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NEW METHODS AND TECHNIQUES

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New Innovations in Combination Therapy

Combination Therapy in Clinical and Cosmetic Dermatology: The Marriage of Device and Drug

Advances in the Topical Treatment of Acne and Rosacea

Combination Therapy for Solar Lentigines

Utilizing Combination Therapy to Optimize Melasma Outcomes

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New Innovations in Combination Therapy

Original Articles:

Combination Therapy in Clinical and Cosmetic Dermatology: The Marriage of Device and Drug

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Abstract

The first generations of lasers used in clinical and cosmetic dermatology achieved their effects by means of epidermal and dermal ablation. While effective in removing some of the stigmata of photodamage including pigmentary changes and rhytides, vascular abnormalities associated with such conditions as melasma and rosacea, were not sufficiently effective. The new generation of laser and non-laser light devices (eg, intense pulsed light or IPL) offer excellent results in the management of clinical and cosmetic conditions, including significant changes in improvement in vascular conditions such as rosacea and actinic damage and stimulating dermal collagen production, without significant injury to the epidermis. The combination of light therapies and topical agents adds to the efficacy of these procedures, particularly in post-procedural maintenance. Light-based therapies have been an important addition to the anti-acne armamentarium as they are effective and do not add to the increasing bacterial resistance problem.

Introduction

Over the past decade, lasers and non-laser light-based therapies have become increasingly popular in dermatology both for the management of clinical conditions and for cosmetic procedures and cutaneous rejuvenation[1-5]. The first generation of these devices included several types of ablative lasers, which achieved their effects via epidermal ablation and heat-wounding of the dermis. The thermal destruction caused by the procedures usually required a prolonged recovery period during which time the skin had to be continually dressed and treated with the attendant risks of infection. However, they were effective in producing new collagen synthesis and improving signs of photoaging, including pigmentary changes and rhytides. Building on knowledge gained with these earlier procedures, a variety of non-ablative technologies has been introduced in recent years. These newer procedures are able to target pigmentary and/or vascular abnormalities and induce new collagen synthesis without significant epidermal and dermal wounding and postoperative healing considerations that pertained with ablative resurfacing techniques. Actinic damage, rosacea, melasma, and acne-clinical conditions with a cosmetic overlap and significant effects on many patients' psychosocial functioning respond to these new procedures with dramatically less recovery time.

Physicians and patients have embraced these new therapies and new technologies, yet the expectations of each continue to rise. Patients continue to seek cosmetic and clinical improvement with less "down time" and less expense, while physicians are striving to provide care for these overlapping areas of skin disease, photodamage and cosmetic enhancement with greater efficacy and safety. One of the most important advances in the effort to achieve these ends has been increased use of the combination of newly developed non-ablative lasers, non-laser light sources and pre-existing gold standard topical medications.

Examples of these non-ablative technologies include intense pulsed light (IPL), pulsed dye laser (PDL), 1320 nm neodimium doped yttrium aluminum garnet (Nd: YAG), long-pulsed erbium substituted: yttrium aluminium garnet (Er:YAG),

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radiofrequency (RF), light-emitting diodes (LED) and photodynamic therapy (PDT) using light of varying wavelengths. The U.S. Food and Drug Administration (FDA) has now approved the IPL for the treatment of rosacea and hyperpigmentation and the 1320 and 1440 nm Nd:YAG lasers and blue light are approved for the treatment of acne. New indications are being added continually.

The pharmaceutical treatments that are being used in conjunction with these devices include topical 0.75% metronidazole (MetroCream®, MetroLotion®) and oral metronidazole (MetroGel®) for rosacea, retinoids for acne and actinic damage (Differin®, Retin-A®, Avage®, Avita®, Renova®), and the prescription triple-combination cream (Tri-Luma® Cream) based on the original Kligman and Willis formulation for melasma and other pigmentary disorders6. Newer agents, such as the topical 2% mequinol/0.01% tretinoin solution (Solagé® Topical Solution) for solar lentigines, botulinum toxin (Botox®) and an increasing array of fillers for expression lines and rhytides (Restylane®) are all important components of this new combination armamentarium.

Skin Damage and Photorejuvenation

Three types of photodamage have been identified[1,7]. Type A damage may result from UV-related photoaging and other environmental causes such as infrared damage, rosacea, melasma, post-inflammatory hyperpigmentation (PIH) or laser resurfacing. Lesions include telangiectasias, erythema and flushing associated with rosacea, lentigines, ephelides and the pigmented plaques of melasma.

Type B damage consists of dermal and epidermal structural changes caused by the effects of photodamage on collagen and connective tissue. Lesions include rhytides, expression lines, elastotic changes and large pores.

Type A and B damage can be treated with photorejuvenation techniques, including IPL, aminolevulinic acid photodynamic therapy (ALA/PDT) and LEDs. Type B changes can be treated with radio-frequency tightening at 1320 and 1540 nm (Thermage®), and YAG lasers (CoolTouch®, SmoothBeam™) in combination with botulinum toxin (Botox®) and fillers (CosmoPlast™, CosmoDerm™, Restylane®).

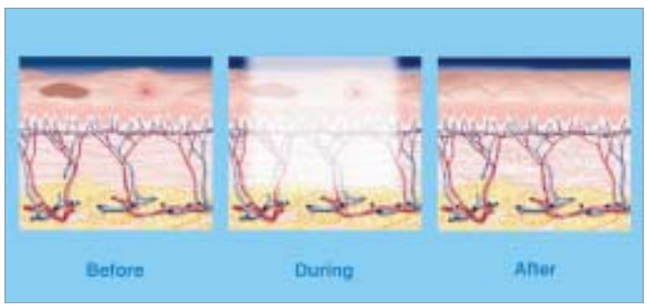

Figure 1. IPL Photorejuvenation: How it Works

Type C damage includes chronic actinic damage, elastotic changes, actinic keratosis and superficial skin cancers coupled with Type A and B damage and changes. Type C can be treated most sufficiently with photodynamic skin photorejuvenation using ALA/PDT[1].

Treatment of Vascular and Pigmented Lesions

Vascular and pigmented lesions associated with Type A damage have been treated successfully with pharmaceutical agents. The flushing and erythema associated with rosacea can been treated with some success with topical or oral metronidazole or antibiotics. Melasma, PIH, and other pigmented lesions have typically been treated with hydroquinone, retinoids, topical corticosteroids, the prescription triple-combination cream containing all three of those components (Tri-Luma® Cream), kojic acid or alpha- and beta-hydroxy peels.

Now, several non-ablative laser and light therapies are proving to be effective in treating pigmented and vascular lesions, either alone or in combination with topical therapies. The introduction of IPL has been an important advance in this arena. IPL emits a noncoherent light at wavelengths between 500-1200 nm and has proven to be effective in the treatment of a variety of vascular lesions including telangiectasias and brown pigmented lesions such as solar lentigines and the macules of melasma[7]. It is currently FDA-approved for the treatment of rosacea and melasma. In addition, IPL is capable of addressing some of the pigmentary changes emblematic of Type B damage. It can be used on the full face, neck, chest and dorsum of the hands with little or no down time[2]. Generally, 5-6 full-face treatments are given at 2 to 3-week intervals. An IPL 550 or 560 filter is used with double-pulsing 2.4/4.0 with a 10 or 20-millisecond delay at fluences from 33-38 J/cm^2. Figure 1 shows how IPL works to remove superficial pigmented lesions.

Melasma is an extremely common acquired disorder of hyperpigmentation. It generally involves the cheeks, forehead, upper lip, nose and chin. Melasma occurs in men, but 90% of cases occur in women, and it is particularly prevalent in darker-complected individuals. While its etiology is somewhat unclear, genetic influences, exposure to UV radiation and exposure to female hormones during pregnancy, hormone replacement therapy or in the form of oral contraceptives all appear to be important in its pathogenesis[8].

To date, one of the most successful treatments for patients with melasma and PIH has been the triple-combination topical cream based on the initial Kligman and Willis formulation[6,9]. It contains 4% hydroquinone, 0.05% tretinoin and 0.01% fluocinolone acetonide and has been shown to be safe and effective in the management of this common acquired hyperpigmentation in conjunction with sun avoidance. In multicenter, randomized, investigator-blinded studies, more than 70% of melasma patients

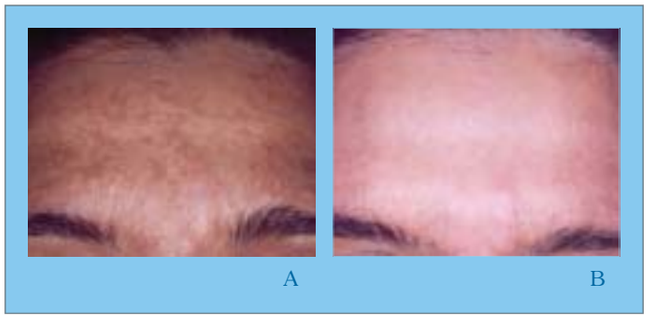

Figure 2A. Patient With Melasma
Figure 2B. Results of Melasma Therapy With Triple-Combination Cream (Tri-Luma® Cream) and IPL at 8 Weeks

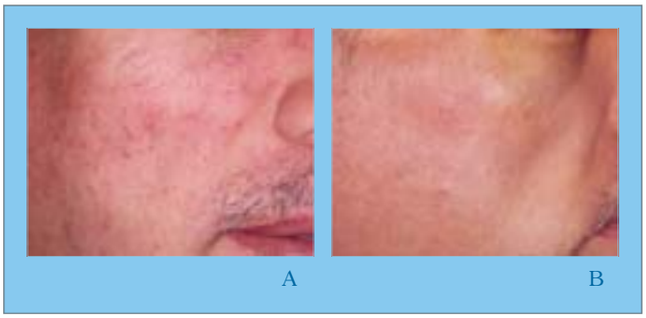

Fig 3A. Refractory Papular Rosacea at Baseline
Fig 3B. Refractory Papular Rosacea at One Year Following Treatment with IPL and Metronidazole Cream (MetroCream®)

treated with this combination cream achieved a 75% reduction in hyperpigmentation at Week 8 compared to only 30% in patients receiving combinations of two of its other ingredients[10].

Figures 2A and 2B show the results that can be obtained with the combination of IPL to clear hyperpigmentation, followed by long-term maintenance therapy with the triple-combination cream. This patient had had a long history of melasma and had received treatment with a variety of prescription and over-the-counter topical products to little avail. She received 5 treatments using IPL with a 560 nm filter at 2.4/4.0 T1/T2 double-pulsing with a 20 ms delay. Treatment fluences ranged from 22-28 J/cm^2. The patient was instructed to use a broad spectrum sunscreen, an essential concomitant to therapy, and to begin daily use of the triple-combination cream. She maintained significant clearance of hyperpigmentation at 8 weeks.

Rosacea is a common cutaneous vascular disorder primarily of the central face. Its early stage is characterized by inflammatory papules and pustules on an erythematous background with multiple telangiectasias. In its most extreme manifestation, it can progress to disfiguring phymatous changes, such as rhinophyma, which generally must be treated surgically. Although rosacea is not curable, it can be controlled. The imidazole metronidazole which has anti-inflammatory, immunosuppressive and antimicrobial effects, has been a mainstay of therapy. However, this treatment alone is rarely effective for the eradication of telangiectasias. IPL is partially effective in treating papules and pustules and is extremely effective in treating the erythema and telangiectasias of rosacea[2]. While topical and oral metronidazole, topical azelaic acid, benzoyl peroxide/clindamycin and oral antibiotics, have been helpful in treating the erythema and inflammatory lesions of rosacea, the standard therapies have been less successful in the treatment of telangiectasias[2,11-13].

