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The Evolution of Melasma Therapy: Targeting Melanosomes Using Low-Fluence Q-Switched Neodymium-Doped Yttrium Aluminium Garnet Lasers

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Melasma is an acquired disorder of pigmentation that commonly affects women with phototypes III-V, and it has a negative impact on the quality of life in affected individuals. It presents clinically as symmetric tan or brown patches on the face, most often involving the forehead, cheeks, perioral region, and periorbital region. On histologic examination, there is increased melanin in the epidermis and/or an increased number of melanosomes in the dermis, with a normal number of highly melanized and dendritic melanocytes. The mainstay of treatment is the use of sunscreen along with topical medications that suppress melanogenesis. Clearance is usually incomplete and recurrences or exacerbations are frequent, probably because of the poor efficacy in clearing dermal melanosomes. Treatment with high-energy pigment-specific lasers, ablative resurfacing lasers, and fractional lasers results in an unacceptably high rate of postinflammatory hyper- and hypopigmentation and rebound melasma. Recently, promising results have been achieved with low-fluence Q-switched neodymium-doped yttrium aluminium garnet laser treatment, which can selectively target dermal melanosomes without producing inflammation or epidermal damage, in all skin phototypes. This article reviews the current treatment modalities for melasma, the rationale for using and the clinical results of combination therapy with low-fluence Q-switched neodymium-doped yttrium aluminium garnet lasers.
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Melasma is a common acquired disorder of hyperpigmentation in the world population that most often affects women with Fitzpatrick phototypes III-V.[1-4] It is characterized by symmetric light to dark brown, sometimes grayish, macules or patches on the face, especially the forehead, malar, chin and lip regions. Melasma is sometimes referred to as chloasma, or the mask of pregnancy. Various clinical patterns of melasma have been described, including a centrofacial, malar, and mandibular pattern.[5] Melasma is further classified based on the location of the pigment as epidermal, dermal, or mixed type, where the epidermis and dermis are involved. Historically, Wood lamp examination was used to differentiate between these types. Lesions that enhanced with the Wood lamp were thought to have increased epidermal pigment, and those that did not enhance were thought to have increased dermal pigment. Individuals with enhancing and nonenhancing lesions were deemed to have the mixed type of melasma.[2,6] More recent studies demonstrated that Wood lamp examination may not accurately detect dermal melanin in persons with melasma.[5,7] Histologic analysis reveals that melanin deposition occurs in the basal and suprabasal layers in the epidermal form; in the dermal form, there are superficial and deep perivascular melanosomes. The melanocyte number is not increased, but electron microscopy reveals that they are larger, highly dendritic, and more densely melanized stage IV melanocytes. The relatively common finding of dermal melanin and melanophages in melasma may contribute to the difficulty in treating melasma, even in those patients clinically deemed to have epidermal melasma.[5,7]

Various treatment options have been used for melasma, including topical skin care regimens used to suppress melanogenesis, chemical peels, and multiple laser and light source

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therapies; but the results of most treatments are generally disappointing with incomplete clearances, frequent remissions, and rebound hyperpigmentation. One of the main obstacles to developing an effective therapy has been our limited ability to destroy dermal melanosomes without producing inflammation that would in turn stimulate melanogenesis and exacerbate the melasma.[1,8] This report reviews the current treatment modalities used for melasma and describes the author's experience using a new noninvasive combination treatment approach, using a low-fluence Q-switched (QS) neodymium-doped yttrium aluminium garnet (Nd: YAG) laser in conjunction with microdermabrasion and a hydroquinone-based skin care regimen that provides rapid clearance of melasma and remissions lasting as long as 12 months.

Epidemiology

The incidence of melasma varies among different populations. It is most prevalent in Southeast Asia, where the prevalence is reported to be as high as 40% in females and 20% in males.[9] In Asia, melasma accounts for >50% of all esthetic consultations.[10] An estimated 50%-70% of pregnant women in the United States develop melasma.[2,5] Melasma occurs in up to 50%-80% of Latina women.[11] A recent survey of females from 9 countries found that 41% of females developed melasma after pregnancy but before menopause, and only 8% had spontaneous remission of their melasma.[12] Patients with melasma report that even clinically mild melasma interferes with their leisure time activities and their emotional and psychological well being.[13-16]

