Disorders of hyperpigmentation. Part II. Review of management and treatment options for hyperpigmentation

Dayoung Ko, MD, Rebecca F. Wang, MD, David Ozog, MD, Henry W. Lim, MD, and Tasneem F. Mohammad, MD
Detroit, Michigan

Learning objectives
After completing this learning objective, the reader will be able to better discuss this aspect of the literature.

Disclosures
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Jeremy Brauer, MD, FAAD, is a consultant for Cutera, Inc. and Solta Medical and receives honoraria. Matthew Zirwas, MD, FAAD, is a consultant and investigator for Galderma Global and receives honoraria and grants/research funding.

Reviewers
Kara Melissa Tiangco Torres-Culala is a speaker for Galderma and receives honoraria. George Hruza, MD, MBA, FAAD, is a stockholder for Teva and does not receive compensation.

Key challenges in the management of pigmentary disorders such as melasma and postinflammatory hyperpigmentation are their resistance to treatment, tendency to recur after treatment, and the risk of exacerbating hyperpigmentation with many treatment modalities. The second article in this 2-part continuing medical education series on pigmentary disorders focuses on the evidence behind medical and procedural treatments of dyschromias, including photoprotection, topical lightening agents, oral agents, chemical peels, and laser therapy. (J Am Acad Dermatol 2023;88:291-320.)

Key words: ablative fractionated lasers; chemical peels; hydroquinone; intense pulsed light; lasers; lightening cosmeceuticals; melasma; nonablative fractionated lasers; oral lightening agents; photoprotection; picosecond lasers; pigmentary disorders; postinflammatory hyperpigmentation; Q-switched lasers; sunscreen; topical lightening agents.

PHOTOPROTECTION

Key points

- UV and visible light (VL) exacerbate existing dyschromias.
- All patients with a pigmentary disorder should be advised to use a daily broad-spectrum tinted sunscreen with SPF ≥30.

The photobiologic effects of UV are well studied, including erythema, increased pigmentation, photoaging, and photocarcinogenesis.[1] VL (400-700 nm) comprises almost 50% of the solar radiation reaching the surface of the earth, compared to 5% of UV radiation. VL induces persistent pigmentation, erythema, and DNA damage. It acts synergistically with

From the Department of Dermatology, Henry Ford Hospital, Detroit, Michigan.
Funding Sources: None.
IRB approval status: Not applicable.
Accepted for publication December 31, 2021.
Reprints not available from the authors.
Correspondence to: Tasneem F. Mohammad, MD, Department of Dermatology, Henry Ford Hospital, 3031 W Grand Blvd, Suite 800, Detroit, MI 48202. E-mail: tmohamm2@hfhs.org.
0190-9622/$36.00

https://doi.org/10.1016/j.jaad.2021.12.065
Date of release: February 2023.
Expiration date: February 2026.

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Abbreviations used:

AA:	Ascorbic acid
EDP:	erythema dyschromicum perstans
IPL:	intense pulsed light
LPP:	lichen planus pigmentosus
MASI:	melasma area and severity index
PIH:	postinflammatory hyperpigmentation
QS:	Q-switched
QSL:	Q-switched laser
TCA:	trichloroacetic acid
TCC:	triple combination cream
TXA:	tranexamic acid
UV:	ultraviolet
VL:	visible light

minimal amounts of UVA1 to induce greater pigmentary changes.[2-5] A study showed that postinflammatory hyperpigmentation (PIH) can be prevented when suction blisters are completely protected from all sun radiation by an opaque dressing for the first 15 days.[6] Iron oxides in tinted sunscreen also offer protection against VL and prevent exacerbation of pigmentation in dyschromias, such as melasma, PIH, and lichen planus pigmentosus (LPP).[7] In one study, 4% hydroquinone plus sunscreen with and without VL protection were compared in patients with melasma. Both groups showed significant reduction in melasma area and severity index (MASI) scores, such that MASI score decreased by 78% in the UV plus VL sunscreen group compared to 62% in the UV alone sunscreen group ($P < .001$).[8] A split-face study on the efficacy of sunscreen use after ablative fractional CO_2 resurfacing in 26 subjects with skin type IV showed that the side treated with petrolatum ointment plus broad-spectrum sunscreen had a significantly lower melanin index 1 week after laser treatment than the side with petrolatum only.[9] Lightening of preexisting hyperpigmented macules and overall skin lightening with daily use of broad-spectrum sunscreen also has been demonstrated.[10]

During pregnancy, photoprotection is a safe treatment for hyperpigmentation as many first-line treatments, such as hydroquinone, may have potential adverse effects on the fetus. The incidence of melasma in 185 pregnant Moroccan women using a broad-spectrum SPF 50 plus sunscreen showed only 5 new cases of melasma (2.7%),[11] compared to 53% in a previous study.[12] These studies suggest that tinted broad-spectrum sunscreens are important adjunctive recommendations in the prevention and treatment of hyperpigmentation.

TOPICAL TREATMENTS

Key points

- Topical 4% hydroquinone and triple combination cream (TCC) therapy are effective first-line treatments for dyschromias, however, their use may be limited by irritation and, rarely, ochronosis.
- Several natural compounds, including azelaic acid, kojic acid, ascorbic acid, niacinamide, arbutin, bakuchiol, and thiamidol, have shown mild efficacy with better tolerability. These compounds are often formulated together.
- Studies show mixed results on the efficacy of topical tranexamic acid (TXA), with or without laser treatment.
- Limited studies exist on the efficacy of cysteamine; the current evidence is mixed.

Hydroquinone

Hydroquinone is a tyrosinase inhibitor that is commonly used to treat hyperpigmentation (Table I).[13-31] Adverse effects include irritation, allergic contact dermatitis, erythema, inflammation, xeroderma, and stinging. Chronic unsupervised use of high concentrations (>4%) of hydroquinone can lead to ochronosis and colloid milium. Hypopigmentation can develop if applied to normal skin. As such, it needs to be used with caution for small or numerous hyperpigmented macules (eg, acne-induced PIH), as targeted application can be difficult. Rarely, it can cause leukoderma at sites distant from application, particularly in those of African descent (Fig 1).[32,33] Because 35% to 45% of topical hydroquinone is absorbed systemically and because of its unknown effect on fetuses, it is generally not regarded as safe in pregnant or breastfeeding women.[34]

To avoid both short- and long-term sequela of hydroquinone, practitioners should limit treatment duration to 3-6 months continuously, after which the patient should take a break from the treatment. Given the concerns for high rates of irritation with the use of daily hydroquinone, which may lead to PIH, frequency of application should be decreased to a twice weekly regimen for patients who have irritation.[35] If leukoderma develops, hydroquinone should be stopped immediately and oral corticosteroids initiated to prevent spread. Although hydroquinone is an effective treatment for pigmentary disorders, alternative treatment modalities should be considered if patients discontinue hydroquinone due to adverse effects or during break periods.[36-40]

Hydroquinone, retinoid, corticosteroid combination

The lightening effect of hydroquinone is augmented when combined with a retinoid and a

Table I. Mechanism of action of topical agents

Topical agent	Mechanism of action
Hydroquinone	• Inhibits enzymatic oxidation of tyrosinase, which normally converts L-3,4-dihydroxyphenylalanine (L-DOPA) to melanin[13,14] • Covalently binds to histidine and interacts with copper at the active site of tyrosinase[14] • Destroys melanocytes, degrades melanosomes, inhibits DNA and RNA synthesis[14,15]
Hydroquinone, retinoid, steroid combination	• Retinoids decrease melanosome transfer, inhibit tyrosinase transcription, and interrupt the synthesis of melanin[16] • Corticosteroids are nonselective suppressors of melanogenesis
Azelaic acid	• Interferes with DNA synthesis, inhibits mitochondrial oxidoreductase, competitively inhibits tyrosinase, and decreases free radical formation[17]
Kojic acid	• Inhibits tyrosinase and exhibits antioxidant properties by scavenging reactive oxygen species[18]
Ascorbic acid (vitamin C)	• Protects against UVA-dependent melanogenesis; interacts with copper ions at the tyrosinase active site and reduces oxidized dopaquinone, a substrate in the melanin synthetic pathway[19-21] • May also have an advantage to sunscreen in that it is retained in the epidermis for a longer time[22]
Niacinamide	• Inhibits the transfer of melanosomes to epidermal keratinocytes to combat hyperpigmentation[23]
Arbutin	• Induces reversible tyrosinase activity[24]
Bakuchiol	• Modulates retinoic acid receptor genes and upregulates collagen and extracellular matrix synthesis enzymes[25] • May also have a role in blocking alpha-melanocyte-stimulating hormone activation and tyrosinase[26]
Thiamidol	• Competitive tyrosinase inhibitor; not converted to a quinone which potentially induces leukoderma[27]
Tranexamic acid	• Prevents binding of plasminogen to keratinocytes and thus inhibits UV-induced plasmin activity in keratinocytes, thereby decreasing arachidonic acid and alpha-melanocyte-stimulating hormone. By inhibiting plasminogen activation, TXA mitigates UV radiation-induced melanogenesis and neovascularization[28-30]
Cysteamine	• Acts as an intrinsic antioxidant and has potent depigmenting properties via the inhibition of tyrosinase and peroxidase leading to decreased melanin[31]

corticosteroid.[41-44] Seventy subjects with melasma were treated with TCC (4% hydroquinone, 0.05% tretinoin, and 0.01% fluocinolone acetonide) daily for 12 weeks. Pigmentation was significantly reduced at weeks 12 and 24, however, mild adverse events, such as erythema and peeling, were reported in 53% of patients.[45] TCC therapy was shown to be more effective than hydroquinone 4% alone[41] and a significantly larger proportion of patients treated with TCC experienced complete or near complete resolution when compared to each of the other 2 ingredients combined (tretinoin plus hydroquinone; tretinoin plus fluocinolone, and hydroquinone plus fluocinolone).[43]

It has been proposed that the treatment period with TCC therapy should be daily for 8 weeks, then twice weekly for 6 months afterwards for maintenance.[42] Although adverse effects such as erythema and peeling are less common than with hydroquinone alone, they are still present and patients should be counseled accordingly.[43,46]

Natural compounds

Natural topical compounds have been well established for the treatment of pigmentation, and are utilized in many cosmeceuticals. Promising lightening effects have been shown with azelaic acid, kojic acid, ascorbic acid, niacinamide, arbutin, bakuchiol, and thiamidol (Table II).[47-74] They are usually formulated in combination with one another and have the benefit of being available over the counter, although higher concentrations of azelaic acid are only available by prescription.