Figures 3A and 3B show a patient with papular rosacea who was unresponsive to most treatment (except oral tetracycline which caused stomach problems) at baseline and at one year following 5 treatments with IPL using a 550 nm filter, 2.4/4.0 double-pulsing with a 20 msec delay at fluences ranging from 33-38 J/cm^2 in combination with metronidazole cream maintenance therapy.

Poikiloderma of Civatte is another common combination disorder of dyschromia and vascular changes that affects middle-aged sun-exposed individuals. It consists of an irregular, dark pigmentation or telangiectases over an erythematous field and typically appears on the neck. Exposure to UV light, and possibly, endocrine factors are important in its pathogenesis. Until recently, the best treatment has been photoprotection and sun avoidance for the pigmentary component[14]. Recently, the triple-combination cream has been used successfully as maintenance therapy following non-ablative photorejuvenation in poikiloderma of Civatte[2].

Figures 4A and 4B show the lesions of a female patient at baseline and at 6-months post-treatment. She had received 5 IPL treatments using a 560 filter, 2.4/4.0 double-pulsing, 20 msec delay at fluences ranging from 33-38 J/cm^2. The patient was also treated with the triple-combination depigmenting cream during the IPL therapy and as maintenance following its discontinuation with continued excellent results for up to 6 months.

Treatment of Type C Damage

Type C damage encompasses Type A and B damage as well as some of the more serious clinical conditions that are related to chronic UV damage. They include actinic keratoses (AKs), elastotic changes, deep rhytides and superficial skin cancers. IPL alone has not proven to be highly effective in the management of Type C damage. These conditions can be addressed with imiquimod (Aldara™) or topical 5-fluorouracil (5-FU) (Efudex®). However, the latter treatment can be painful, prolonged and cosmetically unacceptable during its course. These therapies do not deal with the overall underlying elastotic changes and dermal changes that are associated with Type C damage. Furthermore, patient understanding of and compliance with treatment must be of the highest order.

In 1999, a new light-based therapy called ALA/PDT, received FDA approval for the treatment of multiple AKs on the head

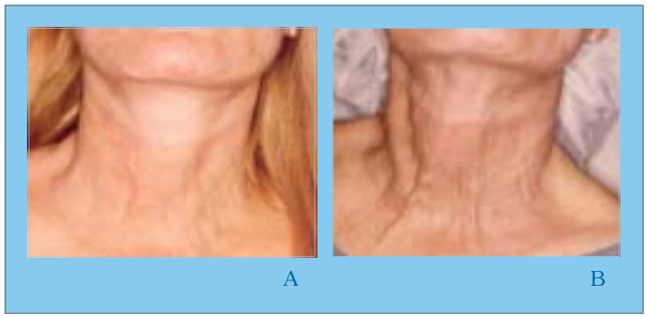

Figure 4A. Poikiloderma of Civatte at Baseline
Figure 4B. Poikiloderma of Civatte at 6 Months Following Treatment With IPL and Triple-Combination Cream (Tri-Luma® Cream)

and scalp. It uses a porphyrin precursor, 5-aminolevulinic acid, which is applied to the AK lesions where it is converted to protoporphyrin IX (PpIX) within atypical keratinocytes. PpIX is a potent photosensitizer that can be activated by exposure to light at wavelengths from 405 nm to 635 nm (blue to red). Once photoactivated, PpIX generates singlet oxygen species that kill targeted lesions. Precancerous, malignant or fast-growing cells selectively take up topically applied ALA sparing the surrounding normal cells.

In Phase III studies of ALA/PDT, 83% (n=243) of patients with AKs of the face or scalp had >75% clearance 8 weeks after treatment with a 20% ALA topical solution (Levulan® Kerastick®) followed 14-18 hours later by PDT using a 417 nm blue light at a dose of 10 J/cm^2 [15]. Thin AKs had higher response rate in these studies than thicker, more hyperkeratotic lesions. Adverse events related to ALA/PDT typically consist of burning and stinging during light treatment as well as temporary erythema and edema[15].

ALA can be activated by a variety of light sources, including blue light, intense pulsed light (IPL) and PDL. ALA/PDT is also being used successfully for skin rejuvenation in combination with IPL. Actinic damage, sebaceous thickening and deep rhytides all can be treated by this means.

Microdermabrasion is applied initially to enhance penetration of the ALA, which is applied to the full face and left for 15-60 minutes. IPL is used with a 550-560 filter, double-pulsing with a 20 msec delay, beginning at fluences of 24-26 J/cm^2. Figures 5-7 show the level of photorejuvenation that can be achieved with this technology when treating actinic damage, deep rhytides, skin cancers and AKs.

Avram and Goldman treated a small series of 17 patients with ALA/IPL[16]. The subjects had more than 3 AKs on the face as well as signs of photodamage, including fine wrinkling, telangiectasias, skin coarseness and pigmentary irregularities. One hour after application of ALA to the entire face, IPL was used with a 560 nm filter at a 28-32 J/cm^2 fluence with a double pulse

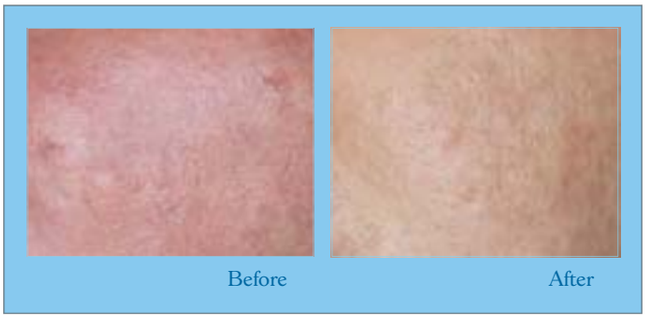

Figure 5. Treatment of Actinic Damage with Microdermabrasion and ALA/PDT

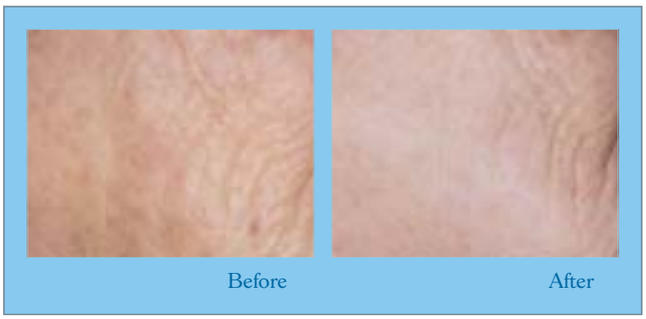

Figure 6. Treatment of Deep Rhytides with Microdermabrasion and ALA/PDT

Figure 7. Treatment of Actinic Keratoses and Skin Cancers with Microdermabrasion and ALA/PDT

of 3.0 and 6.0 msec with a 10 msec delay. Following the procedure, the patients were instructed to protect themselves from the sun and to use a moisturizer. In this study, 68% of AKs resolved after one treatment. Telangiectasias improved by 55%, mottled hyperpigmentation by 48% and skin coarseness by 25%. Fine wrinkling was only minimally affected.

A newer protocol using a shortened ALA application of 15-60 minutes rather than overnight, is more practical as only one office visit may be required by the patient for treatment. Further study will be needed to determine whether short-application time ALA will be equally effective[1,17].

Treatment of Acne

Acne is a multifactorial disease that afflicts 30%-85% of adolescents as well as a smaller percentage of adults[18]. It is a chronic inflammatory process that arises from dysfunction of the pilosebaceous unit and results in abnormal desquamation. The initial pilosebaceous dysfunction is due to increased sebum production under the influence of androgens at pubarche, abnormal keratinization of the follicular epithelium, colonization with *Propionibacterim acnes (P. acnes)* and consequent perifollicular inflammation. It affects areas of the skin, such as the face, chest and back with large numbers of sebaceous follicles. The initial acne lesion is the invisible microcomedo, which becomes either a closed comedo or whitehead, or an open comedo or blackhead, both visible, non-inflammatory lesions inside follicles. As *P. acnes* proliferate and are nourished by sebum, a variety of inflammatory mediators are recruited and accumulate within the follicular epithelium. Figure 8 shows the papules and pustules of the first stage of inflammatory acne, and Figure 9 shows the more severe inflammatory lesions of nodulocystic acne.

The goals of acne treatment are to limit or eradicate the disease, prevent scarring and minimize psychological stress and embarrassment. Current best practice as outlined in the recent Consensus Recommendations for the Management of Acne states that effective acne management should target as many of its pathogenetic factors, as possible[19]. The recommendations also state that a topical retinoid should be used in the initial treatment of almost all patients with acne, because they are the most effective anticomedonal agents currently available. Retinoids help disrupt acne pathogenesis by preventing the development of new microcomedones, and some possess both direct and indirect anti-inflammatory activity[20]. Because retinoids do not possess direct anti-bacterial activity, the use of oral or topical antibiotics may also be necessary to treat inflammatory activity. Retinoids enhance the follicular penetration of topical antibiotics and thus help increase the effectiveness of antibiotics[19,21]. This is an important added benefit because of the increasing problem of *P. acnes* resistance to antimicrobials. Non-specific antimicrobials, such as benzoyl peroxide (BP), are also an important component of the strategy to minimize *P. acnes* resistance by providing more than one mode of antibacterial activity[19]. In severe cases, oral therapy such as oral antibiotics and the oral retinoid isotretinoin (Accutane®; Roaccutane®) may also be used.

While retinoid/antibiotic/BP combination regimens remain the gold standard for acne treatment, there are drawbacks to these existing treatments. Compliance issues can sometimes render topical retinoid therapy less than optimally effective, and bacterial resistance is an increasingly significant issue with respect to both oral and topical antibiotics. Isotretinoin is reserved for severe acne as it is a known teratogen. It has serious side effects including anemia and/or thrombocytopenia and elevations of serum triglycerides liver function tests necessitating frequent monitoring[22].

While ultraviolet (UV) light was used several decades ago for the treatment of acne, its use is limited by the theoretical risks of UV radiation[23]. Recently, a new technique that employs narrow band blue light has proven highly effective in the treatment of acne. Figure 10 shows fluorescing porphyrins in sebaceous glands. These endogenous porphyrins are excited by light at the near-UV and blue-light portion of the spectrum without the use of a photosensitizer, such as ALA, as is used in the management of AKs.

Visible blue light leads to bacterial destruction via the production of reactive oxygen species produced by photoexcitation of the bacterial porphyrins. Red light is believed to possess anti-inflammatory properties through its effects on inflammatory cytokines[23].

A study by Papageorgiou and colleagues compared the use of blue light (415 nm), mixed blue and red light (peaks at 415 and 660 nm), cool white light and 5% BP in the treatment of 107 patients with mild-to-moderate acne[23]. Patients were irradiated for 15 minutes daily and assessments for the subjects in the light treatment groups (but not the BP group) was carried out every 4 weeks by blinded observers. At 12 weeks of treatment, there was a mean improvement of 76% in inflammatory lesions in the combined blue + red light group. It was significantly superior to the results obtained with blue light at all time points except the final

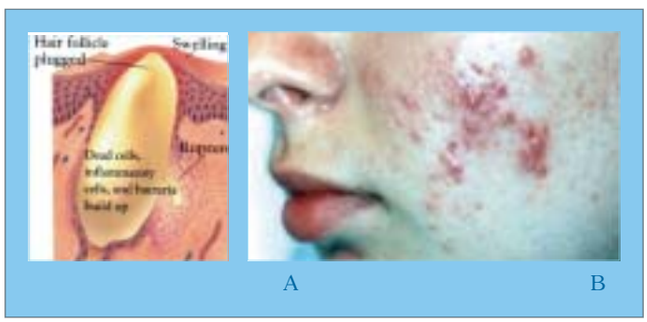

Figure 8. Papulopustular Acne

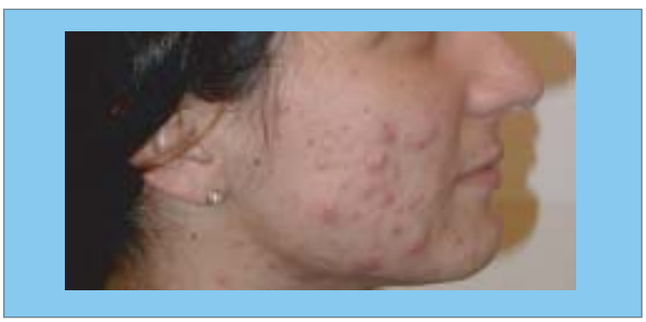

Figure 9. Nodulocystic Acne

visit. The combined light treatment was also superior to treatment with white light and 5% BP. The mean improvement in comedo count was 58% in the group that received blue + red light, but the difference was between it and the other active treatments did not achieve statistical significance.