Pathogenesis

The etiology of melasma remains unknown, but multiple factors are known to play a role in its pathogenesis.[1] Various studies demonstrate a high incidence of melasma in affected family members, suggesting a genetic predisposition.[4,12,17,18] Other risk factors include Fitzpatrick phototype III and IV skin, ultraviolet (UV) light exposure, pregnancy, and exogenous hormones, whether in the form of oral contraceptives or hormone replacement therapy. The exact link between melasma and hormones remains unclear.[19] Several studies have documented the onset of melasma with oral contraceptive use; in such cases, patients are advised to stop taking the oral contraceptive pills when possible.[12] Less commonly associated risk factors include thyroid disorders, phototoxic medications, and cosmetics.[1,2]

Melasma is often initiated or exacerbated by UV light exposure.[1,2] UV exposure stimulates melanogenesis and melanocyte proliferation and migration. It also induces the production of multiple cytokines, including α–melanocyte-stimulating hormone, and adrenocorticotropic hormone from keratinocytes, which further increase melanogenesis and melanocyte proliferation.[20]

In recent studies, increased expression of stem cell factor was found in lesional skin form melasma patients. Stem cell factor increases melanocyte size, number, and dendricity when injected into human skin explants, and patients receiving recombinant stem cell factor injections often develop hyperpigmentation at the injection sites.[21,22] Another study showed that affected skin had an increase in keratinocyte staining for nerve growth factor receptor, but the implications of these results are unclear. There may also be a vascular component in the etiology of melasma. Keratinocyte expression of vascular endothelial growth factor is greater in involved skin compared with nonlesional skin in melasma patients.[23] Clinically, there is often increased vascularity in the affected skin of melasma patients.

Treatment Options

The treatment goals in melasma are the suppression of melanogenesis and the removal of excess melanin already present in the epidermis and dermis. The first goal can be accomplished by a combination of sun-protective measures, including daily use of sunscreen, and the use of topical preparations known to suppress melanogenesis. Epidermal pigment can often be removed by various methods of skin exfoliation, as long as melanin production is simultaneously suppressed. The greater challenge and perhaps the most important obstacle to clearing melasma is the removal of dermal melanin. Various laser and light treatments have been investigated for this purpose with mixed results. Therapies used for melasma include topical medications, sun protection, avoidance of trigger factors, chemical peels, and laser and light source procedures.

Topical Preparations and Chemical Peels

The most important component of melasma treatment is the regular use of a broad spectrum sunscreen to prevent induction of melanogenesis.[24-26] Sunscreen is helpful in preventing melasma recurrences and exacerbations and is a useful and necessary adjuvant for other therapies. Most topical treatments are aimed at interfering with melanin formation. Tyrosinase is the rate limiting enzyme in the process of melanin production, and many of the molecules used in melasma treatment are tyrosinase inhibitors.[2] These include hydroquinone, mequinol, azelaic acid, arbutin, licorice extract, resveratrol, and N-acetyl glucosamine. Kojic acid and ascorbic acid are also used in the treatment of melasma and inhibit melanogenesis by interacting with copper, which acts at the enzyme's active site.

Of these agents, the best studied and most effective is hydroquinone.[2] Hydroquinone has been in use for more than 50 years in the United States and is available in a 2% concentration over-the-counter and in a 4% concentration by prescription. Although there has been some controversy generated in recent years about the safety of hydroquinone, recent reviews concluded that there is no evidence to support the concern for an increased risk of malignancy, and the risk of exogenous ochronosis using 4% hydroquinone is minimal.[27,28] Topical retinoids are widely used alone in the treat-

ment of melasma and in combination with hydroquinone. Retinoids can decrease skin pigmentation via several presumed mechanisms of action, including increasing epidermal cell turnover, inhibition of melanosome transfer, and enhancing the penetration of other topical agents.[29] Retinoids also inhibit tyrosinase transcription and interrupt melanin synthesis. When used as monotherapy, improvement in melasma is not seen until 24 weeks after initiation of therapy.[30] Topical retinoids commonly cause skin irritation and inflammation, which often results in worsening of melasma.

Hydroquinone has been used for the treatment of melasma in combination with several ingredients, including retinoids, corticosteroids, and glycolic acid. The original triple combination of hydroquinone 5%, tretinoin 0.1%, and dexamethasone 0.1% was first described by Kligman and Willis[31] in 1975. More recently, several studies[14,32,33] have been performed with a Food and Drug Administration-approved triple-combination formulation consisting of hydroquinone 4%, tretinoin 0.05%, and fluocinolone acetonide 0.01%. Clinical studies show improved outcomes in melasma patients with triple-combination therapy compared with 4% hydroquinone alone.