Tranexamic acid

TXA is increasingly used as a lightening agent and is available over the counter. Topical TXA (2% to 3%) has been shown to be effective in treating PIH and melasma when combined with 1% kojic acid and 5% niacinamide[75] or combined with niacinamide alone.[76] Other studies have found equal and significant efficacy for melasma treatment, between 3% TXA and 3% hydroquinone plus 0.01%

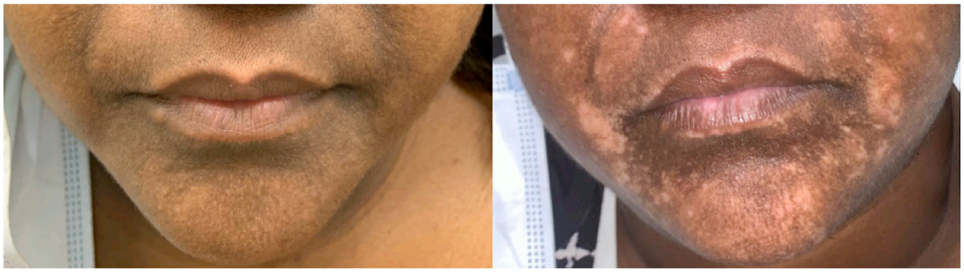

Fig 1. Hydroquinone-induced leukoderma. **Left,** Before **Right,** After. Patient had used 8% hydroquinone-0.1% tretinoin-0.1% fluocinolone cream nightly for 1 month, only around the eyes and subsequently developed depigmented spots on the lower portion of the face.

dexamethasone[77] and equal and significant efficacy between 5% TXA gel plus sunscreen and vehicle plus sunscreen.[78] TXA caused erythema in both studies, however, it was less compared to hydroquinone.[77]

Overall, the evidence for the efficacy of topical TXA is mixed, with many studies citing inefficacy. Further evidence is needed before this can be broadly recommended.

Cysteamine

Cysteamine is a thiol compound that occurs naturally in the body as a degradation product of the amino acid L-cysteine.[31] Its use as a topical treatment can be limited by its malodor, as it has a sulfurous scent. Two randomized controlled trials showed that cysteamine cream was significantly more efficacious in treating melasma than placebo[31,79] A small portion of subjects in both studies reported erythema, dryness, itching, and irritation. A study of 40 women with facial melasma compared topical 5% cysteamine cream to 4% hydroquinone cream and found that cysteamine was well-tolerated but inferior to hydroquinone in decreasing pigmentation.[80] Another study of 20 patients with melasma showed equal efficacy between 5% cysteamine and 4% hydroquinone cream, with more side effects in the cysteamine group.[81] Case studies have reported the efficacy of topical cysteamine in a melasma patient resistant to TCC[82] and a patient with PIH refractory to TCC.[83]

ORAL AGENTS

Key points

- Low-dose oral TXA is a well-tolerated treatment option for hyperpigmentation as long as patients have no risk factors for thromboembolic events.
- Low-dose isotretinoin is a potential treatment for LPP and erythema dyschromicum perstans (EDP).
- Preliminary studies suggest that oral polypodium leucotomos extract could be beneficial for treating dyschromias; however, larger studies are needed.

Tranexamic acid

Oral TXA has been shown to be effective for the treatment of pigmentary disorders, but most studies report a recurrence of hyperpigmentation following cessation. A retrospective study of 561 Asian patients with melasma found that 89.7% of patients who received oral TXA 250 mg twice daily reported improvement, with a response usually within 2 months. After cessation of therapy, 27.2% of patients relapsed.[84] A multitude of studies have similarly reported drastic improvement in pigmentation with oral TXA, but relapse rates as high as 72% occurred within 2 months of treatment cessation.[85-91] Often, oral TXA is used to induce remission of disorders of hyperpigmentation,[92] with other agents being used for maintenance. Oral TXA can also be used in combination with other topical and procedural treatments to increase efficacy.[93-96] TXA has been used to treat hyperpigmentation at doses of 500 to 1,500 mg in 2 or 3 divided doses daily, compared to the dose employed as a hemostatic agent at 3,000 mg daily. We recommend starting at 325 mg twice daily for at least 2 months and titrating up as needed.

Thromboembolic events are rare and the most common side effects are gastrointestinal discomfort and menstrual irregularities. Contraindications to therapy include hypercoagulable comorbidities, such as renal dysfunction, malignancy, current anticoagulant therapy, pro-coagulant therapy, including oral contraceptive pills, and history of thromboembolic disease, including hereditary conditions, DVT, PE, arterial thrombosis, and stroke.[97] Relative contraindications include concomitant hormonal therapy, recent infection with COVID-19, and smoking, given increased risk of thrombosis. Patients should be screened for risk factors prior to starting treatment.

Table II. Natural topical treatments

Ingredient	Description	Studies	Conclusions
Azelaic acid	• Saturated 9-carbon dicarboxylic acid derived from the fungus *Pityrosporum ovale*[17]	• 20% azelaic acid compared to 4% hydroquinone in 29 melasma patients. Azelaic acid improved pigmentation more compared to hydroquinone[47] • 20% azelaic acid + 15 or 20% glycolic acid was as effective as 4% hydroquinone cream in reducing pigment intensity; higher rates of irritation seen in hydroquinone group[48] • 15% azelaic gel twice daily showed a reduction in acne and PIH[49]	• Well-tolerated with only minor local burning or itching • Versatile topical agent and thus may be especially useful in treating patients with a combination of acne and hyperpigmentation
Kojic acid	• Metabolic product of the fungal species *Acetobacter, Aspergillus,* and *Penicillium*[18]	• Same reduction in pigmentation between 2% hydroquinone + 5% glycolic acid versus 2% kojic acid + 5% glycolic acid[50] • 4% hydroquinone was superior to 0.75% kojic acid + 2.5% vitamin C in the lightening of melasma[51] • 4% hydroquinone had the same efficacy in skin lightening as a compound containing kojic acid, emblica extract, and glycolic acid[52]	• Limited studies evaluating kojic acid as monotherapy for skin lightening, however it has shown good efficacy when used in combination with other skin lightening agents • Patients who do not respond to or cannot tolerate topical hydroquinone may benefit from the addition of kojic acid[50,53]
Ascorbic acid (vitamin C)	• Acidic, hydrophilic antioxidant most commonly found in citrus fruit	• 4% hydroquinone cream led to better subjective improvement in melasma than 5% ascorbic acid cream, however had higher rates of side effects[39] • C'ensil, a formulation containing 25% AA and a chemical penetration enhancer significantly decreased pigmentation after 16 weeks[34] • 0.5% retinol + 30% AA for 12 weeks significantly improved pigmentation in patients with mild to moderate hyperpigmentation and photodamaged facial skin[54,55] • 20% TCA peel every 2 weeks + 5% AA cream daily was more effective in decreasing pigmentation than 20% TCA peel every 2 weeks alone for melasma; very well tolerated[56] • 20% TCA peel weekly for 6 treatments + 5% AA cream daily was more effective in decreasing pigment than 20% TCA peel weekly for 6 treatments alone, at 16 week follow-up in skin type III-IV melasma patients[57] • Vitamin C iontophoresis is an effective treatment for melasma[59,60]	• AA's instability and difficulty with penetration is a challenge • Cost and difficulty in formulation may result in the variability of its clinical efficacy, and thus makes it difficult to judge its efficacy as a topical depigmenting agent[58]

Continued

Table II. Cont'd

Ingredient	Description	Studies	Conclusions
Niacinamide	• Active form of vitamin B3 (niacin) which is found in yeast and root vegetables; a precursor to NAD (nicotinamide adenine dinucleotide), a molecule that participates in many cellular enzymatic reactions[23,61]	• 5% niacinamide moisturizer led to improvement in appearance of fine lines/wrinkles, hyperpigmentation, erythema, and yellowing by decreasing collagen oxidation products; well tolerated and chemically stable[62] • Topical 4% niacinamide and 0.05% desonide showed lightening effects[63] • Topical 0.5% retinol, 4.4% niacinamide, 1% resveratrol, and 1.1% hexylresorcinol showed lightening effects[64]	• Very well-tolerated agent and has many proposed cosmetic benefits • Its efficacy as monotherapy for the treatment of pigmentary disorders needs to be explored further
Arbutin	• Derivative of hydroquinone found in herbs such as bearberry	• 1% arbutin in 10 patients with melasma significantly improved pigmentation in all participants[24] • 7% alpha arbutin + frequency-doubled Q-switched Nd:YAG laser showed favorable results in treating melasma[65] • Micellar formulated arbutin cream improved both drug delivery and cellular melanin suppression[66]	• Limited studies, however positive early results
Bakuchiol	• Purified meroterpene phenol found in the seeds of the Indian plant *Psoralea corylifolia*[67]	• 0.5% bakuchiol versus 0.5% retinol cream daily both significantly decreased wrinkle surface area and hyperpigmentation with no significant difference between the compounds. Retinol users had more facial skin scaling and stinging[68] • Bakuchiol cream significantly improved pigmentation in TCA-induced PIH lesions[69] • 0.5% bakuchiol cream twice a day for 12 weeks significantly improved lines and wrinkles, pigmentation, elasticity, firmness and overall reduction in photo-damage[25]	• Although studies are limited, Bakuchiol shows similar anti-aging and lightening properties as retinoids, with less side effects
Thiamidol	• Isobutylamido thiazolyl resorcinol (Thiamidol) is a new resorcinol derivative developed specifically to inhibit human tyrosinase[27]	• 0.15% Thiamidol is an effective agent in the prevention of pigmentary changes from UVB irradiation[70] • 0.2% Thiamidol twice a day versus 4% hydroquinone cream qhs both improved pigmentation in melasma patients; no difference was seen in melasma improvement or adverse effects, between the groups[71]	• Thiamidol is a promising potent inhibitor of tyrosinase that is very well tolerated; more studies are needed