The sebaceous gland itself can also be targeted and destroyed. Hongcharu treated the backs of 22 patients with topical ALA 20% followed 3 hours later by exposure to a broadband light source. Patients showed clinical improvement of their acne lesions. A decrease in sebum output was still measureable 20 weeks after a single treatment. Patients who received one treatment per week for 4 weeks showed sebaceous gland atrophy that was still measureable 20 weeks following the termination of therapy. Patients experienced significant pain, edema and crusting[24].

This type of therapy that is capable of damaging or destroying the sebaceous glands holds promise as an effective alternative to a 2-3-year course of conventional topical and/or oral therapy for acne[25].

While the majority of lasers and light-based devices used in acne target *P. acnes*, the sebaceous glands also can be targeted. While a 1450 nm laser alters the sebaceous glands thermally, ALA also can be used in combination with a low-power light source to destroy *P. acnes*[26].

Table 1 summarizes results of other recent studies in the literature of the effect of 420 nm narrow band blue light without an exogenous photosensitizer in the treatment of patients with

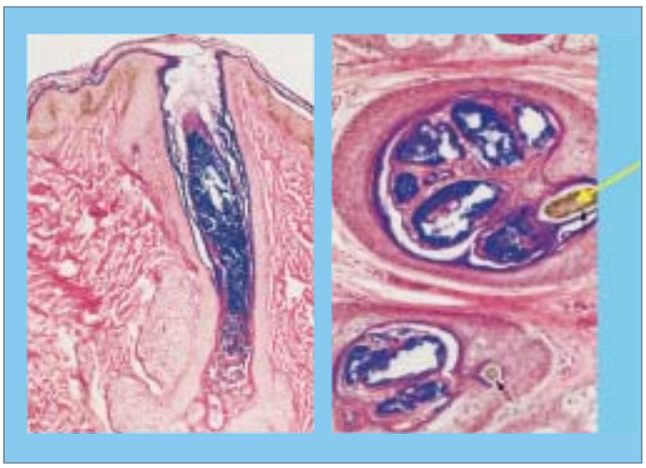

Figure 10. Fluorescing Porphyrins in Sebaceous Glands

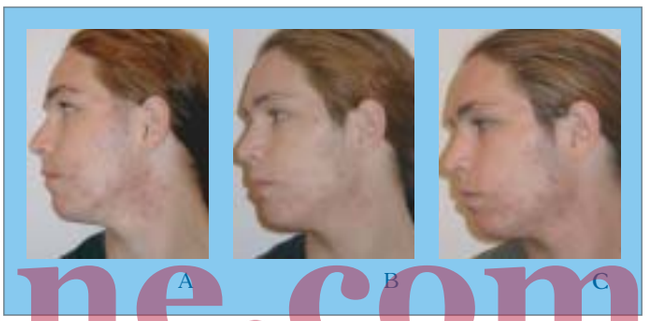

Figure 11A. Patient at Baseline
Figure 11B. Patient After 8 Bi-Weekly Treatments with 420 nm Narrow-Band Blue-Light
Figure 11C. Patient at One-Month Follow-Up

Table 1. **Summary of Recent Studies Utilizing Narrow-Band Blue-Light Therapy in the Treatment of Acne Vulgaris**[26-28]

Study	Acne Severity (N)	Protocol	Results	Adverse Events
Acne phototherapy with a high-intensity, enhanced, narrow-band, blue light source	Mild-to-moderate (58)	Bi-weekly treatments, up to 5 weeks	– Lesions decreased 64% – Decreased *P. acnes in vitro* – Did not reduce *S. epidermis in vitro*	2 patients experienced dryness. No discontinuations
Effective treatment of *acne vulgaris* by a high-intensity, narrow band 405-420 nm light source	Papulopustular (46)	8 bi-weekly treatments 8-15 minutes	– 80% response – Lesions decreased 59%-67% – Prolonged remissions >8 weeks post-therapy	No adverse events or patient discomfort noted in any patients
Effects of high-intensity, enhanced metal halide lamp on acne-affected skin	Mild-to-moderate papulopustular (>120)	8 bi-weekly treatments	– 80% of patients showed significant improvement of non-inflammatory, inflammatory and total facial lesions – Inflammatory lesion count decreased >60% – Lesion count decreased by nearly 70% 2 weeks after last treatment	No adverse events reported

acne[26-28]. The time to response is relatively swift. Most clinicians report a reduction in the size and number of inflammatory acne lesions after the second week of treatment. Skin oiliness also tends to decrease within this time frame. Results improve further over time.

Figures 11A-11C show a male patient from the 420 nm narrow band blue light phototherapy clinical trials (ClearLight Acne PhotoClearing™) at baseline and then after 8 bi-weekly treatments and again at the one-month follow-up. The continuing improvement one month following the cessation of treatment was noted.

In our clinical practice, we employ a protocol of 8 flexible, bi-weekly treatments with 15-minute exposures. Although narrow-band blue-light therapy can be used as acne monotherapy, it is most useful in treating the pustular component of the disease. The inflammatory component typically requires treatment with retinoids between treatments (not applied prior to light treatment) and afterwards. Narrow-band blue-light therapy can be used on the face, chest and back of all skin types. Results obtained with this protocol can last for a year or longer. Following therapy, a maintenance protocol should be initiated for continuing treatment of the comedonal component of the disease. This should include adapalene or another retinoid, with or without topical or oral antibiotics, and/or BP. Light treatment should be continued at monthly intervals.

Light therapy may be helpful as a first-line treatment for acne in patients who fail to respond adequately to other therapies or who have serious side effects and in patients with compliance issues. Moreover, it is a useful way of reducing exposure to antibiotics and further escalating bacterial resistance to these therapies.

Conclusion

As non-ablative therapies continue to evolve and new topical medications are added, there are likely to be increasing interest in combining prescription and procedural management of skin disease, sun damage and cosmetic enhancement and rejuvenation. This new approach, which marries pharmaceutical management and light-based therapies, is proving to be valuable in the treatment of such skin diseases as acne, melasma and rosacea, which, in addition to their underlying pathology, also pose significant appearance and quality-of-life issues for patients. In addition, combination therapy is fulfilling patients' desires for management of photoaging with excellent cosmetic results and minimal recovery time.

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Advances in the Topical Treatment of Acne and Rosacea

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Abstract

Acne and rosacea are common skin diseases which may present similarly and both involve inflammation. Both can result in significant cosmetic impairment and lead to quality of life decrements if not optimally treated. The conventional approach for both diseases involves the use of topical therapy to treat inflammatory lesions in combination, when needed, with a systemic or topical antibiotic. An important issue in the management of both diseases at present is the need to reduce antibiotic usage due to the increasing problem of bacterial resistance. One of the emerging treatment paradigms that is becoming increasingly useful as an antibiotic-sparing strategy is the use of procedural therapies in combination with medical management. Such procedural modalities include lasers, intense pulsed light (IPL), and photodynamic therapies (PDT). Topical regimens are used pre-treatment and following physical modalities for maintenance of remission.

Introduction

Acne vulgaris and rosacea are two common skin diseases that may be challenging to diagnose and treat. Both can be cosmetically disfiguring to those afflicted with them and both can result in significant psychosocial impairment. Acne and rosacea are frequently discussed together, because their clinical presentation has a certain degree of overlap. Both are at least partly inflammatory disorders and both present with papules and pustules. Rosacea was once considered a form of acne. However, increasing understanding of the pathogenesis of acne and the new classification of subtypes of rosacea have permitted clinicians to diagnose these two skin diseases with more precision and to target therapies to specific aspects of their underlying pathophysiology. This is especially true in the case of acne, whose pathogenesis is well delineated, versus rosacea where less of its etiology and pathogenesis are known. Advances in the understanding of these diseases have led to much more effective therapies. Accordingly, the psychosocial and quality of life decrements that patients with these two diseases suffered in the past have been greatly reduced. An important new paradigm in the management of acne and rosacea is the use of appropriate combinations of topical, systemic and light or laser-based therapies to optimize clinical, but also cosmetic, results.

Recently, the Global Alliance to Improve Outcomes in Acne published a set of consensus guidelines. The guidelines were evidence-based where possible and included input from numerous countries around the world. Their goal was to provide a comprehensive overview of acne therapy to "form the basis for more uniform therapeutic strategies throughout the world, enhanced patient compliance and more effective use of healthcare resources[1]."

Perhaps one of the most important advances in the management of acne has been the discovery of the role of vitamin A

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derivatives and other molecules that can interact with retinoid receptors. There are presently three topical agents—tretinoin, adapalene and tazarotene—that are active at retinoid receptors and can combat acne at its most proximal stage—the formation of the microcomedo.

In February 2002, a committee within the National Rosacea Society established a standard classification system for rosacea[2]. The Committee delineated primary and secondary features of rosacea as well as subtypes that comprise clusters of primary and secondary features that tend to manifest together. The new system is intended to facilitate the diagnosis and treatment of rosacea as well as communication among researchers, healthcare providers, insurers, patients and the general public[2].

This paper will review relevant findings in the pathophysiology and topical treatment of acne and rosacea in the context of both the consensus recommendations of the Global Alliance to Improve Outcomes in Acne and the New Standard Classification of Rosacea.

Introduction to Acne

Acne is the most common of skin disorders. It affects 35%-85% of adolescents[3]. A community-based study showed that 12% of women older than 25 had clinical acne and that this rate of prevalence did not decrease until after 44 years of age[4]. Despite its wide prevalence, acne is a cause of great distress among many of its sufferers.

Acne Pathophysiology

A consensus of the Global Alliance to Improve Outcomes in Acne was that the increasing understanding of acne pathophysiology should guide its treatment. According to the guidelines, the primary pathophysiologic features in acne are: 1) excessive sebum production under androgenic stimulation, 2) abnormal desquamation of the follicular epithelium leading to the formation of the microcomedo and the creation of an environment conducive to bacterial growth, 3) proliferation of *Propionibacterium acnes (P. acnes)* and, 4) inflammation leading to the formation of papules and pustules (Table 1). The treatment of acne should target as many of these factors as possible.

Excessive sebum production: At pubarche, increasing levels of androgens, the major sebotrophic hormones, begin to drive an increase in sebum production. However, while androgenic stimulation is important in the pathogenesis of acne, the typical acne patient does not have significant endocrine abnormalities. Hormonal therapy is not indicated in the initial management of mild to moderate acne, although females who require oral contraception may be candidates for anti-androgen therapy early in the course of treatment.