Chemical peels, most notably glycolic acid, are the most effective peeling agent for melasma, but must be used cautiously because of the risk of inducing hyperpigmentation as a result of excessive skin irritation.[34,35] Therefore, peels are best used in conjunction with topical pigment suppressing preparations. Salicylic acid peels have a high risk of inducing postinflammatory hyperpigmentation when used to treat melasma and are, therefore, of limited benefit.[36,37]

Good initial clearance of melasma is possible with various combinations of topical therapies and/or chemical peeling, but the improvement is usually temporary and recurrences are inevitable.

Laser and Light Treatment

QS Lasers

Many lasers and light therapies have been used for melasma, including QS lasers, ablative carbon dioxide and erbium: YAG lasers, as well as nonablative and ablative fractional lasers. Melanosomes have strong absorption throughout the visible and near-infrared regions of the electromagnetic spectrum and thermal relaxation times in the range of 50-500 nanoseconds. Nanosecond-domain QS lasers target melanosomes without damaging surrounding tissue structures based on their selective absorption by melanin and delivery of pulse energy in a period shorter than the thermal relaxation time, or cooling time of the melanosome.[38-40] The QS lasers induce high local temperature gradients between the melanosome and its surrounding structures, causing the melanosome to fracture. High-pressure acoustic waves from this interaction lead to melanocyte or phagocyte cell death. The QS lasers safely and effectively treat a variety of pigmented skin lesions, but when used to treat melasma, they cause a high incidence of hyperpigmentation, hypopigmentation, and rebound melasma.[41-44]

In a study of 8 subjects with refractory melasma or postinflammatory hyperpigmentation treated with a QS ruby laser (694 nm, 40 ns) at fluences up to 7.5 J/cm^2, either no improvement or worsening of pigmentation was observed.[43] Histologic examination immediately after laser treatment revealed an increase in extracellular melanin, suggesting that the melanocytes and/or melanosomes ruptured, but several months after laser treatment, the number of melanosomes increased in number. In another study, split-face treatment of melasma patients with QS ruby and Nd: YAG lasers resulted in worsening of melasma and postinflammatory hyperpigmentation.[45]

Intense-Pulsed Light

Intense-pulsed light (IPL) has also been used to treat melasma. IPL is a noncoherent light source with an emission spectrum ranging from 500 to 1200 nm and millisecond pulse durations. It is an effective modality for various vascular lesions and epidermal-pigmented lesions. However, with millisecond pulse durations, it is not possible to target dermal melanosomes, which have thermal relaxation times in the nanosecond range. Consequently, IPL treatment will produce transient improvement in epidermal, but not dermal, melasma. Treatment will often result in crusting of the pigmented lesions, and the resultant epidermal disruption may cause postinflammatory hyperpigmentation.[46,47]

Ablative Resurfacing Lasers

Ablative resurfacing lasers are used to precisely vaporize away thin layers of skin on the order of 10-100 μm per pass, while leaving behind varying zones of coagulation, depending on the laser wavelength and pulse duration. Resurfacing lasers are used to treat sun-damaged or scarred skin and produce open exudative wounds that require 1 to 2 weeks for reepithelialization. The carbon dioxide 10,600 nm and erbium: YAG (2940 nm) lasers target water as their chromophore. The erbium: YAG wavelength is more strongly absorbed by water and, therefore, produces predominantly ablation with much less coagulation than resurfacing carbon dioxide lasers. Resurfacing lasers were investigated for melasma treatment either alone or in combination with QS lasers with the intention of physically removing the involved portions of skin, and with the addition of QS lasers to selectively target dermal melanosomes. An erbium: YAG laser was used to treat 10 patients with refractory melasma and phototype II-V skin, and it produced some transient improvement in melasma.[48] Despite the use of postoperative oral steroids for 5 days, all subjects developed postinflammatory hyperpigmentation within 3 to 6 weeks of laser treatment. Disappointing results were also obtained when QS lasers were combined with ablative carbon dioxide lasers in the same treatment. One split-face study examined the benefit of carbon dioxide laser alone versus a combination of carbon dioxide laser and QS alexandrite laser,[49] and another split-face study evaluated the QS alexandrite laser alone versus the combination of both lasers.[50] In both studies, there was a

high incidence of postinflammatory hyperpigmentation and hypopigmentation.[49,50]