Continued

Table II. Cont'd

Ingredient	Description	Studies	Conclusions
		• 0.2% Thiamidol improved mild to moderate melasma more effectively than 2% hydroquinone cream[72] • Thiamidol containing products (serum and day care SPF 30) twice a day improved facial hyperpigmentation and skin roughness[73] • Thiamidol containing products improved pigmentation in suction blister-induced PIH and acne-related PIH[74]	

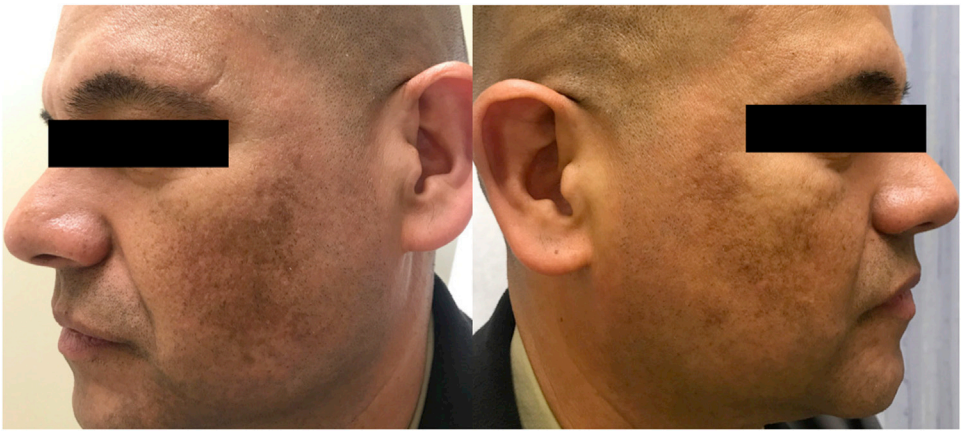

Fig 2. Melasma, baseline before tranexamic acid treatment.

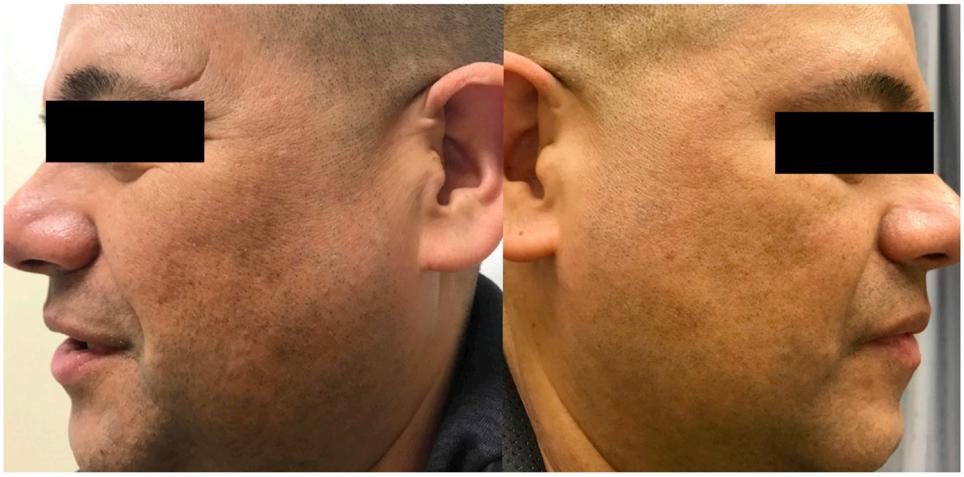

Fig 3. Melasma, after 7 months of tranexamic acid 325 mg twice a day.

The evidence for the efficacy and safety of oral TXA is robust and this agent can be used alone or as adjunctive therapy in patients with hyperpigmentation who have no risk factors for a thromboembolic event (Figs 2 and 3).

Isotretinoin

Oral isotretinoin is a retinoid with anti-inflammatory properties. Low-dose isotretinoin (20 mg daily) showed improvement in 25 out of 27 subjects with LPP. A 75% reduction of

hyperpigmentation was seen in 4 of 27 patients by 3 months of treatment, but no subjects had complete clearance; no relapses were seen at 3 months post treatment.[98] Another case report of a patient with recalcitrant LPP showed a marked response to isotretinoin 20 mg daily; at 1 year from treatment initiation, the patient continued on isotretinoin 20 mg every other day and continued to have improvement of pigmentation.[99] A case series of 4 patients with EDP, showed that combined oral prednisone and low-dose isotretinoin for 1-4 months was effective in improving the erythematous border and hyperpigmentation seen in EDP; relapse was seen in 2 of 4 cases at 2 and 16 months after stopping isotretinoin.[100]

Polypodium leucotomos extract

Polypodium leucotomos extract (PLE) is an over-the-counter supplement derived from a fern from the *Polypodiaceae* family. The extract is a potent antioxidant with photo- and immunoprotective activity against UVA and UVB radiation.[101,102] A study evaluated the efficacy of 4% hydroquinone plus SPF50 sunscreen with and without oral PLE in patients with melasma; mMASI scores of the PLE group were lower than that of placebo group ($P < .05$). The study suggests that PLE improves the lightening effect of hydroquinone and sunscreen in melasma.[103] PLE has also shown to decrease the persistent pigment darkening and delayed tanning induced by VL in subjects with skin of color.[104] Another study compared the efficacy of PLE plus SPF55 broad-spectrum sunscreen with placebo plus the same sunscreen in subjects with melasma; PLE group had 29% improvement in melanin index while placebo group had 14% ($P = .14$).[105]

Other oral agents

Cases of successful use of oral dapsone have been reported in LPP[106] and EDP.[107,108] Corticosteroids in pulse[109] or in continuous dosing with gradual tapering[110] have also been used successfully in LPP. Doxycycline has been used in EDP.[111] Despite these encouraging cases, the data are limited and cannot be recommended as treatment.

Glutathione is a thiol-containing antioxidant that has been implicated in skin lightening. Intravenous glutathione has been used anecdotally for skin lightening in Asia; however, it can have detrimental neurologic and renal effects, increased risk of hepatitis and HIV, as well as skin reactions, such as Stevens-Johnson syndrome or toxic epidermal necrolysis, and thus is not recommended.[112] Oral glutathione, ranging from 250 to 500 mg total daily dose, has been studied in several healthy populations and found to improve melanin indices and decrease UV-induced pigmented lesions.[113-115] However, it has not yet been studied as a skin-lightening agent in pigmentary disorders and thus further investigation is needed.

PROCEDURAL

Key points

- Chemical peels can treat hyperpigmentation if the appropriate peel is used with adequate preprocedural and postprocedural care.
- Microneedling may be beneficial for treating pigmentary disorders, although studies are limited and inconclusive.
- Intense pulsed light (IPL) is effective for treating dyschromias, however has high risk of recurrence and PIH, especially in darker skin tones.
- Q-switched nanosecond laser (QSL) and picosecond laser are effective for treating dyschromias with less risk of PIH, although with risk of recurrence.
- Nonablative fractionated laser can be effective for treating dyschromias in lighter skin types, although there is still a risk of recurrence.
- Ablative fractionated laser is not recommended for the treatment of pigmentary disorders.

Chemical peels

Many studies have shown superficial chemical peels to be a well-tolerated treatment for various pigmentary disorders (Table III, Figs 4-6).[56,57,116-129] Given the risk of PIH, chemical peels should be offered as an adjunctive modality or once topical therapies have failed. Patients should be informed of the risk of additional pigmentation from treatment.

Superficial peels with less inflammatory potential can be used in all skin types, including patients with skin types IV-VI. In skin types I-III, medium depth and deep peels can be used, which also have the added benefit of rejuvenation. Strict photoprotection and pretreatment and posttreatment with topical hydroquinone should be initiated to minimize the risk of PIH in high-risk patients. In 1 study, PIH was seen in 20% of patients receiving glycolic acid peels without a priming agent for melasma, while observed in 14.3% and 5.5 % of patients pretreated with 0.025% tretinoin and 2% hydroquinone nightly for 2 weeks, respectively.[130] A similar study found that pretreatment with 2% hydroquinone nightly for 2 weeks was superior to pretreatment with 0.025% tretinoin in decreasing PIH in patients treated with trichloroacetic acid peels for melasma.[131] Pretreatment with retinoids allow for even peel penetration, but these should be stopped 7 days