Abnormal desquamation of the follicular epithelium: In acne, keratinocytes, hyperproliferate and accumulate within the sebaceous follicle. As these abnormally desquamated cells accumulate in the sebaceous follicle, they lead to microcomedo formation. The microcomedo, is the precursor to all acne lesions and is present in 80% of acne papules but is invisible to the unaided eye[5]. However, as the already clogged follicle begins to fill with lipids, bacteria and cell fragments, the microcomedo progresses to open or closed comedones (blackheads and whitehead, respectively), both of which are non-inflammatory lesions. If *P. acnes* proliferates, inflammatory mediators are generated and inflammatory papules and pustules occur.

Bacterial proliferation: The microenvironment of the follicle in acne is conducive to colonization with *P. acnes*. This leads to inflammation and the production of the visible papules and pustules with which acne patients typically present to dermatologists.

Inflammation: Inflammation in acne occurs as a result of humoral and cellular immune reactions to *P. acnes* proliferation. It has been suggested that changes in sebum production or composition irritate infundibular keratinocytes leading to the release of interleukin 1a (IL-1a)[6]. In addition, CD4 lymphocytes and neutrophils migrate to the follicle[5,7]. Rupture of the follicular duct leads to the extravasation of lipids, corneocytes and bacteria into the dermis, causing further inflammation[8].

Targeting Therapy to Pathophysiology

Using the above four-part model of acne pathophysiology, it is possible to design a rational approach to the management of the disease. Figure 1 shows the activity of the different classes of anti-acne therapies on each of these components of the disease process.

Table 1. **Primary Pathophysiologic Factors in Acne**[1]

Excessive sebum production
Abnormal desquamation of follicular epithelium
P. acnes proliferation
Inflammation

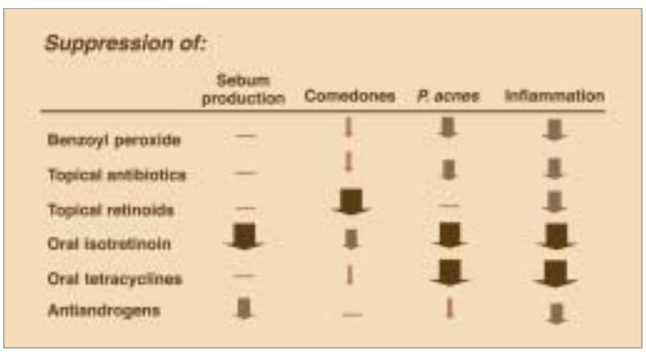

Figure 1. Action of Anti-Acne Therapies

Table 2. **Recommendations for Initial Acne Therapy by Stage**[1]

Mild Comedonal Acne	Mild to Moderate Inflammatory Acne	Moderate to Severe Acne	Severe Nodulocystic Acne
Topical Retinoid	Topical Retinoid	Topical Retinoid	Oral Isotretinoin
	BP ± Topical Antibiotic	Oral Antibiotics For Up to 3 Months ± BP OCs for females	

The Consensus Guidelines state that combination therapy should be started as early as possible in all acne patients, except those requiring oral isotretinoin, so as to attack two or more pathogenic factors. Table 2 summarizes the recommendations for initial therapy in different stages and levels of acne severity.

Mild comedonal acne with minimal inflammatory lesions should be treated with topical retinoids. Acne with a predominantly inflammatory component should be treated with a topical retinoid plus benzoyl peroxide (BP) with or without topical antibiotics. Moderate to severe acne should be treated with a topical retinoid and BP plus oral antibiotics. Females with moderate and severe acne can also be treated with oral contraceptives as an androgen-reduction strategy, especially if they require birth control. Oral isotretinoin should be used in severe and refractory acne, including severe nodular or conglobate acne. Patients who are unresponsive to other therapies may be treated with hormonal therapy (primarily for females) and oral isotretinoin[1].

Consensus Recommendations and Rationales

Topical Retinoids Should Be First-Line Therapy in Acne

An important paradigm in the treatment of acne is the early use of topical retinoids. Topical retinoids have multiple anti-acne actions. Retinoids target the microcomedo, the earliest precursor to all acne lesions. Formerly, therapy was not initiated until visibly apparent lesions had formed. The ability of retinoids to inhibit microcomedo formation prevents their progression to closed and open comedones and inflammatory lesions. The rationale for the use of topical retinoids from the start of therapy is that they can achieve a parallel reduction in both noninflammatory and inflammatory lesions. Initially, it was believed that retinoids were effective only against noninflammatory lesions, but research indicates that topical retinoids possess both direct and indirect anti-inflammatory activity[9].

Adapalene has been shown to produce greater reductions in noninflammatory, inflammatory and total lesion counts than tretinoin after 12 weeks of therapy[10].

Figure 2 shows the mechanism of action of topical retinoids. They reverse abnormal desquamation by increasing normal turnover of the follicular epithelium as well as cellular differentiation and maturation[11]. This action prevents the blockage and distension of the follicle with epithelial cells and sebum which leads to microcomedo formation and provides an ideal environment for bacterial colonization.

Bacteria colonizing the blocked follicle digest sebum lipids and release lipases which hydrolyze triglycerides into free fatty acids. Free fatty acids are comedogenic and irritate the follicular wall, leading to rupture and further irritation and inflammation of the surrounding dermis. It has been shown that adapalene, like antibiotics, decreases free fatty acid levels in microcomedones which may be one mechanism of adapalene's anti-inflammatory activity[1,12,13].

Topical retinoids interfere with the interaction of *P. acnes* exoproducts and toll-like receptor-2 (TLR-2) which is a specific "pathogen recognition receptor." This probably occurs through the reduction of TLR-2 surface membrane expression as well as by interference with the follicular microclimate conducive to bacterial proliferation. In addition, topical retinoids inhibit activation of the activator protein-1 (AP-1) transcription factor pathway which is believed to be a component of acne inflammation and scarring. This may relate to retinoids' ability to reduce inflammation and may correlate with a decreased risk of acne scarring[14,15].

In contrast to the early experience with first-generation tretinoin formulations, the newer generation of retinoids do not result in an initial acne flare early in the treatment course.A dramatic decrease in inflammatory lesions may be visible earlier with adapalene than with other retinoids[16]. Figure 3 shows a patient with inflammatory acne at day 23 after the initiation of adapalene monotherapy.

Retinoids have been shown to enhance the penetration of other topical agents that are used in acne[17]. They may affect skin permeability by loosening the attachments among skin surface corneocytes and reducing the number of cell layers[18]. In addition, retinoids increase turnover of the follicular epithelium which permits the enhanced delivery of antibiotics to their intended site of action[19].

Because of their ability to prevent the formation of microcomedones, retinoids are highly effective monotherapy in the essential maintenance phase of acne treatment. As during the active treatment phase, the retinoid should be applied to the entire affected area rather than just to lesions.

Combination Therapy is the Standard of Care for Mild-to-Moderate Acne

While retinoid monotherapy is capable of treating both noninflammatory and inflammatory lesions, the Acne Consensus Recommendations state that topical retinoids should be combined with antibiotics from the start of therapy when inflammatory lesions are present. This recommendation is in keeping with the consensus view that acne therapy should be targeted to as many of its pathophysiologic mechanisms as possible. This combination targets ductal hypercornification, *P. acnes* proliferation and inflammation. These mechanisms are independent, but also to some extent additive, processes. By addressing all of these mechanisms, combination retinoid and antibiotic therapy offers additive and synergistic effects that can potentially increase efficacy and accelerate response[20].

Numerous studies over the past 30 years have shown that the combination of topical retinoids and topical or oral antibacterials reduce both noninflammatory and inflammatory acne lesions more rapidly and to a greater degree than can be effected with antibacterial therapy alone[1,20].

Through their comedolytic action, retinoids enhance the penetration of topical antibiotics, thus facilitating delivery to their intended site of action in the follicle where *P. acnes* resides. It has been suggested that topical retinoids can potentiate the antibiotic effect by increasing tissue concentrations[21]. Retinoids also offer indirect antibacterial activity because of their ability to normalize the follicular microclimate which discourages the growth of *P. acnes*[17].

Antibiotics are Adjunctive Therapy in Inflammatory Acne

Both topical and systemic antibiotics are suitable and efficacious in a combination regimen with topical retinoids for inflammatory acne. The choice should be based on the extent and severity of inflammatory lesions. Severe acne that is refractory to topical therapy or acne which covers a large area of the body may respond better to systemic antibiotic administration in combination with a topical regimen

Systemic antibiotics eradicate or decrease *P. acnes* and *S. epidermis*. *P. acnes* is believed the trigger the inflammatory response in acne that leads to later scarring. Antibiotics offer indirect anti-inflammatory activity by inhibiting the growth of the bacteria and reducing their production of inflammatory mediators. Erythromycin and tetracyclines directly suppress inflammation by their action on neutrophil chemotaxis and the production of chemotactic factors[1,22]. The microcomedo contains significant lipid concentrations and is thus poorly penetrated by hydrophilic antibiotics[22]. The preferred antibiotics are tetracyclines and erythromycin. Topical antibiotics are not used as monotherapy due to their slow onset of action and because of the potential for the development of bacterial resistance if they are used for a prolonged course. A topical antibiotic may be used in combination with a systemic antibiotic.

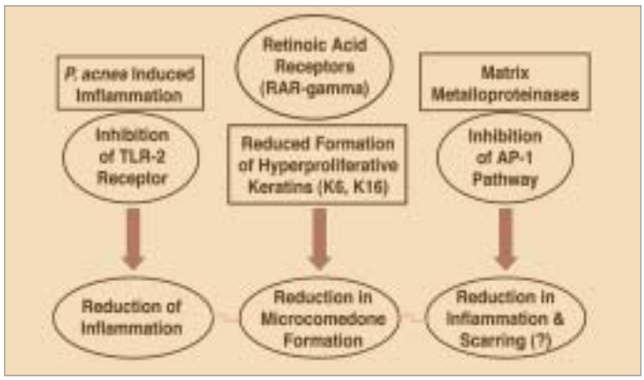

Figure 2. Mechanism of Action of Topical Retinoids

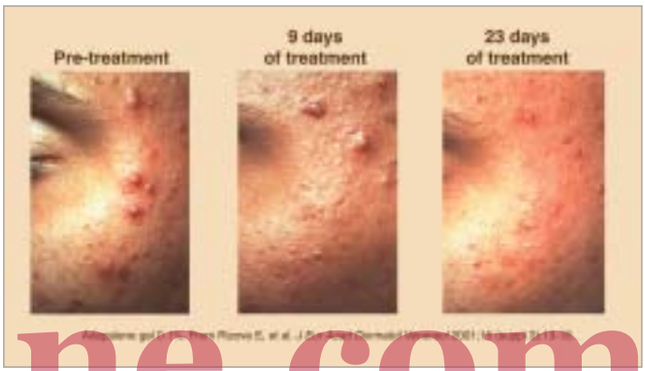

Figure 3. Patient With Inflammatory Acne at Day 23 After Initiation of Adapalene

Topical antibiotics that are useful in acne include erythromycin, clindamycin, benzoyl peroxide (BP) and combinations of BP and erythromycin and clindamycin[1]. They are available in many different types of formulations and in combination with BP.

The increasing problem of bacterial resistance to antibiotics by many pathogens is a serious one and is an important concern in acne therapy. In 2003, the Food and Drug Administration finalized a mandatory warning to be placed in the package inserts for all systemic antibiotics warning about antibiotic overuse and the emergence of resistant bacterial strains. The Consensus Guidelines state that, in addition to always combining antibiotics with topical retinoids, antibiotics should only be used for as long as necessary to control inflammatory lesions. Combined therapy using a topical retinoid and

a topical antibiotic has been shown to yield more rapid results while also targeting several pathogenetic factors and reducing antibiotic use[22]. If antibiotic therapy is to be used for longer than three months, it is recommended that BP be added to the regimen so to reduce the emergence of resistant *P. acnes* populations[1,22]. BP may be initiated earlier in the course of therapy, exercising caution to reduce the risk of irritation when combined with a topical retinoid.