Fractional Resurfacing

Fractional laser technology was developed in an attempt to resurface skin without producing full thickness wounds, to eliminate long recovery times and minimize the risk of scarring and pigmentary alteration sometimes seen with aggressive ablative resurfacing treatments.[51-53] The nonablative fractional lasers use midinfrared wavelengths (1320 nm to 1550 nm) to target water and produce columnar microzones of coagulated tissue on the order of 150 μm to 250 μm in diameter, while leaving surrounding zones of untreated tissue. This enables healing form both the follicular units as well as from the wound perimeters. The damaged zones of tissue are eliminated through the skin surface. The epidermal barrier remains intact after these procedures, and treated patients experience 3 to 4 days of erythema and edema, and require no wound care. A series of 4 to 6 nonablative fractional laser treatments improve photodamage-related dyschromia, skin texture, and scars.

Ablative fractional resurfacing lasers were subsequently developed using carbon dioxide, erbium: YAG, and yttrium scandium gallium garnet (2790 nm) wavelengths to ablate rather than coagulate microzones of tissue. The ablated holes collapse and close within 6-12 hours after treatment; there is usually pinpoint bleeding and transudate for 12 to 24 hours and healing takes 5 to 7 days. Patients must apply occlusive ointments for several days to speed reepithelialization, but clinical improvement is seen in fewer treatment sessions compared with the nonablative fractional treatments.

Early studies of nonablative fractional lasers for the treatment of melasma showed promising results.[54-56] In one study, 6 out of 10 patients treated 4 to 6 times with a 1550 fiber laser had 75%-100% clearance of their melasma, and postinflammatory hyperpigmentation developed in 1 subject.[54] Subsequent studies with longer-term follow-up demonstrated a high incidence of melasma recurrence and exacerbation.[57-60] The incidence of rebound melasma and postinflammatory hyperpigmentation is even greater when ablative fractional lasers are used in patients with melasma (A. Kauvar, personal observation).

QS Nd: YAG Lasers

Recently, there has been great interest in using QS Nd: YAG lasers for the treatment of melasma. The rationale for this treatment is that the 1064-nm wavelength can be safely used in all skin phototypes; because of its relatively weaker absorption by melanin, it selectively damages melanosomes without producing epidermal damage and it penetrates to the deep dermis. In a study of 35 subjects treated with a 5 ns to 7 ns QS Nd: YAG laser in conjunction with topical arbutin, 67% of subjects had >50% reduction in melasma; but there was an 8.6% incidence of guttate hypopigmentation and recurrence in 5.7% at 6 month follow-up.[61] Each subject received 10 weekly laser treatments, each with 20 passes of the laser at 3.0-3.4 J/cm^2. The treatment was painful and resulted in erythema and edema and whitening of the hairs in the treatment area. The subjects received a high-cumulative dose of laser treatment with this protocol. In another study of 23 Korean subjects, clearance of melasma was observed after 10 weekly laser treatments.[62] The immediate side effects were similar with pain, urtication, and hair whitening; hyper- and hypopigmentation were present in some subjects at 3 month follow-up. A split-face study evaluated 5 weekly QS Nd: YAG laser treatments in conjunction with 2% hydroquinone versus 2% hydroquinone alone and found 92.5% lightening of the laser-treated side compared with 19.7% on the control side. At 12 week follow-up, melasma recurred in all subjects; 3 had punctate leukoderma and 4 had hyperpigmentation.[63]

The development of permanent depigmentation after multiple repetitive QS Nd: YAG laser treatments was described by several authors.[64-66] It is believed that the depigmentation observed after repetitive high-fluence QS Nd: YAG laser is the same entity as leukoderma punctata, which has been reported in patients receiving long-term psoralen and ultraviolet light A therapy. The high-cumulative laser fluences used in these studies produce skin inflammation and epidermal disruption that result in a high incidence of pigmentary alteration and rebound melasma.