Table III. Superficial chemical peels

Study, year	Study design; N	Treatment	Duration	Skin type(s)	Condition	Outcome(s)	Adverse effects
Glycolic acid peels							
Javaheri et al[116]	Prospective; 25	50% glycolic acid peels once per month for 3 months, pretreated with sunscreen and 10% glycolic acid lotion for 2 weeks	3 months	--	Melasma	Improvement of melasma (reduction in MASI) was observed in 91% of patients; epidermal-type melasma showed a better response than mixed-type melasma.	1 patient with PIH, resolved with 4% hydroquinone and mid-potency topical steroid
Dayal et al[117]	Prospective; 60	Group 1: 30-50% glycolic acid peels every 3 weeks for 6 months + 20% azelaic acid twice daily Group 2: 20% azelaic acid twice daily	6 months	IV-V	Melasma	MASI, percent decrease in MASI, and MELASQOL scores were significantly reduced in both combination and control group; percent decrease was greater in combination therapy group.	Mild adverse effects such as erythema, burning, PIH, and pruritus were seen, however were not significantly different between the groups
Rendon et al[118]	Prospective, open-label; 20	Glycolic acid peels every 2 weeks x 5 sessions, each session alternating with 2 weeks of TCC	12 weeks	II-VI	Melasma	Investigator global assessment ratings showed 1 of 20 participants had treatment success (clear/almost clear) as early as week 6 and most participants (13 of 20) achieved treatment success by week 12; MI differences, as measured by absorption spectrometry, was significantly reduced at weeks 6 and 12 compared to baseline.	8 participants experienced mild adverse events
Sarkar et al[119]	Prospective, open-label; 40	Group 1: 6 30-40% glycolic acid peels every 3 weeks + TCC (5% hydroquinone + 0.05% tretinoin + 1% hydrocortisone) Group 2: TCC only	21 weeks	III-V	Moderate-severe melasma, epidermal type	Significant decrease in MASI score from baseline was observed in both groups; the glycolic acid peels group showed a more rapid and greater improvement than TCC alone.	6 patients in the peels group experienced manageable adverse events: focal superficial vesiculation, PIH, persistent erythema, and herpes labialis
Khunger et al[120]	Prospective, open label, split-face; 10	One half: 70% glycolic acid peel weekly Other half: 1% tretinoin peel weekly	12 weeks	III-V	Moderate to severe melasma	Significant decrease in modified MASI score from baseline to 6 weeks, then from 6 to 12 weeks was observed on both sides; no difference was observed between the sides.	4 patients on glycolic acid side experienced side effects: superficial desquamation, burning, and PIH. 2 patients on tretinoin side: erythema and superficial desquamation

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Table III. Cont'd

Study, year	Study design; N	Treatment	Duration	Skin type(s)	Condition	Outcome(s)	Adverse effects
Wolff et al[121]	Case report; 1	Combination therapy with 5% azelaic acid daily + 0.1% tretinoin cream nightly + Jessner's peel every 2-4 weeks to the arms and 35-50% glycolic acid peel every 2-4 weeks to the face	16 weeks	--	LPP	After 16 weeks of treatment, a marked improvement in appearance of facial lesions was noted; dyschromia on the arms only mildly improved.	none
Sonthalia et al[122]	Retrospective analysis; 17	Modified phenol peels (Croton oil free phenol combination) every 3 weeks for 6 sessions	18 weeks	IV-V	LPP	5 of 17 (29%) showed excellent improvement with >75% reduction in pigmentation; 13 of 17 (76%) had moderate to excellent improvement (≥25% reduction in pigmentation)	Temporary burning, nasopharyngeal irritation due to phenolic odor, temporary PIH
Lim et al[123]	Prospective, split-face; 10	Other half: cream containing 10% glycolic acid + 2% hydroquinone twice a day, Other half: cream containing 10% glycolic acid + 2% hydroquinone BI, followed by 20-79% glycolic acid peels every 3 weeks	26 weeks	IV-V	Moderate to severe melasma	Both sides showed lightening of melasma, as determined by patient and dermatologist; peels side had greater lightening, however the difference was not significant.	Burning, erythema, and transient PIH on the peels side
Hurley et al[124]	Prospective, split-face; 21	One half: 20-30% glycolic acid peels every 2 weeks + 4% hydroquinone twice a day Other half: 4% hydroquinone twice a day	8 weeks	IV-V	Moderate to severe melasma	Both sides had a significant effect in reducing skin pigmentation (MASI); however the difference between the 2 sides was not significant.	Erythema on the peels side
Jessner's peel (14% salicylic acid, 14% lactic acid, 14% resorcinol)							
Ejaz et al[125]	Randomized controlled trial; 60	Group 1: Jessner's solution every 2 weeks for 12 weeks Group 2: 30% salicylic acid every 2 weeks for 12 weeks	24 weeks	III-V	Melasma, epidermal type	Both groups had significant improvement in melasma, as measured by MASI scores; there was no difference between the groups.	Adverse effects were mild and comparable in both groups and included excessive crusting, sunburn, pigmentation, and acneiform eruption
Sharquie et al[126]	Prospective, split-face; 24	One half: 92% lactic acid peel every 3 weeks for 3 to 5 sessions Other half: Jessner's solution every 3 weeks for 3 to 5 sessions	6 months	III-V	Melasma	All patients showed significant improvement in melasma, as measured by MASI score on both sides; degree of improvement was similar on both sides.	none

Salicylic acid							
Grimes et al[127]	Prospective, open-label; 25	20% to 30% salicylic acid peel every 2 weeks for 5 sessions + 4% hydroquinone, pretreated with 4% hydroquinone for 2 weeks	12 weeks	V-VI	Acne, PIH, melasma, rough and oily skin	Moderate to significant improvement (>50% improvement) was observed in 88% of participants; >50% improvement was seen in 100% of participants with PIH and 66% of participants with melasma.	Temporary crusting and hypopigmentation, transient dryness and hyperpigmentation
Joshi et al[128]	Prospective, open-label, split-face; 10	One half: 20% to 30% salicylic acid peel every 2 weeks for 5 sessions to half of the face Other half: no treatment	12 weeks	IV-VI	PIH	Subjects' self-assessments on the visual analog scale indicated a statistically significant improvement on the treated side; peels did not result in a significant improvement when assessment by photography or in quality of life.	Burning, redness, dryness, crusting, itching, hyperpigmentation, and hypopigmentation
Kodali et al[129]	Prospective; 18	Group 1: 20% to 30% salicylic acid peels every 2 weeks for a total of 4 peels + 4% hydroquinone cream twice a day Group 2: 4% hydroquinone cream twice a day alone	14 weeks	III-V	Moderate to severe melasma	Both sides resulted in significant pigment reduction, by MASI score and the difference in narrow band reflectance spectrophotometer readings; however there was no difference between the groups.	Adverse events occurred in 20% of participants: erythema, burning, and peeling
Trichloroacetic acid 10 to 35% (TCA)							
Dayal et al[56]	Prospective, open-label; 60	Group 1: 20% TCA peel every 2 weeks + 5% AA cream daily Group 2: 20% TCA peel every 2 weeks alone	12 weeks	--	Melasma, epidermal type	Both groups were effective in improving pigmentation and quality of life scores, as measured by MASI and MELASQOL, respectively; combination group was more effective than control.	Adverse effects were mild and not significantly different between the groups; side effects included post peel erythema, burning/stinging, PIH
Soliman et al[57]	Prospective; 30	Group 1: 20% TCA peel weekly for 6 treatments alone, pretreated with 0.05% tretinoin gel daily + 4% hydroquinone cream daily x 2 weeks Group 2: 20% TCA peel weekly for 6 treatments + 5% AA cream daily, pretreated with 0.05% tretinoin gel daily + 4% hydroquinone cream daily x 2 weeks	16 weeks	III-IV	Melasma, epidermal type	Both groups were effective in improving pigmentation, by MASI score; combination group was more effective than control.	Erythema, discomfort, and acne

AA, Ascorbic acid; *LPP*, lichen planus pigmentosus; *MASI*, Melasma Area Severity Index; *MELASQOL*, Melasma Quality of Life; *TCC*, triple combination cream.

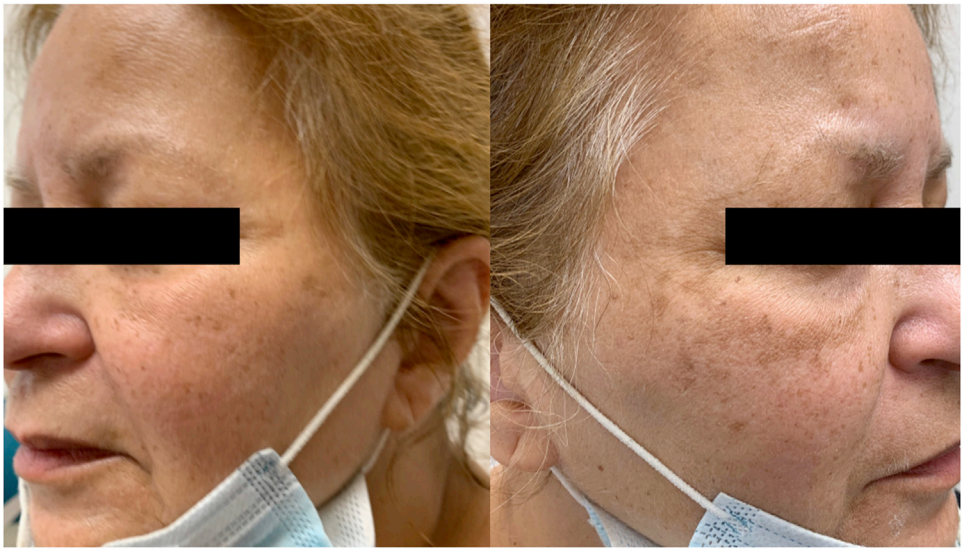

Fig 4. Melasma, baseline before chemical peel.

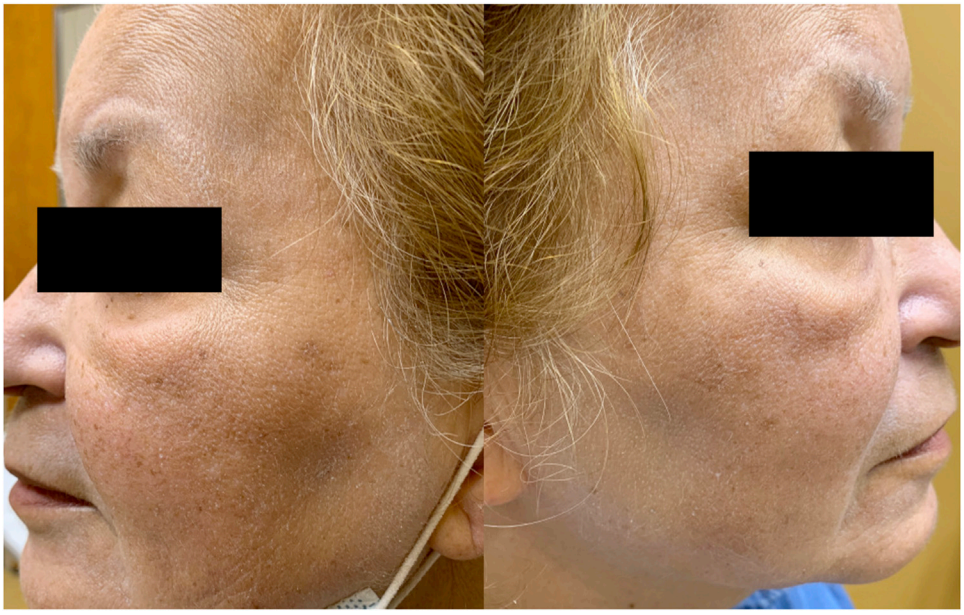

Fig 5. Melasma, 4 weeks after Jessner's peel.

prior to procedure to prevent deeper penetration of peels into the dermis.