The complementary, nonspecific antibacterial action of BP is believed to help reduce the selection of drug resistant *P. acnes* variants. BP has not been associated with bacterial resistance. However, if used as monotherapy, BP does not target microcomedones, therefore should be used in combination with a topical retinoid. One study showed that the combination of adapalene and BP was less irritating than either of its components alone[16]. A synergism between BP and erythromycin has also been demonstrated[23]. A randomized, double-blind comparison of BP/clindamycin versus clindamycin monotherapy showed significantly greater reductions in total and inflammatory lesion counts after 16 weeks of therapy. Importantly, there were significant reductions from baseline in the numbers of clindamycin-resistant isolates in the combination therapy group versus a 1600% increase in resistant isolates in the monotherapy group[24].

Once control of inflammatory lesions has been achieved, and antibiotic therapy is discontinued, topical retinoid therapy, with or without BP, should continue so as to maintain remission by preventing the formation of new microcomedones. It is important to note that some patients may require intermittent course of antibiotics to control flares. The Guidelines state that if re-treatment is necessary, the same antibiotic should be used if it was effective. The use of BP for a minimum of 5-7 days between antibiotic courses may enhance antibiotic efficacy by removing resistant bacteria from the skin[1].

Hormonal Therapy is Useful in Androgen-Driven Acne

Hormonal therapy is used in acne to oppose androgenic effects on the sebaceous gland. It is aimed at reducing sebum production. While, excessive sebum production is the most proximal event in the acne pathogenetic cascade, hormones are rarely used as monotherapy. Hormonal therapy should be combined with topical retinoids and when necessary, antibiotics and BP.

The mainstays of hormonal therapy include oral contraceptives (OCs), and the androgen antagonist, spironolactone. Hormonal therapy can be used early in the treatment of women with clinical signs of hyperandrogenism and in those with normal serum androgens who have been non-responsive to more conventional therapies. Hormonal therapy is a particularly good choice for women who desire oral contraception and/or those who require medical therapy to control their menstrual periods. Triphasic norgestimate/ethinyl estradiol is approved for the treatment of acne in women not controlled by topical therapy[1].

The Consensus Guidelines state that hormonal therapy seems to work best in adult females and sexually active teens who have persistent papules and nodules, particularly of the lower face. These women frequently report acne flare-ups in conjunction with menstruation. Such patients often note little improvement with multiple courses of antibiotics and sometimes with isotretinoin[1].

Oral Isotretinoin is the Standard of Care for Severe Acne

Isotretinoin is an oral retinoid which targets all acne pathophysiologic factors. It decreases the size and activity of sebaceous glands, normalizes follicular keratinization, prevents the formation of new comedones, has some anti-inflammatory effect as well as an indirect antibacterial effect by virtue of its normalization of the follicular environment[1].

Oral isotretinoin is indicated as first-line treatment in severe nodular acne or moderate to severe acne that is unresponsive to conventional therapy. It is also indicated in the treatment of patients with moderate to severe acne with scarring and in patients whose acne is causing them significant psychosocial distress.

Patient counseling is imperative when treating with oral isotretinoin. Its use is associated with side effects such as dry skin and eyes and chapped lips. Rare side effects include skeletal changes and osteoporosis. There is also a potential for mood swings and depression during therapy. Oral isotretinoin is teratogenic, and patients must be using highly effective contraception. Because of these possible adverse events, patient counseling and frequent followup, as well as specific monitoring of serum lipids and liver function, is essential.

While oral isotretinoin can provide rapid and dramatic improvement, relapse may occur. Most cases of severe acne respond to a 4-6-month course. Some patients can be treated successfully with conventional therapy while others will require another course of oral isotretinoin. After completion of oral isotretinoin, topical retinoid therapy is important for maintenance and may reduce the risk of relapse by preventing the formation of new microcomedos.

General Acne Management Strategies Are A Useful Part of Therapy

Daily skin care, patient counseling and office procedures are all essential adjuncts to pharmacologic treatment of acne. Compliance is aided by patients having an accurate understanding of acne and the rationale for each of the agents that are prescribed for them. Take-home materials instructing them in the correct use of their medications (e.g., applying topical medications to the entire affected area), the possibility of flare-ups, proper cleansing and moisturizing and the need for sun protection, are all important in ensuring the success of acne treatment.

Skin care in acne should be gentle, first and foremost. Patients should be taught that acne is not a hygiene problem and that vigorous cleansing with harsh soaps, hot water and physical exfoliants, are detrimental. Take-home materials should contain suggestions for cleansers and non-comedogenic moisturizers and sun protection at several price levels.

In-office procedures, such as comedo extraction, chemical peels and intra-lesional corticosteroid injections can be helpful adjuncts in selected patients. Comedo extraction, if skillfully performed so that extraction is complete and tissue damage does not occur can show an immediate, visible improvement. Chemical peels can help correct scarring and hyperpigmentation once the acne is controlled. Intralesional corticosteroid injections can be helpful for large inflammatory lesions that are of recent origin.

Light-Based Therapies

Photodynamic therapy (PDT) using blue (peak 415 nm) or mixed red and blue lights (peaks at 415 and 660nm) with or without aminolevulinic acid as a photosensitizer, and several types of lasers including the pulsed-dye laser have shown excellent results in the treatment of inflammatory acne[25-28]. Light therapies have been shown to produce results that are comparable to those obtained with traditional antibiotics, although lesional clearance is significantly faster (4 vs 8-12 weeks), and adverse events are much fewer[26]. In one study, 30 patients with mild to moderate acne were treated with a high-intensity, narrow-band blue light source twice weekly for up to 5 weeks. There was a 64% reduction in acne lesions and a reduction in the numbers of *P. acnes*, but not *S. epidermis* with this regimen[27]. Light therapy can be considered as a strategy for reducing the dose of oral isotretinoin. Most clinical experience suggests a reduction in the size and number of inflammatory lesions as well as reduced skin oiliness after the second week of light-based treatment. Improvement may not be evident until after the eighth treatment[26].

Topical Therapies in Combination With Light Based Therapies

The excellent results that have been obtained with light-based therapies have led to the newest acne treatment paradigm—the combined use of light therapy and medical management with systemic and topical agents. Topical therapy including BP, topical retinoids or chemical peels is used as pre-treatment and maintenance. This new way of combining modalities is advantageous as a strategy for reducing the use of antibiotics and isotretinoin, as well as improving cosmetic results in a shorter time frame.

The selection of a pre-treatment topical regimen is an important challenge when treating patients with light-based modalities. At present, the pre-treatment protocol is based on the guidelines recommended by the Global Alliance to Improve Outcomes in Acne. Retinoids in combination with a topical or systemic antibiotic to gain control over the formation of new microcomedones and inflammation should be the first-line therapy. While all topical retinoids have proven efficacy, adapalene has been shown to be the least irritating of the topical retinoids[16,29]. Oral or topical antimicrobial therapy should also be instituted if inflammatory lesions are present.

Topical maintenance therapy, preferably with retinoid monotherapy is an essential follow-up to light-based therapies. It has been suggested that that the destruction of *P. acnes* continues for a few weeks following the termination of light treatments and that the effects of light therapy will be maintained until bacterial populations rebuild to their initial concentration. Some patients may require a maintenance retreatment with light 6 months following the initial round of treatment[26]. If retinoid monotherapy does not offer sufficient reductions in inflammatory lesions, then combination BP and retinoid or antibiotic and retinoid therapy should be instituted. Chemical peels applied between light treatments may be beneficial.

Introduction to Rosacea

Rosacea is a chronic, progressive erythematous skin condition that is associated with flushing, blushing, papules, pustules and telangiectasia. Its stigmata typically appear on the central face. According to a report by the National Rosacea Society the disease afflicts at least 14 million people in the United States, typically between 20 and 50 years of age[2]. While it is most common in fair-skinned individuals, it can also affect darker-complected individuals[9]. Rosacea is more common in women, but it is generally more severe in men, with men more apt to present with phymatous changes. Risk factors for its development include photodamage, Northern or Eastern European origin, the use of topical corticosteroids, genetics and a tendency to flushing[30].

Rosacea: Pathophysiology

Rosacea is a cutaneous vascular disorder. Rather than a disease, it may actually be a phenotype that is expressed in rosacea-prone individuals[31]. It has no specific etiology although a variety of causes have been suggested, including gastrointestinal infection with *Helicobacter pylori (H. pylori)*, psychogenic factors, immunologic response to colonization with *Demodex* mites or disturbances of the microvasculature. Underlying the contribution to the clinical picture of many of the above factors is inflammation. Rosacea, with its inflammatory papules and pustules can potentially be considered an inflammatory disorder.

The first stage of rosacea is vascular and consists of erythema. Flushing reactions are due to trigger factors such as temperature extremes, wind, alcohol, and leads to increased blood flow through the dermis. Extracellular fluid accumulates faster than the lymphatics can drain it[31]. In the setting of this lymphatic failure, plasma protein exudates accumulate and produce a self-sustaining inflammation. These plasma proteins may also play

a role in the fibroplasia which is characteristic of later stages of the disease[32,33]. As the rosacea progresses, continued inflammation leads to the release of cytokines and other inflammatory mediators as well as enzymes, such as neutrophil elastase, which can degrade elastin and collagen. This leads to reduced capillary wall integrity and the sustained accumulation of extravascular fluids. Elastin degradation is also the result of photodamage which is commonly encountered in the typical rosacea-prone phenotype. The telangiectatic phase of rosacea may be due to actinic damage and angiogenesis as well as the disruption of the mechanical integrity of the superficial dermal connective tissue, allowing the passive dilation of blood vessels[31,34]. The issue of whether or not *Demodex folliculorum* overgrowth is present and whether an immunologic response to the mites or their products contribute to the inflammation of rosacea is an ongoing controversy. Likewise, the role of *H. pylori* infection is controversial[30].

Table 3. **Rosacea Features: New Standard Classification[35]**

Primary Features (presence of one or more)
Flushing (transient erythema)
Nontransient erythema
Papules and pustules
Telangiectasia
Secondary Features (one or more may also be present)
Burning or stinging
Plaque
Dry appearance
Edema
Ocular manifestations
Peripheral location
Phymatous changes

Table 4. **Subtypes of Rosacea[35]**

Subtype	Characteristics
Erythematotelangiectatic	Flushing, central facial edema ± telangiectasia
Papulopustular	Central facial edema ± papules/pustules
Phymatous	Thick skin, nodularities, enlargement
Ocular	Foreign body sensation, burning/stinging, dryness, itching, blurred vision, telangiectasia of sclera or other parts of eye. Periorbital edema

New Standard Classification of Rosacea: Subtypes of Rosacea

In 2002, an expert committee within the National Rosacea Society developed a new classification system for rosacea, aimed at simplifying diagnosis and facilitating the sharing of information among physicians, patients, researchers and insurers.

Guidelines for Diagnosis: The committee developed guidelines for the diagnosis of rosacea that require the presence of one or more primary features. One or more secondary features must also be present (Table 3)[35].

The primary rosacea features include flushing (transient erythema), nontransient erythema or persistent redness of the central face, which is the most common sign of rosacea. Papules and pustules, which often appear in clusters, and telangiectasia are also considered primary features.

The secondary features, which are not required for diagnosis, frequently appear in combination with one or more of the primary features or may appear on their own. They are: burning or stinging, plaques, dryness resembling xerosis, edema often in concert with prolonged flushing, ocular manifestations, peripheral location and phymatous changes, typically rhinophyma.