Low-Fluence QS Nd: YAG Laser Combined With Microdermabrasion and Topical Hydroquinone

Kauvar[67] studied the combination of microdermabrasion and low-fluence QS laser in conjunction with a hydroquinone-based skin care regimen in 27 subjects with refractory melasma and phototype II-V skin. QS Nd: YAG laser treatment (1064 nm, 5-7 or 50 ns) was performed with fluences of 1.6-2 J/cm^2 with a 5- or 6-mm spot, using only 2 laser passes to achieve complete coverage of the affected skin, and was administered immediately after microdermabrasion. Treatment was repeated at 4-week intervals. Daily application of a broad-spectrum sunscreen began immediately. Subjects began using a topical skin care regimen of 4% hydroquinone with tretinoin or vitamin C 2 days later. Results were assessed based on standardized digital photographs obtained before each treatment session and at follow-up visits that were scored by blinded comparison using a quartile grading system.

Patients received a mean of 2.6 treatment sessions and a maximum of 4 laser treatments. All subjects achieved at least a 50% improvement in the appearance of their melasma (Fig. 1). More than 80% of the subjects experienced >76% improvement in melasma at 3-, 6-, and 12-month follow-up. In the 25 subjects observed at 6-month follow-up, there was only a 1-point, or 25%, decrease in pigment clearance from the 3-month follow-up in 16% of subjects, and in the 9 subjects who had 1-year follow-up, there was a 1-point decrease in clearance score in 11% of subjects from the 6-month follow-up. The only observed adverse effect was mild posttreatment erythema, which developed after the microdermabrasion and lasted approximately 30-60 minutes. During the 6- to 12-month follow-up period, 4 subjects noted temporary exacerbation of their melasma after