Microneedling

Microneedling is a minimally invasive procedure that involves repetitive puncturing of the skin with sterile fine diameter needles, which can enable transdermal drug absorption and also induce dermal regeneration.[132]

In a retrospective analysis of recalcitrant melasma, microneedling was followed by TCC (0.05% tretinoin + 4% hydroquinone + 1% fluocinonide acetonide) and daily tinted sunscreen (SPF 60); microneedling was repeated 30 days later. All 22 patients reported satisfaction with results at 2-month follow-up and skin-lightening effects were maintained in 11 patients at 24-month follow-up.[133] Another study demonstrated no significant difference in lightening between topical 4% hydroquinone nightly and combination microneedling plus topical 4% TXA monthly for 3 treatments; both groups showed effective skin lightening.[134] The efficacy of microneedling with topical TXA (4 mg/mL) was not significantly different than microneedling with 20% vitamin C in improving melasma; both were efficacious.[135]

As suggested by these studies, microneedling may be beneficial in treating pigmentary disorders, especially melasma. Given its minimal risk of PIH,

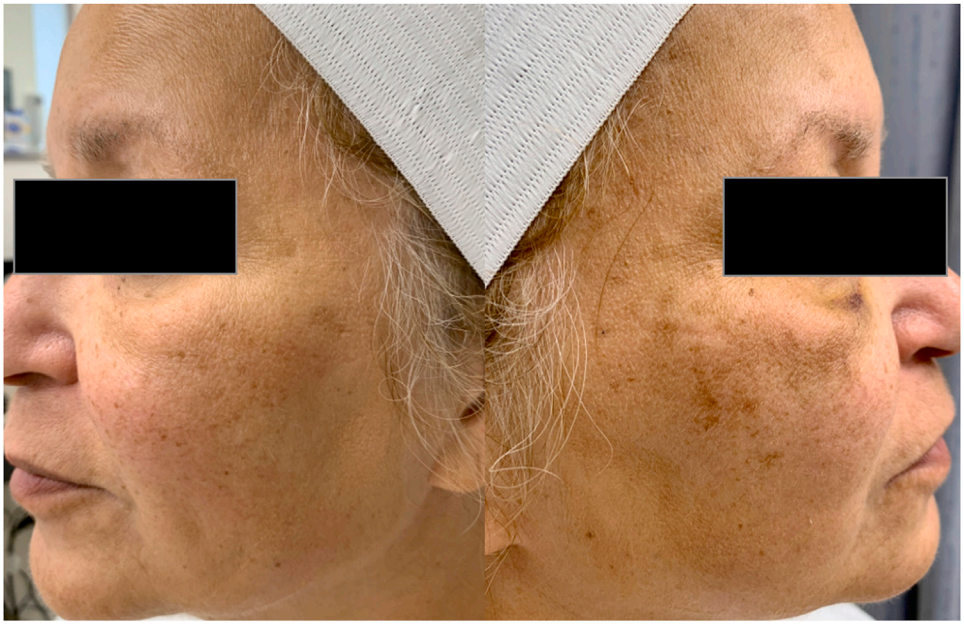

Fig 6. Melasma, 4 weeks after 30% glycolic acid peel and prior Jessner's peel 8 weeks earlier.

microneedling may be a viable alternative to peels and laser treatment in darker skinned individuals.

Intradermal tranexamic acid

TXA microinjections are intradermal injections of TXA (often 4 mg/mL) directly into the lesion to be treated and may have limited benefit,[136,137] however, efficacy of intradermal TXA was not significantly greater than topical TXA[138] or topical TXA with microneedling.[139] Another study compared the efficacy of intradermal TXA (4 mg/mL), topical silymarin cream, and 50% glycolic acid peels in the treatment of melasma. Localized microinjections of TXA significantly decreased MASI scores from baseline, however, the injections were less effective than silymarin cream or glycolic acid peels.[140]

Lasers and light devices

Intense pulsed light. IPL uses a light source that delivers a broad-spectrum of light (wavelength 500-1200 nm) at millisecond pulse duration, and targets all skin chromophores—melanin, hemoglobin, and water.[141] These devices are not commonly used in darker skin types due to the significant risk of inducing postinflammatory hyperpigmentation and hypopigmentation. IPL has been shown to be effective for the treatment of melasma,[142-145] PIH,[146] as well as superficial melanocytic lesions, such as ephelides and café au lait macules[147] in lighter skin types (Table IV).

Q-switched nanosecond lasers. QSL at 1064 nm is commonly used in the treatment of melasma due to its deeper penetration and relative safety in darker skin types. QSLs produce high-intensity laser beams with very short pulse duration (nanoseconds). Studies show that QSLs at higher fluences, normally used to treat benign pigmented lesions, are ineffective in treating melasma and complicated by rebound hyperpigmentation.[141] In recent years, low-fluence QSL, which utilizes multiple passes over short (weekly) intervals, has shown increased efficacy. "Low-dose" QS Nd:YAG laser causes melanin granule fragmentation with minimal thermal damage. QS Nd:YAG has shown great efficacy for the treatment of melasma, but with high recurrence rates.[148-150] Dermal melanocytosis, such as nevus of Ota and Hori's nevus, have also successfully been treated with QS ruby (694 nm),[151-154] QS Nd:YAG,[151,152,155] and QS alexandrite (755 nm)[156,157] (Table V).

Despite high efficacy, QSL, even at low fluences is not recommended as first-line therapy for treatment of hyperpigmentation due to its extremely high recurrence rates as well as risk of PIH and speckled hypopigmentation, especially with frequent use.[158,159] It should be utilized in recalcitrant cases that have failed other treatment modalities.

Q-switched picosecond lasers. Q-switched (QS) picosecond lasers generate picosecond-domain pulses, causing pigment fragmentation due to a photomechanical rather than photothermal effect. Due to the decreased thermal damage to surrounding tissue, there is less theoretical risk of PIH.[138,160] QS picosecond lasers have shown efficacy in the treatment of pigmentary disorders, including

Table IV. Laser treatment: Intense pulsed light

Treatment parameters (Author, year)	Study design; N	Treatment	Duration	Condition; Skin type	Outcome(s)	Adverse effects
Fluence: 13.0 J/cm^2 Pulse duration: 3 ms Wavelength: 560 to 800 nm Mode: Pulse in pulse (Single pulse with 90% on-time and 10% off-time) (Park et al, 2016)[142]	Prospective; 25	Pulse-in-pulse mode IPL for 4 weekly sessions followed by 4 bi-weekly sessions	19 weeks	Facial PIH; III-V	92% of patients had over 50% improvement and 88% were satisfied with treatments	none
Fluence: 26 to 33 J/cm^2 Pulse duration: 3 to 4 ms and 4 to 5 ms Wavelength: 570 to 615 nm Mode: double pulse (Wang et al, 2004)[143]	Prospective; 17	Group 1: IPL every 4 weeks for 4 sessions + 4% hydroquinone Group 2: 4% hydroquinone alone	36 weeks	Refractory melasma, mixed type; III-IV	Combination group achieved a 39.8% improvement in RMI compared to 11.6% in the hydroquinone-only group, which was significantly different; % improvement in the combination group decreased to 24.2% at 24 weeks, suggesting recurrence	Erythema, pain during IPL; microcrust
Fluence: 14-18 J/cm^2 (fluence increased by 10% each treatment) (Shakeeb et al, 2018)[144]	Randomized controlled trial; 96	Group 1: TCC nightly for 2 months Group 2: IPL every 2 weeks for 4 treatments Group 3: TCC nightly for 2 months + IPL every 2 weeks for 4 treatments	12 weeks	Melasma, epidermal type; II-V	Combination group (IPL + TCC) was more efficacious in improving pigmentation than either one alone: Group 1 showed 68.8% of participants with efficacious reduction in MASI, Group 2 showed 62.5%, and Group 3 showed 93.8%	--
Fluence: 8.0-9.4 J/cm^2 Pulse duration: 2.5 ms Wavelength: — Mode: double pulse (Chung et al, 2016)[145]	Randomized controlled trial, split-face; 13	Group 1: IPL every 4 weeks for 4 sessions + 2% TXA cream Group 2: IPL every 4 weeks for 4 sessions + vehicle	28 weeks	Melasma	MI and MASI decreased significantly up to 12 weeks after the last IPL treatment on the TXA side, but not the vehicle side	none

Fluence: 13-18 J/cm^2 Pulse duration: 3 and 5 ms, 20-35 ms delay Wavelength: 560, 590 nm Mode: double pulse (Li et al, 2018)[146]	Prospective; 35	IPL every 3-5 weeks for 2-6 treatments	1 year	Postburn PIH; III-IV	IPL significantly decreased hyperpigmentation and repigmentation did not occur 1 year later; 82.9% of participants were satisfied with their treatment outcomes	--
Fluence: 34 J/cm^2 Pulse duration: 3.8 ms, 20 ms delay Wavelength: 590 nm Mode: double pulse (Arias et al, 2001)[147]	Prospective; 20	IPL every 4 weeks for 2 treatments	20 weeks	Café au lait macules, epidermal nevus, epidermal melasma, ephelides; II-IV	100% of café au lait macules, ephelides, and epidermal melasma showed excellent clearance (75-100%); repigmentation was not documented after average follow-up of 10.5 months	Mild to moderate pain, burning sensation

MASI, Melasma area and severity index; *MI*, melanin index; *RMI*, relative melanin index; *TCC*, triple combination cream.

melasma,[160-162] dermal melanocytosis,[163] and epidermal lesions[164,165] (Table VI). QS picosecond lasers are an effective method for treating pigmentary disorders with lower risk of PIH compared to QSLs, but availability and cost may be limiting factors. It should be noted that both QS nanosecond and picosecond lasers have high rates of recurrence.