The new classification system also identifies subtypes of rosacea. These are clusters of primary and secondary rosacea features that often occur together. Subtype 1 is erythematotelangiectatic rosacea, Subtype 2 is papulopustular rosacea, Subtype 3 is phymatous rosacea and Subtype 4 is ocular rosacea (Table 4)[35].

Diagnosis of Rosacea

There are no laboratory tests or clinical markers to verify a diagnosis of rosacea. Observation and history-taking are the two most important diagnostic tools in rosacea (Table 5).

The patient should be questioned regarding what triggers and what palliates symptoms. Triggers have great inter-patient variability. A recent survey of 1066 patients was conducted by the National Rosacea Society identified the most frequent rosacea triggers (Table 6)[36].

Table 5. **Diagnosis: Patient History**

History
• Provocative and palliative factors
• Morphology
• Associated features
• Temporal characteristics
• Frequency of flushing
• Duration of flushing
• Association of flushing with workplace, exercise, food, drugs

The physician should assess the presence and type of lesions and their associated secondary features. The differential diagnosis of rosacea most commonly includes acne, seborrheic dermatitis, perioral dermatitis, carcinoid syndrome, and lupus erythematosus (Table 7).

Table 8 lists some of the neurologic and systemic factors and diseases that might cause the symptoms of rosacea.

Management of Rosacea

Rosacea is not a disease with a cure. There is not currently for rosacea a panoply of rational therapies developed from a thorough understanding of its etiology and targeting known pathogenetic factors. However, it is manageable with a combination of lifestyle measures to reduce exposure to known triggers, topical and systemic medications tailored to the disease manifestations and light therapies.

In addition to avoiding known triggers, rosacea patients should practice assiduous sun avoidance and use a high SPF broad-spectrum sunscreen. Physical sunblocks, such as titanium dioxide and zinc oxide, are particularly useful for erythemic rosacea patients. Rather than converting light energy to heat energy in the skin which could exacerbate the erythemic response, they scatter light before it penetrates the skin.

Topical and systemic therapies are chosen based on the type and severity of the rosacea. For all but the most mild manifestations, initial rosacea treatment often includes an oral antibi-

Table 6. **Most Common Rosacea Triggers**[36]

Percent of Patients Affected	Most Common Factors
81%	Sun
79%	Stress
75%	Hot Weather
57%	Wind
56%	Exercise
52%	Alcohol
51%	Hot Baths
46%	Cold Weather
45%	Spicy Foods
44%	Humidity
41%	Indoor Heat
41%	Skin-Care Products
36%	Heated Beverages

Table 7. **Rosacea vs Acne**

Characteristics	Rosacea	Acne
Papules and pustules	Yes	Yes
Nose and cheeks primarily involved	Yes	No
Erythema	Yes	No
Telangiectasia	Yes	No
Comedones	No	Yes

Table 8. **Underlying Conditions Leading to Rosacea-Like Erythema**

Neurologic Causes	Systemic Diseases
Anxiety	Carcinoid Syndrome
Simple Blushing	Mastocytosis
Brain Tumors	Basophilic Chronic Granulocytic Leukemia
Spinal Cord Lesions	Pheochromocytoma
Migraine Headaches	Medullary Carcinoma of Thyroid
Parkinson's Disease	Pancreatic Tumors
Menopausal Flushing	Renal Cell Carcinoma
Cholinergic Erythema	Horseshoe Kidneys

Table 9. **Systemic Antibiotics in Rosacea**

First-Line Antibiotics Tetracycline Minocycline Doxycycline Erythromycin
Second-Line Antibiotics Trimethoprim-Sulfamethoxazole

otic to help alleviate erythema and gain control of inflammatory lesions. Table 9 lists the first- and second-line oral antibiotics used in rosacea management.

Typically, papules, pustules and sometimes nodules and plaques respond rapidly and completely to systemic tetracyclines. If not, agents from the second tier may be tried. Telangiectasia and phymatous changes are unaffected by systemic antibiotics.

Topical metronidazole, an imidazole with anti-inflammatory and antimicrobial effects is considered the workhorse of topical rosacea therapies and is the most widely studied therapy. Its mechanism of action in rosacea is unclear. It has been suggested that its effects in rosacea may be related to inhibition of neutrophil-generated inflammatory mediators and free radicals[37,38]. Metronidazole is effective against papules and pustules and may, in some patients, reduce erythema. Similar to other topical therapies and oral antibiotics, it is rarely effective for telangiectasias.

Since rosacea is a recurring and potentially progressive disease, maintenance therapy is essential following initial systemic antibiotic use or light- or laser-based therapy. Topical metronidazole has been shown to be effective in maintaining remission. In a 2-phase study, patients who were initially treated with systemic tetracycline in combination with topical metronidazole, were later included in a blinded 6-month study comparing metronidazole gel 0.75% [Metro®Gel] to placebo vehicle. Topical metronidazole was significantly superior to vehicle in maintaining remission (43% relapsed vs 23% relapsed) and in reducing lesion counts. Relapse of erythema was also less frequent in patients treated with metronidazole (74% vs 55%)[39]. Metronidazole is available as a cream [Metro®Cream 0.75%, Noritate® 1%], gel [Metro®Gel 0.75%] and lotion [Metro®Lotion 0.75%]. It is generally well tolerated at both dosages and in all three formulations.

Sodium sulfacetamide 10%/sulfur 5% combinations have been recommended for more than 40 years. This combination is approved for treatment of acne, seborrheic dermatitis and rosacea. Sulfonamides act as competitive antagonists to para-aminobenzoic acid (PABA) which is essential for bacterial growth[40]. It is therefore useful as an antibiotic-sparing strategy, and there is no limitation on its duration of therapy. Sodium sulfacetamide 10%/sulfur 5% combinations also have comedolytic and keratolytic activity which makes it an appropriate adjunct for rosacea with an overlap of acne and/or seborrheic dermatitis. Sodium sulfacetamide 10%/sulfur 5% combinations are not generally regarded as effective monotherapy except in mild cases of rosacea, although studies have shown 78% and 81% reductions in inflammatory lesions and an 83% decrease in facial erythema at 8 weeks of treatment[41,42]. In an 8-week study comparing sodium sulfacetamide 10%/sulfur 5% to metronidazole 0.75% gel, papule/pustule scores, erythema ratings and overall severity were lower in the sodium sulfacetamide 10%/sulfur 5% group. Patient global evaluations of improvement were similar and tolerability was favorable and similar for both agents[43].

A sodium sulfacetamide 10%/sulfur 5% cleanser is available and has been shown to be useful in rosacea management. When the cleanser was used alone or in combination with metronidazole 0.75% twice daily in an 8-week, investigator-blinded trial, the cleanser alone was found to be efficacious as monotherapy for reducing papule counts and erythema. However, when used in combination with metronidazole, better results were obtained in reducing papule counts and overall rosacea severity[44].

The use of the sodium sulfacetamide 10%/sulfur 5% cleanser is advantageous for the treatment of rosacea, acne and seborrheic dermatitis or combinations thereof. The product is applied to moistened skin and massaged for 10-20 seconds and rinsed twice daily. It may be used in both the active treatment phase and in maintenance. The only contraindication is for patients with a known hypersensitivity to sulfonamides, sulfur or other components. In a recent trial comparing 5 topical products for the treatment of rosacea (sodium sulfacetamide 10%/sulfur 5% cream with sunscreens, sodium sulfacetamide 10%/sulfur 5% suspension without sunscreens, metronidazole 0.75% cream and gel and metronidazole 1% cream) all products were found to produce little irritation following a 21-day cumulative irritation patch test. However, the sodium sulfacetamide 10%/sulfur 5% product with sunscreen produced significantly less irritation than a comparative product without sunscreens ($p<0.001$)[45].

Azelaic acid is a naturally-occurring dicarboxylic acid that has been used in the treatment of acne and melasma. Its anti-inflammatory activity has led to investigation of its use in roseacea. An 8-week multicenter, double-blind, randomized, parallel group study comparing 15% azelaic acid gel to 0.75% metronidazole gel found the azelaic acid to be superior in reducing mean nominal lesion count and mean inflammatory lesion percent. Erythema severity was improved in 56% of azelaic acid-treated patients versus 42% of metronidazole-treated patients. Neither treatment produced notable improvements in telangiectasias[46]. Azelaic acid is available as a 15% gel [Finacea™] or 20% azelaic acid creams [Finevin®, Azelex®].

Surgery and Light-Based Therapies

Telangiectasia and phymatous changes, most notably rhinophyma, are not manageable with topical or systemic therapy. Their treatment has traditionally been surgical. Telangiectasia have been treated by electrodestructive methods or with lasers targeted to vascular lesions such as the KTP, 1064 nm Nd:YAG, visible light lasers and intense pulsed light (IPL).

Phymatous changes can be treated using a variety of ablative lasers. A new approach has been the use of photodynamic therapy with ALA-PDT as is being used to treat actinic keratoses[47].

Skincare in Rosacea

As in the case of acne, appropriate daily skincare is an essential aspect of management. In addition to avoiding known triggers, patients should receive a regimen and a list of recommended products for cleansing, moisturizing and sun protection in addition to their medications. They, like acne patients, should be instructed to treat their skin very gently. Rather than rubbing, they should blot the skin dry, since rubbing can create a rosacea flare. They should use tepid rather than hot water which can strip oils from the skin and cause vasodilation of the blood vessels near the surface. The importance of sun protection and avoidance should be stressed.

Summary

Acne and rosacea are two very common skin disorders with several characteristics in common which make it useful to discuss them together and for which similar treatment paradigms can be applied. Both are essentially inflammatory in nature. Both present with papules and pustules, and both can cause severe psychosocial disability. For both diseases, combination therapy employing combinations of topical and systemic therapies are the treatment of choice.

For acne, current best practice mandates the early use of a topical retinoid for all patients so as to normalize the follicle, treat existing comedones and prevent the formation of new ones, as well as to modulate inflammation and enhance the penetration into the follicle of other topically applied agents. In cases where inflammatory lesions are present, a topical or systemic antibiotic is also required for the shortest interval possible so as to minimize the risk of acquiring resistant bacterial variants.

Topical therapy with metronidazole is the standard and most widely used topical agent for rosacea, but an oral antibiotic may be required to more rapidly clear papules and pustules in all but the most mild cases. As in acne treatment, the use of systemic antibiotics should be discontinued as early as possible after the presenting lesions have resolved. Azelaic acid 15% gel and sodium sulfacetamide 10%/sulfur 5% either as a topical lotion or a cleanser have also been shown to confer benefits similar to those obtained with topical metronidazole in rosacea.

The new paradigm that is emerging, however, is the use of laser or light-based modalities in combination with the topical/systemic regimens to improve and hasten the cosmetic results obtained with conventional therapy. As this combination of prescription and procedural therapy becomes more commonplace, there will be continued evolution in the ways in which light-based therapies can be optimally combined with topical and systemic regimens. The use of conventional topical therapies is essential to maintain the remission obtained with the combined conventional and procedural treatment regimens.

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Combination Therapy for Solar Lentigines

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Abstract

Solar lentigines are benign, hyperpigmented lesions that present a significant cosmetic nuisance for many middle-aged and elderly patients with chronic accumulated sun exposure. While previous monotherapies designed to lighten these lesions offer relatively modest improvement, there are several new treatment options. Combination topical therapy using 2% mequinol/0.01% tretinoin [Solagé® Topical Solution] has been shown to markedly reduce lesion darkness with few side effects. Chemical peels can give good results either alone or in combination with topical therapy. Cryotherapy is an effective and inexpensive way of treating solar lentigines while IPL and lasers are more costly treatment options. For patients desiring treatment, optimal cosmetic improvement can be achieved using a combination of topical and procedural therapies.