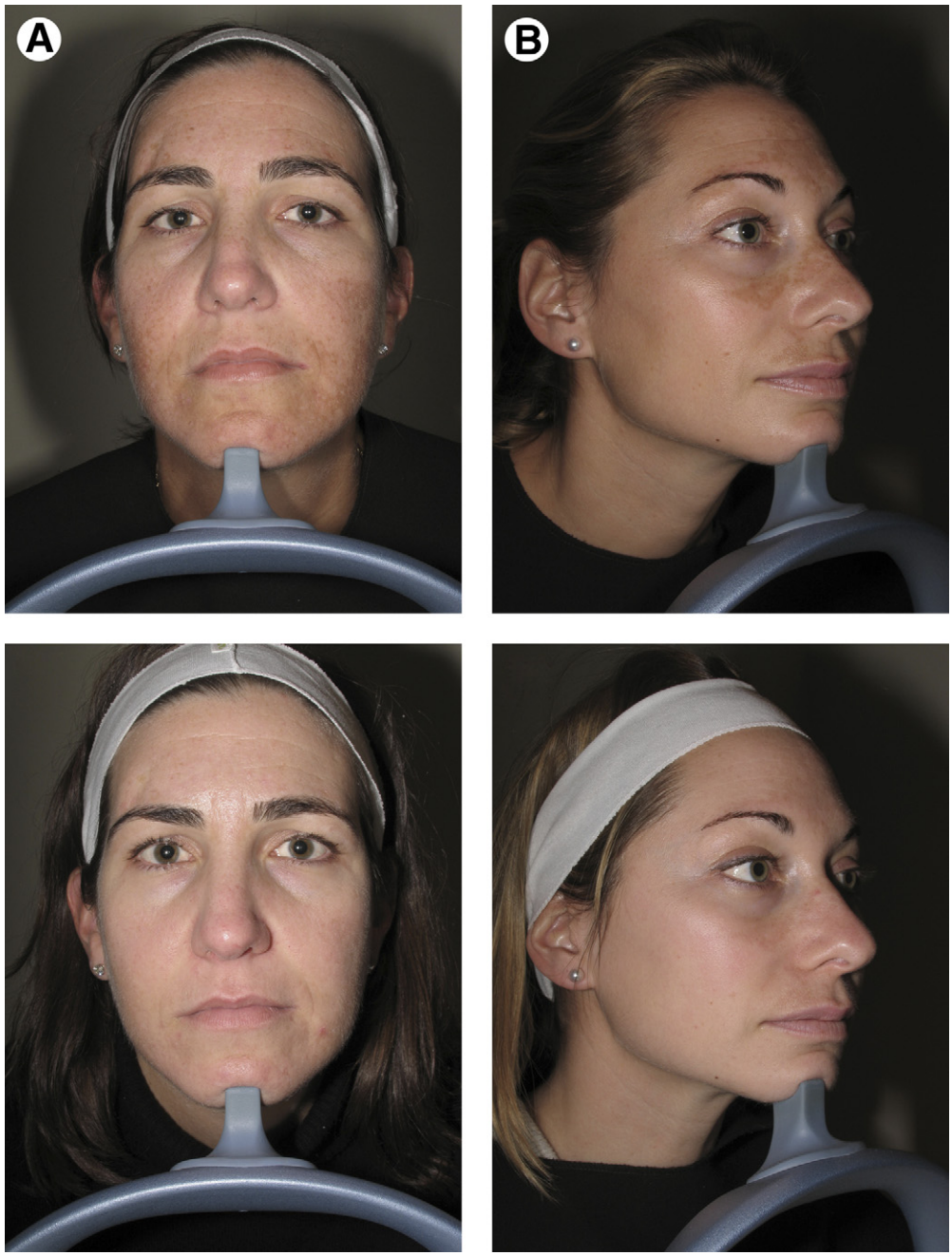

Figure 1 (A) Before and 6 months after 3 microdermabrasion and Q-Switched Neodymium-Doped Yttrium Aluminium Garnet laser treatments. (B) Before and 3 months after 1 microdermabrasion and Q-Switched Neodymium-Doped Yttrium Aluminium Garnet laser treatments.

inadvertent sun exposure, but this resolved within several weeks of resuming the topical skin care regime. Approximately 80% of subjects maintained their melasma clearance for up to 12 months.

A number of factors likely contribute to the success of this combination procedure. The microdermabrasion, the low-fluence QS Nd: YAG treatment, and the maintenance skin care regimen have synergistic effects. The microdermabrasion decreases scattering of laser light, improving the depth of penetration of the QS Nd: YAG laser. By exfoliating the stratum corneum, the microdermabrasion also increases epidermal skin turnover, which speeds the elimination of epidermal melanin. The skin care regimen suppresses melanogenesis. The QS Nd: YAG laser, even when used at very low fluences, appears to selectively damage melanocytes and dermal melanosomes. A recent study examined the effect of low-fluence QS Nd: YAG laser treatment on the structure of melanocytes and melanosomes in patients with melasma. A total of 2 laser passes were performed using a 5- to 7-ns QS Nd: YAG laser, with a 7-mm spot size and fluence of 1.6-2.0 J/cm^2. Biopsies were obtained for ultrastructural analysis immediately after treatment. Scanning electron microscopy

showed fewer dendrites in epidermal melanocytes as well as a reduction in melanocyte volume after laser treatment, and transmission electron microscopy demonstrated a decrease in stage IV melanosomes. These studies confirm that, even at these very low fluences that do not disrupt the epidermis, selective melanosome damage is possible.

This unique combination of microdermabrasion and low-fluence QS Nd: YAG laser treatment in conjunction with a pigment-reducing skin care regimen is a safe and effective treatment for melasma for patients of all skin types. This noninvasive combination therapy offers substantial benefits over more invasive, high-risk, and costly procedures, such as nonablative or ablative fractional laser treatment, and appears to provide improved results compared with those of the individual modalities used alone in published reports.

Conclusions

Melasma is a common problem worldwide, particularly in females with phototype III-IV skin, and is usually a persistent condition. For most patients, topical skin care regimens are only of limited value, probably because of the high incidence of dermal and mixed-type melasma, which cannot be cleared by suppressing melanogenesis alone. Because melasma is a chronic disorder in most individuals and exacerbations are inevitable, it is important to develop a procedure that is simple to perform, has minimal risks and recovery time, and a high safety and efficacy profile in all skin phototypes. The most practical approach to eliminating dermal melanosomes is with nanosecond-domain lasers because of their selectivity, and of these, the QS Nd: YAG laser appears to have the best suited wavelength; it has a high safety profile in darker phototypes and the capacity for deep dermal penetration. Microdermabrasion plus low-fluence QS Nd: YAG laser treatment is a simple noninvasive procedure with minimal risk and no recovery time and usually induces a rapid remission. Treatment works in all skin phototypes in just 2 to 3 treatment sessions and can produce long-lasting improvement. Histologic assessment of melanocytes and dermal melanosomes after new therapeutic interventions for melasma will help to clarify the mechanism of action and optimize treatment outcomes. Prospective, randomized, controlled studies are underway by the author to definitively examine the benefits of this combination therapy.

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