Nonablative fractionated resurfacing lasers. Fractional resurfacing induces selective thermal damage in the form of microbeams with a diameter less than 400 μm, leading to the formation of microscopic thermal zones which affects collagen fibers and keratinocytes. Nonablative fractional lasers create columns of coagulative damage in the dermis that are below the ablative threshold and thus the stratum corneum stays intact. Recovery is rapid and the most common posttreatment effect is erythema and swelling.[141] Nonablative fractionated laser at 1440 nm, 1550 nm, 1540 nm, and 1927 nm are effective for treating pigmentary disorders, with possible later recurrence than other lasers, however, with high risk of PIH (Table VII). As such, use with darker skin tones is not recommended.[166-178]

Ablative fractionated resurfacing lasers. Ablative fractionated lasers target water as the chromophore and include 10,600 nm CO_2 lasers and 2,940 nm Er:YAG lasers most commonly. Ablative fractionated lasers are generally not used for the treatment of pigmentary disorders, due to their high risk of hyperpigmentation, with 1 study citing PIH in 46% and 42% of patients treated with a single pass of CO_2 laser and Er:YAG, respectively.[179] Thus, ablative lasers are generally not utilized in patients with skin types greater than III and should not be utilized for the treatment of melasma and other pigmentary disorders (Table VIII).[179-183]

CONCLUSION

Photoprotection with daily use of a broad-spectrum tinted sunscreen in addition to other photoprotective behaviors should be recommended to all patients with pigmentary disorders. Given the low risk of adverse effects, topical therapies are first line, followed by oral therapies, which can be extremely effective in the right patient population. Procedural therapies, such as microneedling, peels, and laser treatments can be considered for refractory cases and are often used in combination with other oral or topical treatments, given the higher risks of PIH and recurrence. Treatment plans should be tailored based on patients' skin types, tolerability, prior adverse reactions experienced, and medical history. Further studies as well as novel modalities need to be established for the treatment of pigmentary disorders.

Table V. Laser treatment: Q-switched nanosecond lasers

Treatment parameters (Author, year)	Study design, N	Treatment	Duration	Condition	Outcome(s)	Adverse effects
Fluence: 3.0-3.8 J/cm^2 Spot size: 6-mm Wavelength: 1,064 nm Frequency: 10 Hz Collimated homogenous flat-top beam (Wattanakrai et al, 2010)[148]	Randomized controlled trial, split-face; 22	One half: low-fluence Q-switched (QS) Nd:YAG laser weekly for 5 treatments + topical 2% hydroquinone Other-half: 2% hydroquinone alone	17 weeks	Melasma, mixed; III-V	Laser-treated side achieved 92.5% improvement in relative lightness index versus 19.7% on the hydroquinone-only treated side; 86.4% of participants assessed improvement on laser-treated side as >50% improvement, compared to only 13.6% on control side; melasma recurred in 100% of patients	3 of 22 patients developed mottled hypopigmentation and 8 patients developed confetti type hypopigmentation; rebound hyperpigmentation in 4 patients
Fluence: 2.5-3.4 J/cm^2 Spot size: 6-mm Wavelength: 1,064 nm Frequency: 10 Hz (Zhou et al, 2011)[149]	Prospective, open-label; 50	QS Nd:YAG weekly for 9 treatments	21 weeks	Melasma; III-IV	MI decreased 35.8%, MASI scores decreased 61.3% after therapy; 70% of subjects had >50% decrease in MASI scores; recurrence rate at 3-month follow-up was 64%	Transient nonpruritic wheal, transient purpura
Fluence: 0.8-1.6 J/cm^2 Spot size: 8-mm Wavelength: 1,064 nm Frequency: 10 Hz (Hofbauer et al, 2016)[150]	Prospective, open-label; 16	QS Nd:YAG weekly for 10 treatments	36 weeks	Mild to severe melasma; III-V	Low-fluence QS Nd:YAG treatments resulted in reduction in MASI scores 1 week and 30 days after treatment; 81% of patients had recurrence or worsening of melasma by 3 months	Mild erythema, transient local warmth
Fluence: 3.0-3.4 J/cm^2 Spot size: 6-mm Wavelength: 1,064 nm Frequency: 10 Hz (Polnikorn, 2010)[65]	Prospective; 35	QS Nd:YAG weekly for 10 treatments + 2 monthly treatments + 7% alpha arbutin solution twice a day	6 months	Refractory melasma; --	30% of participants achieved excellent clearance (>81% reduction of melasma) by 6 months and 36.7% achieved good clearance (51-80% reduction); 2 cases had recurrence of melasma	Mild, transient discomfort, erythema, whitening of fine hair, and urticaria; 3 cases of mottling hypopigmentation
Wavelength: 694-nm (QS-ruby); 1,064 nm (QS Nd:YAG) (Belkin et al, 2017)[151]	Retrospective case series; 24	13 of 17 patients with skin type IV were treated with QS ruby laser, 4 were treated with QS Nd:YAG; all	--	Nevus of Ota; IV-VI	Mean number of treatments was 9.3; 70% of subjects achieved >75% clearance	2 participants had PIH

		7 skin type V and VI were treated with QS Nd:YAG			and 86% achieved >50% improvement	
Fluence: 4-5 J/cm^2 Spot size: 5-mm Wavelength: 694 nm Pulse duration: 20 ns (Momosawa et al, 2003)[153]	Prospective, open-label; 19	0.1% tretinoin gel and an ointment (5% hydroquinone + 7% lactic acid) twice a day for 6-8 weeks followed by QS ruby laser every 8 weeks for 3 treatments	30 weeks	Acquired dermal melanocytosis, including nevus of Ota and Hori's nevus; --	78.9% of participants showed "excellent" (≧80% clearance) clearing and 21.1% achieved "good" (50-79% clearance) after 2-3 laser treatments	PIH in 10.5% of participants after first treatment, but was not observed in second or third treatments; irritant dermatitis from topical bleaching treatment
Fluence: 6-7 J/cm^2 Wavelength: 694 nm Pulse duration: 30 ns (Watanabe et al, 2006)[154]	Retrospective analysis; 12	QS ruby laser 1-5 times	--	Dermal melanocytosis	Of 5 patients who received at least 2 laser treatments, 2 showed a good response (40-69% clearance) and 2 showed an excellent response (>70% clearance)	Transient swelling and purpura
Fluence: 2.5-5.0 J/cm^2 Spot size: 7-mm Wavelength: 1,064 nm (Choi et al, 2013)[155]	Retrospective analysis; 19	Low-fluence QS Nd:YAG laser every 2 weeks for 6 to 32 treatments; adjuvant 4% hydroquinone used in 8 subjects	--	Nevus of Ota; IV	Mean number of treatments was 17.1; 18 of 19 participants achieved near total improvement; adjuvant hydroquinone treatment had no effect on treatment efficacy	PIH in 1 patient, erythema, pain
QS Alexandrite: Fluence: 5.5-8.0 J/cm^2 Spot size: 4-mm Wavelength: 755 nm *QS Nd:YAG:* Fluence: 6.0-12.0 J/cm^2 Spot size: 2-mm Wavelength: 1064 nm (Choi et al, 2015)[156]	Retrospective analysis; 76	Each laser every 1-3 months	--	Nevus of Ota; III-IV	19 of 31 patients (61%) in the QS alexandrite group and 24 of 45 patients (53%) in the QS Nd:YAG attained pigment clearance of more than 50%. QS alexandrite was more likely to achieve a better response compared with QS Nd:YAG	QS alexandrite: 1 patient developed a hypertrophic scar; QS Nd:YAG: 2 patients with hypopigmentation, 1 with atrophic scar and 1 with nonspecific scar
Fluence: 3.8-4.8 J/cm^2 Spot size: 3-mm Wavelength: 755 nm Pulse duration: 60 ns (Liu et al, 2011)[157]	Retrospective analysis; 806	Laser treatment every 3 to 6 months for at least 3 treatments	--	Nevus of Ota; --	757 of 806 patients (93.9%) had complete clearance after 3 to 14 treatments	5 out of 590 patients had recurrence after achieving complete clearance with mean time of recurrence at 56 months

MASI, Melasma area and severity index; *MI*, melanin index; *PIH*, postinflammatory hyperpigmentation.