Introduction

Solar lentigines, also termed senile lentigines, are extremely common hyperpigmented macular lesions, ranging from pale yellow to dark brown, that appear on sun-exposed areas of the body (Figure 1). Solar lentigines are most common on the dorsa of the hands, the forearms, and the face. They are characterized by increased numbers of active melanocytes and increased melanin production resulting from years of cumulative sun exposure[1]. They are virtually ubiquitous in elderly Caucasians and appear in 90% of light-skinned individuals over the age of 60[2].

Although benign, solar lentigines pose a significant cosmetic problem for many patients. Not only do they detract from the appearance when they are present in large numbers, but many people associate them with aging. The lay terms for these lesions are "age spots" or "liver spots." Due to their benign nature, many dermatologists and family physicians downplay them to patients. However, it is important to understand the level of psychosocial stress that may attend solar lentigines and to offer treatment to those patients who are distressed by these lesions.

The ideal therapy for lentigines would be inexpensive, achieve results rapidly, involve no down-time and have no risk of complications. No perfect therapy exists, however, there are numerous treatment options. Their selection depends upon patient factors including budget, ability to comply with therapy and time constraints.

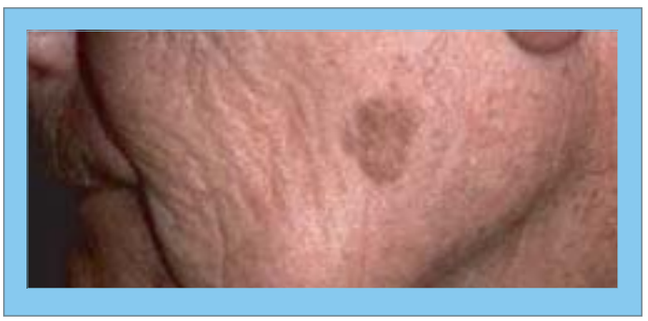

Figure 1. Solar Lentigines

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Topical Therapies

A variety of topical monotherapies have been used to treat solar lentigines including hydroquinone, topical retinoids, and kojic acid. However, a long latency is required before their results become visible and many patients become discouraged before significant improvement occurs. Hydroquinone monotherapy is minimally effective for lentigines and may cause irritation.

Combination topical therapy offers a significant advantage over monotherapy. It is an inexpensive option for patients who may not be able to make frequent office visits. It requires a relatively long treatment period, and diligent compliance with therapy is essential for their success.

A dual-combination topical solution of 2% 4-hydroxyanisole (mequinol) and 0.01% tretinoin [Solagé® Topical Solution] has been introduced for the treatment of lentigines and other hyperpigmented lesions. Mequinol has been shown to be less irritating than hydroquinone in animal studies and has no known cytotoxicity to human melanocytes[3]. The efficacy and safety of the combination mequinol/tretinoin product in the treatment of solar lentigines was studied in two phase III randomized, controlled double-blind trials[4]. The first trial consisted of a 24-week treatment phase followed by a 24-week no-treatment regression phase to study the duration of effect. The study enrolled 595 subjects whose mean age was 62.6 (± 9.51 SD) years. The patients were randomized to receive either mequinol/tretinoin (n=217), tretinoin alone (n=217), mequinol alone (n=106), or vehicle (n=55). The second Phase III trial included a 24-week treatment phase followed by a 4-week no-treatment phase. It enrolled 580 subjects whose mean age was 63.9 (± 9.14 years). There were 212 subjects in the mequinol/tretinoin group, 210 in the tretinoin group, 105 in the mequinol group and 53 in the vehicle group. Lightening of the treated lesions occurred gradually over 24 weeks.

In both trials, the mequinol/tretinoin combination was clinically superior to monotherapy with either of its components and vehicle on the forearm and face ($P \leq .03$). In Trial 1, 52% and 56% of the mequinol/tretinoin group achieved moderate or better clinical success, by physician's global assessment, on the face and forearms compared with 35% and 43% in the tretinoin group, 24% and 33% for the mequinol group and 17% and 19% for vehicle. The combination formulation continued to demonstrate statistically significant superiority ($P \leq .003$) to each of its active ingredients alone and to vehicle. It was also superior to each of its active components and vehicle for "target lesion pigmentation" and "physician's assessment of overall cosmetic effect" for forearms and face. In Trial 2, the mequinol/tretinoin combination demonstrated significant superiority in the physician's global assessment over each of its active ingredients and vehicle on the forearm at the end of treatment. For the face, the combination formulation achieved significant superiority over mequinol and vehicle ($P=.0001$) and was directionally superior to tretinoin in achieving moderate or greater improvement. However, the difference (57% vs 48%) was not statistically significant ($P=.2$).

Most of the treatment-related adverse effects were mild or moderate in intensity. Erythema, burning/stinging/tingling, desquamation and pruritus were the most common adverse events in the mequinol/tretinoin group. Hypopigmentation of treated skin occurred in 5% of patients, and hypopigmentation of the surrounding skin occurred in 7%. However, the majority of these resolved upon discontinuation of application to the lesion and/or re-instruction on correct application to the lesion only. Hypopigmentation resolved in another 8% of patients within 120 days following treatment discontinuation.

The treatment effect was well maintained. At the end of the 24-week regression phase, 70% of treated lesions on the face and 56% of the lesions on the forearms maintained their level of improvement. However, the authors of the study noted that some of the patients began to show signs of repigmentation suggesting the need for retreatment in some patients. Two advantages of this topical combination therapy are the ability to control the depigmenting effect and the ability to treat multiple lesions over large areas since individual lesions are treated rather than the whole field. At our clinic, many patients see visible improvement at 3-4 weeks, with significant improvement at 6-8 weeks.

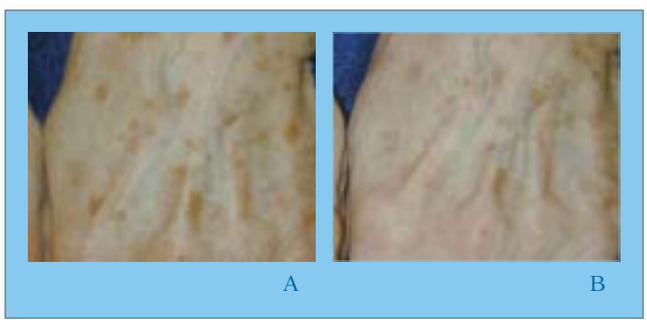

Figure 2. Baseline Solar Lentigines and Post-Cryosurgery

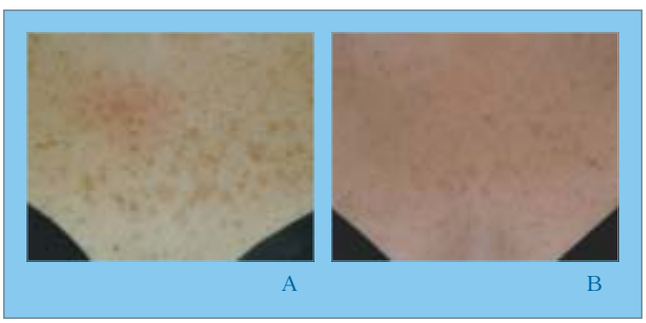

Figure 3. Sunburn Lentigines at Baseline and Following 2 IPL Treatments

Cryotherapy and Peels

Cryotherapy remains the standard in-office procedure for the treatment of solar lentigines. Its main drawbacks are the level of discomfort experienced by some patients, erythema and crusting during healing, prolonged healing time, especially on the legs, and the need for multiple treatments. In addition, operator skill is an issue since it is possible to cause hypopigmentation with overzealous freezing. Multiple light dustings provide better results. Cryotherapy results can be seen in Figure 2.

Chemical peels using either glycolic acid, trichloracetic acid (TCA) or Jessner's solution are a highly effective treatment option for treating solar lentigines. TCA is one of the most frequently used peeling agents and can be used at concentrations ranging from 10%-35% depending upon the area to be treated. While diffuse lentigines on the chest and forearms are best treated with a series of lighter peels, lentigines on the face are often treated with medium depth peeling agents. There will be some downtime following medium depth peeling since healing takes 5-7 days. There is always a risk of hyper- or hypopigmentation after chemical peeling so close follow-up is necessary in the post-procedural period. Vigilant sun avoidance after the peeling procedure will minimize the risk of hyperpigmentation.

An open-label, randomized trial of 10 patients with solar lentigines on the dorsa of the hands examined the combined use of a 25% to 35% trichloracetic acid (TCA) peel and cryotherapy with liquid nitrogen, followed by treatment with mequinol 2%/tretinoin 0.01% to determine if it improved or maintained the results of the procedures. Patients ranged in age from 50 to 72 years with Fitzpatrick skin types I-IV[5]. After 30 days of treatment with TCA/cryotherapy, study subjects were dispensed the mequinol 2%/tretinoin 0.01% topical solution to apply to the lesions of one hand twice daily. No sunblocks were applied so that the effects of the pharmacologic treatment could be studied alone. Response to therapy was rated by both the investigator and patients based on a 4-point scale: 0= no improvement; 1=discrete improvement; 2=moderate improvement; and 3= marked improvement. Both investigator and patient evaluation of treatment noted that the effects of the procedural therapy were maintained or improved with the pharmacologic treatment. At a 10-month telephone follow-up, patients were asked to assess their level of improvement. One patient noted 100% resolution while 3 patients noted 90% resolution. The author of the study suggested that the use of a broad- spectrum sunblock might have increased the rate of resolution by preventing the formation of new lentigines.

The pharmacologic treatment was well-tolerated. The patient who achieved 100% resolution of lesions showed a discrete residual hypochromia at 6 months after the initial treatment and was attributed to cryotherapy.

Intense Pulsed Light and Lasers

Intense pulsed light (IPL) meets several of the criteria for the ideal treatment for solar lentigines in that it is highly efficacious with virtually no downtime. Figure 3 depicts a patient with diffuse lentigines on the chest at baseline and following two treatments with IPL. Although not completely cleared, it is evident that significant improvement has occurred. One drawback to IPL is cost – and it is time consuming requiring multiple treatment sessions. Individual lesions do become accentuated after IPL treatment, and fading occurs over the ensuing weeks. As with all laser and light based technologies, patient selection is important. Lighter skinned patients generally have the best results and are less at risk for developing dyschromia after IPL. Figure 4 shows hypopigmentation which developed on the forearm of a patient who received a single IPL treatment. This patient has skin type IV and a background of diffuse hyperpigmentation due to photodamage. The case illustrates the importance of proper patient selection when using IPL.

Lasers are also useful for treating benign pigmented lesions such as lentigines. The most commonly used lasers include the QS ruby (694 nm) and the QS alexandrite (755 nm). Caution must be used when treating patients with darker skin types as hypopigmentation and depigmentation can occur. Although highly effective, laser treatments are similar to intense pulsed light in that they are expensive and may require multiple treatments.

Combination Procedural and Topical Therapy

Treatment that combines procedures such as cryotherapy, lasers or IPL with topical therapy is a significant advance in the treatment of solar lentigines. Not only does topical therapy minimize the development of post-inflammatory hyperpigmentation (PIH), it also helps maintain remission in conjunction with continuing sun protection.

