]. Unlike other treatments, which aim to decrease melanogenesis (majority of topical agents) or remove pre-existing melanin (peels, lasers), tranexamic acid is postulated to prevent activation of melanocytes by blocking plasminogen binding to keratinocytes [102]. Tranexamic acid may also modulate angiogenic factors involved in the development of melasma [101]. In the largest retrospective study to date of melasma patients with a median follow-up of 4 months (n = 561), 89.7% of patients showed improvement while on tranexamic acid 250 mg twice a day [101]. These promising findings are consistent with multiple previous studies based on Asian populations; however, studies are lacking in other patient populations [103, 104]. Common side effects included nausea, diarrhea, and orthostasis [102].

Prior to initiating treatment, clinicians should screen for a history of thrombosis, angina, and stroke, and consider obtaining monthly coagulation labs. Lightening effects should be expected after 2 months of treatment [101]. If no response is observed, increasing treatment duration is more effective than increasing dosage [101, 102]. Finally, like other topical agents, patients should be counseled on the risk of relapse, as 27% of patients in the Lee et al. study relapsed on cessation of oral treatment [101].

Botanical Agents

Botanical products, such as procyanidin, pycnogenol, and *Polypodium leucotomos* (*P. leucotomos*), are increasingly attractive to consumers because they are inexpensive, easily accessible without prescription, and perceived to be "more safe" than pharmaceuticals. They inhibit hyperpigmentation by exerting antioxidant or anti-inflammatory effects [105]. Only a few studies have been conducted to date and although they found these agents (procyanidin 48 mg/day with vitamins A, C, E, or pycnogenol 75 mg/day) to be safe and efficacious in treating melasma, they are limited by different factors including very short follow-up periods (i.e., 1 or 2 months). Studies on *P. leucotomos* have demonstrated mixed results with respect to efficacy, but one small study showed that it may prevent UVA-induced pigmentary changes [106–110]. Of note, no studies have examined their efficacy in PIH and overall improvement in skin of color. In the interim, while further studies are conducted, clinicians should be aware that botanicals carry an inherent risk of allergic and phototoxic reactions and do not require rigorous safety testing by the Food and Drug Administration (FDA) before marketing. They may also be adulterated with corticosteroids, putting users at risk of steroid-induced atrophy and dyspigmentation [105].

Emerging Oral Treatments

Oral grape seed extract can reduce the appearance of melasma by inhibiting melanin synthesis and UV-induced hyperpigmentation [111]. To date, there have been limited studies in humans, but in one study among Japanese women ($n = 12$), 6 months of oral grape seed extract therapy led to a reduction in the melanin-index score that persisted during the next 6 months [112]. Although it was well-tolerated, more studies with larger sample sizes are needed to further evaluate its efficacy.

Intravenous Agents

Glutathione (GSH) is an endogenously produced antioxidant that is found naturally in food (i.e., watermelon, avocado, spinach) and also commercially, in oral and intravenous formulations. It is more commonly used in Asian countries (i.e., Thailand, Philippines, India), where "fair" skin is highly desired as a symbol of social ranking [113]. While GSH initially appeared promising through its multi-faceted inhibition of melanogenesis—inactivating tyrosinase, mediating the switch from eumelanin to pheomelanin, and quenching formation of free radicals—few studies have examined its efficacy and safety in skin whitening [113]. These agents are currently not recommended or FDA-approved for this purpose. The FDA

has banned injectable versions due to the risk of Stevens Johnson syndrome, toxic epidermal necrolysis, and abnormalities in thyroid and renal function [114]. Injectable formulations are furthermore likely to be counterfeit and administered by untrained personnel, which raises the risk of sepsis, air embolism, and transmission of infectious disease [114]. Finally, it is unknown whether switching from eumelanin (protective against UV radiation) to pheomelanin (potentially photosensitizing to UVA in melanocyte cultures) may result in an increased risk of skin cancer [115].

Conclusion

By 2050, more than half of the U.S. population will be composed of darker ethnic skin types. Consequently, clinicians should be prepared to treat a higher volume of disorders of hyperpigmentation (i.e., melasma, PIH).

Topical agents are generally first-line treatment, with hydroquinone and triple combination therapy often used initially given their long history of safety and efficacy. Chemical peels are considered a second-line agent as they are both more expensive and carry a higher risk of side effects. Oral tranexamic acid demonstrates excellent efficacy but is still limited by a high relapse rate and warrants more study in non-Asian populations. Microdermabrasion, microneedling, and laser treatments are third-line options given the limited data to date and the higher risks of side effects. Finally, maintenance therapy with sunscreen and topical agents are crucial to prevent relapse.

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