Table VI. Laser treatment: Q-switched picosecond lasers

Treatment parameters (Author, year)	Study design; N	Treatment	Duration	Condition; Skin type	Outcome(s)	Adverse effects
Fluence: 1.3-1.5 J/cm^2 Spot size: 6 mm Wavelength: 1,064 nm Frequency: 4 Hz Pulse duration: 450 ps (Chalermchai et al, 2018)[161]	Randomized controlled trial; 30	One half: fractional picosecond 1,064 laser every 4 weeks for 3 treatments + 4% hydroquinone cream daily Other half: 4% hydroquinone daily	12 weeks	Melasma; III-IV	Average MASI scores at 12-week visits were significantly reduced in the combination side compared to the hydroquinone-only side; however, no difference was seen in the melanin index, participant satisfaction score, and DLQI score	Transient mild erythema, mild skin desquamation
Fluence: 0.2-1.5 J/cm^2 Spot size: 7-10 mm Wavelength: 1,064 nm Frequency: 5 or 10 Hz Pulse duration: 750 ps Fluence: 0.1-0.55 J/cm^2 Spot size: 5 mm Wavelength: 595 nm Frequency: 2 or 5 Hz (Choi et al, 2017)[162]	Randomized controlled trial; 39	One half: picosecond laser at 1064-nm followed by 595-nm weekly x 5 weeks + 2% hydroquinone daily x 7 weeks Other half: 2% hydroquinone daily x 7 weeks	18 weeks	Moderate to severe melasma; III-IV	Picosecond laser + 2% hydroquinone had superior efficacy to 2% hydroquinone alone: 76.92% in combination side achieved >50% improvement in RLI vs 2.56% on 2% hydroquinone alone; no significant difference in recurrence rate of test group (76.9%) and control group (69.23%) at 12-week follow-up	5% of subjects developed mild dermatitis
755 nm picosecond: Fluence: 0.88-1.18 J/cm^2 Spot size: 4.4-5.1 mm Wavelength: 755 nm Pulse duration: 650 ps *1064 nm QS Nd:YAG:* Fluence: 2.0-3.5 J/cm^2 Spot size: 4-8 mm Wavelength: 1,064 nm (Lee et al, 2018)[160]	Prospective, split-face, 12	One side: 755 nm picosecond monthly for 4 treatments + TXA 250 mg TID x 1 week after each treatment Other side: 1064 nm QS Nd:YAG monthly for 4 treatments + TXA 250 mg TID x 1 week after each treatment	4 months	Melasma; III-IV	Higher pigmentation clearance was achieved at the 755 nm picosecond laser side after the second treatment; at 3 months follow-up, greater clearance was observed at the 755 nm picosecond laser side compared to the 1064 nm QS Nd:YAG side, by visual analog scale evaluated by 2 independent physicians; no relapse was seen on either side of the face at 3-month follow-up	Temporary erythema

Fluence: 2.73-3.98 J/cm^2 Spot size: 2.9-2.4 mm Wavelength: 755-nm Pulse duration: 650 ps (Hu et al, 2020)[163]	Retrospective analysis, 36	Picosecond 755-nm alexandrite laser every 3 to 12 months for 1 to 4 treatments	--	Nevus of Ota, bilateral nevus of Ota-like macules; III-IV	88.9% of subjects had moderate to marked (25%-74%) improvement following 1 to 4 sessions	1 patient developed hypopigmentation; 2 patients had transient hyperpigmentation
QS KTP 532-nm: Fluence: 1.4-1.7 J/cm^2 Spot size: 3 mm Wavelength: 532 nm Frequency: 1 Hz *KTP 532 nm picosecond laser:* Fluence: 0.3-0.9 J/cm^2 Spot size: 3 mm Wavelength: 532 nm Frequency: 1 Hz (Vachiramon et al, 2018)[164]	Prospective, 28	Group 1: single treatment of QS KTP 532 nm nanosecond laser Group 2: single treatment of KTP 532 nm picosecond laser	12 weeks	Solar lentigines, III-IV	Both lasers showed significant improvement in mean luminance score from baseline; no significant difference was seen between the 2 lasers assessed by physician or patients; however, patient satisfaction score was higher with the picosecond laser	2 lesions from each group developed hyperpigmentation at 12 week follow-up
Picosecond 755 nm: Fluence: 5.56-6.37 J/cm^2 Spot size: 2 mm *QS 755 nm:* Fluence: 6-8 J/cm^2 Spot size: 3 mm *QS 532 nm:* Fluence: 1.5-2.5 J/cm^2 Spot size: 5-6 mm (Cen et al, 2020)[165]	Prospective, split-lesion, 41	Group 1: Picosecond 755 nm every 3 months x 3 treatments Group 2: QS 755 nm every 3 months x 3 treatments Group 3: QS 532 nm every 3 months x 3 treatments	1 year	Café au lait macules	There was no significant difference in visual assessment 3 months after treatment between the laser types; 5 of 19 patients showed lesion recurrence; 46.67% of patients were satisfied with the outcome	Acneiform miliaris, hypopigmentation, hyperpigmentation; picosecond 755-nm laser caused the fewest adverse effects

PS, Picosecond; *QS*, Q-switched; *RLI*, relative lightness index; *TXA*, tranexamic acid.

Table VII. Laser treatment: Nonablative fractionated resurfacing lasers

Treatment parameters (Author, year)	Study design; N	Treatment	Duration	Condition; skin type	Outcome(s)	Adverse effects
Fluence: 3.5 then 4 J/cm^2 Spot size: 1 cm Penetration depth: 300 μm Wavelength: 1440 nm (Kouba et al, 2008)[166]	Case report; 1	Fractionated 1440-nm Nd:YAG for 2 treatments, 4 weeks apart	3 months	Nevus of Ota, not responsive to QS Nd:YAG; III	Nevus of Ota completely resolved within 6 weeks of the second treatment; 3 months later, there was no recurrence of PIH	None
Fluence: 6 to 12 mJ/ MTZ 2,000 to 3,500 MTZ/cm^2 Wavelength: 1535 nm, then 1550 nm (Rokhsar et al, 2005)[167]	Prospective, open-label; 10	Fractionated laser every 1-2 weeks for 4-6 treatments	3 months	Melasma, refractory; III-V	60% of patients achieved 75%-100% clearing and 30% had less than 25% improvement, according to the evaluator assessment; 60% of patients were very satisfied	1 patient with PIH; transient sunburn-like erythema, transient abrasions
Fluence: 15 mJ/MTZ 125 MTZ/pass, 8 passes Wavelength: 1550 nm (Lee et al, 2009)[168]	Prospective, open-label; 25	Fractionated laser every 4 weeks for 4 treatments	36 weeks	Melasma; III-IV	Investigators observed clinical improvement in 60% and patients in 44% at 4 weeks after treatment, but decreased to 52% and 35%, respectively, at 24 weeks after treatment	Transient swelling, long-lasting erythema; 3 patients had hyperpigmentation
Fluence: 10 mJ/MTZ 8 passes, estimated 2000 to 2500 MTZ/cm^2 (Kroon et al, 2011)[169]	Randomized controlled trial; 22	Group 1: nonablative 1550 nm fractional laser every 2 weeks for 4 treatments Group 2: TCC (5% hydroquinone, 0.05% tretinoin, 0.1% triamcinolone) nightly for 8 weeks	6 months	Moderate to severe melasma; II-V	Physician global assessment found a significant improvement in both groups at 3 weeks, however, was not significantly different between the groups; treatment satisfaction was significantly higher in the laser group at 3 weeks; there was recurrence of melasma in 50% of subjects in both groups after 6 months	Laser group: sunburn-like erythema, burning sensation, moderate to severe facial edema Topical treatment group: erythema, burning sensation, scaling
Fluence: 15 mJ/MTZ 8 passes, estimated 2000 to 2500 MTZ/cm^2	Randomized controlled trial; 29	One side: fractional laser for 4-5 treatments + TCC (5% hydroquinone, 0.05%	6 months	Melasma; II-V	Patient global assessment and satisfaction were significantly lower on the	Laser group: sunburn-like erythema, burning

Wavelength: 1550 nm (Wind et al, 2010)[170]		tretinoin, 0.1% triamcinolone) twice weekly Other side: TCC daily for 15 weeks + TCC twice weekly thereafter			laser side; there was worsening of hyperpigmentation on the laser side; on TCC side, no significant changes were observed; at 6 months follow-up, significantly higher number of patients preferred TCC	sensation, 31% of patients with PIH
Fluence: 15 mJ/MTZ 8 passes Wavelength: 1550 nm (Kroon et al, 2012)[171]	Randomized controlled trial; 14	Group 1: fractional laser every 3 weeks for 5 treatments + TCC (5% hydroquinone, 0.05% tretinoin, 0.1% triamcinolone) nightly during 2nd and 3rd week after each laser treatment Group 2: same regimen of intermittent TCC nightly	6 months	EDP and PIH; II-V	Reflectance spectroscopy, melanin index, number of melanocytes and dermal melanin did not significantly differ between the groups; no improvement was observed	23% of patients had PIH after 2-3 laser treatments
Energy: 320 MTZ/cm^2 Pulse duration: 15 ms Wavelength: 1540 nm (Barysch et al, 2011)[172]	Prospective, split-face; 12	One side: fractional laser every 3-4 weeks for 3 treatments Other side: no treatment	28 weeks	Melasma; II-IV	7 patients had a slight but significant reduction in pigment by weeks 26-28; 3 had no improvement and another 2 of patients had worsening of pigment due to PIH	17% of patients had PIH at 26- to 28-week follow-up
Fluence: 15 mJ/MTZ 3,600-4,000 MTZ/cm^2 Pulse duration: 15 ms 320 microbeams/cm^2 Microbeam diameter: 100 μm Wavelength: 1540 nm (Tourlaki et al, 2014)[173]	Prospective, open-label; 76	TCC (4% hydroquinone, 0.03% retinoic acid, 0.1% hydrocortisone butyrate) daily x 3 months followed by fraction 1,540 nm laser every 3 weeks for 4 treatments	6 months	Recalcitrant melasma; II-IV	At 1 month, 61% of patients had >75% clearing and 21% had 51% to 75% clearing. However, at 6 months, only 21% of patients maintained a marked improvement and no improvement in 43.4%	Transient edema and erythema
Fluence: 10-20 mJ 252 -784 MTZ/cm^2 6-8 passes Wavelength: 1927 nm (Polder et al, 2012)[174]	Prospective, open-label; 14	Thulium fiber laser treatments every 4 weeks for 3-4 treatments + 4% hydroquinone	6 months	Melasma; II-IV	51% reduction in MASI score was observed at 1 month post 3-4 laser treatments; at 3 and 6 month follow ups, reduction in MASI	Moderate erythema and mild edema; no PIH or scarring observed

Continued

Table VII. Cont'd

Treatment parameters (Author, year)	Study design; N	Treatment	Duration	Condition; skin type	Outcome(s)	Adverse effects
					scores dropped to 33% and 34%, respectively	
Fluence: 10 mJ 10 passes Wavelength: 1927 nm (Lee et al, 2013)[175]	Prospective, split-face; 25	One side: Thulium fiber laser treatment every 3 weeks for 3 treatments Other side: no treatment	6 months	Melasma; III-IV	33% reduction in MASI score was observed at 2-month follow-up; at 6-month follow-up, reduction in MASI score dropped to 28%	Transient erythema, edema; prolonged erythema in 1 patient
Fluence: 5 mJ Spot size: 140 μm Depth: 170 μm Wavelength: 1,927 nm (Bae et al, 2019)[176]	Retrospective analysis; 61	Low-energy fractional 1,927 nm laser treatments for at least 2 treatments	--	PIH; IV-VI	Mean percent improvement was 43.2% after treatment; no significant difference in treatment response, between skin type groups were observed	No side effects reported; no PIH reported
Fluence: 10-20 mJ 3-5 passes wavelength: 1927 nm (Kim et al, 2021)[177]	Retrospective analysis; 9	Thulium fiber laser treatments every month for 3-7 treatments	--	Riehl's melanosis; III-IV	Average DPASI score decreased from 9.55 to 5.25; 6 patients had 51%-75% improvement, 1 patient had 76%-100% improvement, and 2 patients had 26%-50% improvement	Mild transient erythema in 3 patients
Fluence: 20 mJ 4 passes Wavelength: 1,927 nm (Alharbi et al, 2021)[178]	Prospective; 8	Thulium fiber laser treatment every 6 weeks for 1-4 treatments + oral steroids 0.5 mg/kg after each treatment + clobetasol cream for 7 days + hydroquinone 4% cream twice a day for 6 weeks	--	PIH; IV	3 patients had an excellent response, 4 patients had a satisfactory response, and 1 patient had an unsatisfactory response	No paradoxical PIH reported

DPASI, Dermal pigmentation area and severity index; *EDP*, erythema dyschromicum perstans; *MTZ*, microthermal treatment zone; *PIH*, postinflammatory hyperpigmentation; *TCC*, triple combination cream.

Table VIII. Laser treatment: ablative fractionated resurfacing lasers

Treatment parameters (author, year)	Study design; N	Treatment	Duration	Condition; skin type	Outcome(s)	Adverse effects
532 nm QS Nd:YAG: Fluence: 1.4-1.7 J/cm^2 Spot size: 3 mm Frequency: 2 Hz Fractional CO_2 laser: 300-density tip Energy: 55-70 mJ, 200 spots/cm^2, 2 passes (Vachiramon et al, 2016)[180]	Prospective, intra-individual; 25	One lesion: single session of 532 nm QS Nd:YAG laser Second lesion: single session of fractional CO_2 laser	12 weeks	Solar lentigines; III-IV	532 nm QS Nd:YAG showed significant improvement of pigmentation over fractional CO_2 laser at follow-up at weeks 6 and 12; 80% of patients treated with 532 nm QS Nd:YAG had excellent results compared to 8% in fractional CO_2 laser	24% of lesions treated with QS Nd:YAG and 28% of lesions treated with fraction CO_2 developed PIH at 12-week follow-up; 2 patients with skin type IV developed hypopigmentation from both lasers
694 nm QS ruby laser Fluence: 5 J/cm^2 Spot size: 3 mm Frequency: 2 Hz 10,600 nm CO_2 fractional laser: Energy: 15 mJ Pulse duration: 2 ms Spot density: 250 mm points/cm^2 (Schoenewolf et al, 2015)[181]	Randomized controlled trial, intra-individual; 11	Group 1: QS ruby laser every 4 weeks for 3 treatments Group 2: CO_2 laser every 4 weeks for 3 treatments	24 weeks	Solar lentigines;	QS ruby laser was significantly more efficacious than CO_2 fractional laser for removing solar lentigines on the hands by weeks 16 and 24	QS ruby: spotted erythema and slight edema CO_2 laser: erythematous area
Fluence: 150 mJ Frequency: 50 Hz Pulse duration: 350 ms Power: 7.5 W (Trelles et al, 2010)[182]	Prospective; 30	Group 1: TCC Group 2: fractional CO_2 laser Group 3: TCC + fractional CO_2 laser	12 months	Melasma; II-IV	MASI scores in combination group was significantly improved compared to either treatment alone at 2-, 6-, and 12-month follow-up	Mild stinging/burning sensation during laser treatment
Fluence: 0.4 J/cm^2 (160 mJ) Spot size: 7 mm Pulse duration: 300 μs Repetition rate: 10 Hz 2 passes (Wanitphakdeedecha et al, 2009)[183]	Prospective; 17	2 treatments of VSP Erbium: YAG laser resurfacing monthly	4 months	Melasma, epidermal type; IV-V	Significant improvement in VAS from baseline was observed at 1-, 2-, and 4-month follow-up; however, there was significant improvement in MASI and MI scores at 2-month follow-up, but not at the 1- or 4-month, suggesting recurrence of melasma	17.6% of subjects had temporary PIH; 11.8% had acneiform eruption

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Table VIII. Cont'd

Treatment parameters (author, year)	Study design; N	Treatment	Duration	Condition; skin type	Outcome(s)	Adverse effects
CO_2 laser: Fluence: 300 mJ Spot size: 8 mm Power: 60W Single pass Er:YAG laser: Fluence: 22.5 J/cm^2 (90 μm ablation and 50-μm coagulation) Dual mode Single pass (Tanzi et al, 2003)[179]	Retrospective analysis; 100	Group 1: single-pass CO_2 laser Group 2: multiple-pass long-pulsed Er:YAG laser	--	Facial photodamage and atrophic scars	Postoperative erythema was observed in all patients, lasting 4.5 weeks after single-pass CO_2 laser and 3.6 weeks after long-pulsed Er:YAG laser; hyperpigmentation was seen in 46% of subjects treated with CO_2 and 42% of subjects treated with Er:YAG	Mild acne, transient milia, dermatitis, superficial bacterial infection in both laser type groups

MASI, Melasma area and severity index; *MI*, myocardial infaction; *PIH*, postinflammatory hyperpigmentation; *TCC*, triple combination cream; *VSP*, variable square pulse; *VAS*, visual analog scale.

Conflicts of interest

Dr. Lim is an investigator for Incyte, L'Oréal, Pfizer, and the Patient-Centered Outcomes Research Institute; has served as a consultant for Pierre Fabre, ISDIN, Ferndale Healthcare, La Roche-Posay, and Beiersdorf; and has participated as a speaker in general educational sessions for La Roche-Posay and Cantabria Labs. Dr Mohammad is an investigator for Unigen, AVITA Medical, Arcutis Biotherapeutics, Incyte, National Institute of Allergy and Infectious Diseases, and Estée Lauder. Drs Ko, Wang and Ozog have no conflicts of interest to declare.

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Journal of the American Academy of Dermatology
Volume 89, Issue 1, July 2023, Page 195

DOI: https://doi.org/10.1016/j.jaad.2023.04.004

CORRECTIONS

Correction to: Weinkle A, Carrington AE, Kang A, Armstrong AW, Eisen DB. Aesthetic outcome of simple cuticular suture distance from the wound edge on the closure of linear wounds on the head and neck: A randomized evaluator blinded split-wound comparative effect trial. *J Am Acad Dermatol.* 2023;86(4):863-867.

In the aforementioned article, the second author's surname was spelled incorrectly. The correct spelling of the author's name is: Alexis E. Carrington. This has been corrected online.

Ko D, Wang RF, Ozog D, Lim HW, Mohammad TF. Disorders of hyperpigmentation. Part II. Review of management and treatment options for hyperpigmentation. *J Am Acad Dermatol.* 2023;88(2):291-320.

The term "safe and effective" was used in error in several areas of the article. The corrected text and corresponding page numbers are listed below:

In Table II (Natural topical treatments) on page 295, in the first row (Azelaic acid) under the Conclusions heading, the first bullet point should be corrected as follows:

- Well-tolerated with only minor local burning or itching

On page 294, 10 lines under the heading Cysteamine, the sentence should be corrected as follows:

A study of 40 women with facial melasma compared topical 5% cysteamine cream to 4% hydroquinone cream and found that cysteamine was well tolerated but inferior to hydroquinone in decreasing pigmentation.

At the bottom of page 294, under the heading Oral agents, the first bullet point under Key points should be corrected as follows:

Low-dose oral TXA is a well-tolerated treatment option for hyperpigmentation as long as patients have no risk factors for thromboembolic events.

On page 298, under the Chemical peels heading, the first sentence should be corrected as follows:

Many studies have shown superficial chemical peels to be a well-tolerated treatment for various pigmentary disorders.

The article has been corrected online.

Concilla A, Rundle CW, Militello MW. A comparison of acne products advertised on Instagram to American Academy of Dermatology evidence-based guidelines (abstract). *J Am Acad Dermatol.* 2021;87(3 suppl):AB8.

In the abstract above, the list of authors is incomplete. The correct author list is: Anthony Concilla, BS, Chandler W. Rundle, MD, Michelle Militello, MS, Kayd J. Pulsipher, BS, Taylor Harp, BA, Mindy Szeto, MS, Colby L. Presley, DO, Larissa Rodriguez-Homs, MD, Olivia Jew, MD, MBA, and Robert P. Dellavalle, MD, PhD, MSPH.

The author list has been corrected online.

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Journal of the American Academy of Dermatology
Volume 88, Issue 4, April 2023, Page 963

DOI: https://doi.org/10.1016/j.jaad.2023.01.026

CORRECTION

Wang RF, Ko D, Friedman BJ, Lim HW, Mohammad TF. Disorders of hyperpigmentation. Part I. Pathogenesis and clinical features of common pigmentary disorders. *J Am Acad Dermatol.* 2023;88(2):271-288.

Ko D, Wang RF, Ozog D, Lim HW, Mohammad TF. Disorders of hyperpigmentation. Part II. Review of management and treatment options for hyperpigmentation. *J Am Acad Dermatol.* 2023;88(2):291-320.

In the CME articles above, the disclosures were incorrectly listed in the gray box on the title page. They have been corrected online.