A recent open-label study examined the use of "puff" cryotherapy using the brush technique for the treatment of solar lentigines on the dorsum of the hand[6]. The cryotherapy was delivered

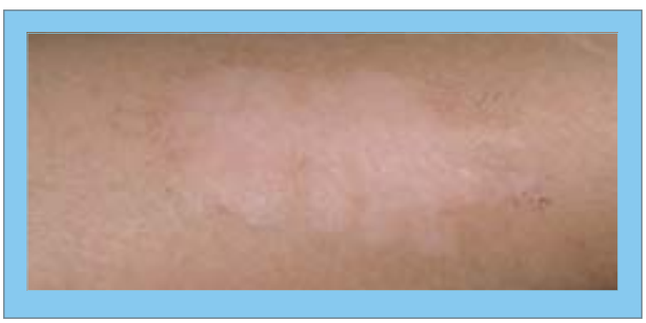

Figure 4. Hypopigmentation Following IPL

Figure 5. Patient at Baseline

Figure 6. Patient at Week 6 with Solagé® Topical Solution

Figure 7. Patient at Week 12 with Solagé® Topical Solution

via a specialized spray tip that lightly paints the area to be treated. Rather than focusing on individual lesions, the operator lightly and evenly sprays the whole dorsa of the hand. The thaw time was 1-2 seconds. Cryotherapy was followed by application of 2% mequinol/0.01% tretinoin topical solution after the cryotherapy session for 6 weeks. At 6 weeks, cryotherapy was repeated and mequinol/tretinoin was continued for another 6 weeks.

Twenty-four Caucasian patients (mean age 64.7± 8.6 years) were entered in the study. Subjects had at least 3 solar lentigines which were at least Grade 6 (moderately darker than surrounding skin). Table 1 shows the investigator's global severity assessments at 6 and 12 weeks. Five of 22 patients had complete clearing, 8 were almost clear, 8 showed marked improvement, and one showed only moderate improvement.

At study end, 64% of the subjects were "very satisfied" with the results of treatment while 36% were "satisfied." Figures 5-7 show the results obtained in a patient from a baseline lesion pigment score of 7 to 5 at week 12.

Table 1. **Investigator's Global Severity Assessments Weeks 6 and 12**[6]

Global Severity Score	6 Weeks*	12 Weeks*
5 - clear	0	5
4 - almost clear	0	8
3 - marked improvement	2	8
2 - moderate improvement	15	1
1 - minimal improvement	6	0
0 - no change from baseline	0	0
-1 - worse than baseline	0	0
Not Recorded	1	2
Mean Score	1.83	3.77
Median Score	2	4

*** Indicates number of patients**

Summary

Solar lentigines are a cosmetic problem for some 20 million Americans. While topical monotherapies previously used to treat them were relatively inadequate, several new treatments can offer excellent results. A new product which combines 2% mequinol/0.01% tretinoin confers significant improvement at a relatively low cost and with no down-time. The mequinol/tretinoin combination has shown to be superior to either of its ingredients alone in the management of solar lentigines. This product can be used alone or in combination with cryotherapy, IPL or laser therapy. In this setting it minimizes the risk of recurrence and PIH that can occur with these therapies and maintains lesion lightening.

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Utilizing Combination Therapy to Optimize Melasma Outcomes

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Abstract

Melasma is a chronic and recurrent disorder. It has been underdiagnosed and undertreated due to lack of effective therapies and the perception that it is merely a cosmetic nuisance. Hydroquinone, corticosteroids, licorice extracts and kojic acid have been used as monotherapy to treat melasma. However, the present standard of care in melasma therapy is combination therapy. To date, the most effective treatment is a triple-combination agent that contains hydroquinone 4%, tretinoin 0.05% and fluocinolone acetonide 0.01%. In clinical trials, its use led to complete or near-complete clearing of melasma in 8 weeks. A long-term study demonstrated its continuing efficacy and safety for as long as 360 days. In an examination of quality of life parameters, patients using the triple-combination cream showed significant improvements in self-perception by all 1290 patients. Various combinations of melasma therapy, such as chemical peels, particularly as adjuvants to the triple-combination cream, are discussed.

Introduction

Melasma is a common acquired hypermelanosis predominantly of the face and neck and, occasionally, the forearms. According to the American Academy of Dermatology, 5-6 million American women have melasma. Melasma is primarily a disease of women of child-bearing age although 10% of cases occur in men[1]. It occurs in all skin types but is most common in Fitzpatrick skin types IV-VI, with dark-haired women more susceptible. Its racial distribution is centered among Hispanic, Asian, Indian, African and African-American peoples[2].

Melasma has largely been underdiagnosed and therefore undertreated in the United States. This is partly attributable to the fact that many physicians consider melasma a "nuisance" rather than a medical problem or one with significant psychosocial impacts. While dermatologists are the specialists most likely to treat melasma, obstetricians and gynecologists (OB/GYNs), family practitioners or internal medicine doctors also see patients with melasma[3]. As it frequently develops during pregnancy, many women first present with melasma during visits for prenatal care. Many physicians outside the dermatologic community have not been aware of available treatments and therefore, have typically not addressed the problem unless asked, or have reassured their patients that the hyperpigmentation would fade after delivery. Likewise, many women with melasma do not ask their physicians about their symptoms and do not visit a dermatologist specifically to address the problem. Due to cultural and ethnic misperceptions about skin diseases in general, particularly disorders of pigmentation, affected individuals may not ever seek help for what is a treatable, though chronic, condition.

Melasma has a significant cosmetic impact for many women. However, it also carries a psychosocial burden. It is particularly distressing to women from cultures which favor flawless, evenly pigmented skin. In some Asian cultures, facial pigmentary abnormalities are associated with bad luck. Melasma and other dyspigmentation is also extremely distressing to women in Latin cultures where such stigmata are frequently associated

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with ill health or poor nutrition. Pigmentary abnormalities are considered disfiguring in Latin cultures where women tend to be especially beauty-conscious. Latina women have the highest prevalence of melasma[2,3].

Melasma Etiology

While the precise etiology of melasma is unknown, multiple factors have been implicated. They include genetic influences, exposure to ultraviolet (UV) and visible light radiation, female hormones in the settings of pregnancy, oral contraception (OC) and post-menopausal hormone replacement therapy (HRT), thyroid autoimmunity, cosmetic ingredients and phototoxic drugs[3]. UV radiation and genetic influences have been suggested to be the most important pathogenic factors[4]. UV radiation increases melanocyte size, tyrosinase activity and the transfer of melanosomes to keratinocytes. These changes may occur as a consequence of DNA repair.

Melasma is estimated to occur in 50%-70% of pregnancies among US women, usually during the 2nd or 3rd trimester[5]. No specific genetic studies have been conducted, but there is a higher incidence in patients with a significant family history (mothers and daughters) as well as in women with skin of color and pigmented races living in areas of high insolation[6].

Among Mexican women, the incidence is estimated to be about 80%, with more than one-third of these patients having the disease for life[7]. However, melasma subsequent to OC use typically does not clear and may last up to 5 years following termination of therapy[6]. Other evidence regarding hormonal influences includes the finding of significantly increased levels of luteinizing hormone and reduced serum estradiol suggestive of mild ovarian dysfunction[8]. Lufti et al found an incidence of thyroid disorders 4 times higher in patients with melasma than in controls. Moreover, there was also a significant association between the development of melasma during pregnancy or subsequent to OC use and thyroid autoimmunity[9].

Figure 1 depicts the interplay of these three pathogenic factors in the increased pigmentation of melasma. Melanocytes in melasma are hyperactive and increase in number. They form melanosomes which are transferred to the dermis and epidermis leading to the characteristic hyperpigmentation.

Melasma Treatment

Sun Protection

The goals of melasma therapy are: 1) to retard the proliferation of hyperactive melanocytes, 2) inhibit the formation of melanosomes, 3) promote the degradation of melanosomes and 4) protect the skin from UV radiation (Table 1).

While there is now highly efficacious treatment available for melasma, sun protection is an equally vital component of melasma management. Therefore, patient education is essential to an optimal melasma management regimen. Patients must be counseled that melasma is a chronic, relapsing disease. Sunscreens must be used whenever they are outdoors. In addition, a hat, protective clothing and sunglasses should be worn and overall sun avoidance practiced assiduously. Patients should be aware that even following successful melasma treatment and clearance of lesions, one weekend of sun exposure can lead to a complete recurrence.

Broad-spectrum sunscreens that offer protection against both UVA and UVB light should be used. Sunblocks that combine chemical sunscreens such as Parsol® with a physical block such as zinc oxide or titanium dioxide should be used. A physical sunblock is essential, because melasma can be exacerbated by heat. Physical sunblocks reflect light rather than converting it to heat energy within the skin. Many cosmetics now contain sun protection factors, making foundation and powders a good adjunct, but insufficient for sun protection on their own. Novel approaches to sun protection, which can be used as adjuncts, include the use of green tea extracts, topical vitamin C, fish oil, and beta-carotene[10-12].

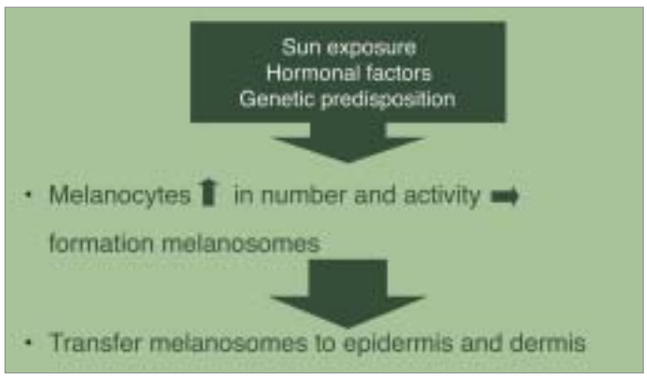

Figure 1. Melasma Pathophysiology

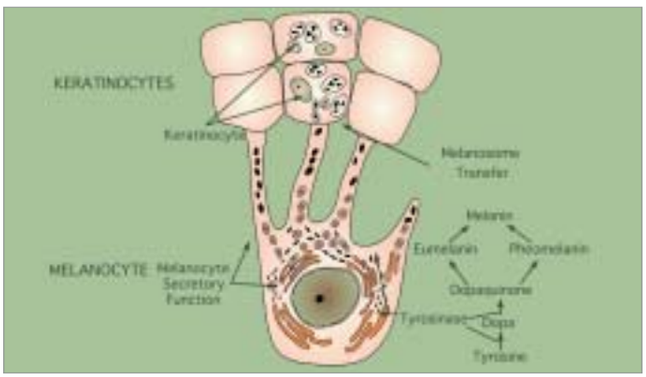

Figure 2. Epidermal Melanin Unit

Polypodium leucotomos (PL) extracted from a fern is a novel oral sun protection agent that has been found to increase the skin's tolerance to the effects of UV radiation[13]. It acts as an antioxidant and prevents actinic erythema. It also acts as an immune modulator by inhibiting UV-induced depletion of epidermal Langerhans cells as well as the inflammatory mediators such as tumor necrosis factor alpha.

Pharmacologic Therapies

A variety of topical agents have been used to treat melasma. They include phenolic hypopigmenting agents such as hydroquinone, mequinol and N-acetyl-4-cysteaminylphenol (NACAP), as well as non-phenolic hypopigmenting agents such as tretinoin, azelaic acid, alpha- and beta-hydroxy acids and topical corticosteroids. In addition, cosmeceutical agents such as kojic acid, arbutin, licorice extracts and mulberry and bearberry have been used. New compounds include nicotinic acid, niacinamide-Vitamin D3, and 4-n-butylresorcinol which affects melanosome transfer to keratinocytes and is widely used in Japan. Non-selective suppression of melanogenesis can be achieved with indomethacin and systemic corticosteroids.

Figure 2 shows the effects of these molecules at different levels of the pigmentation pathway[14]. Glycolic and alpha- and beta-hydroxy acids act at the level of keratinocytes to remove pigment whereas tretinoin inhibits melanosome transfer. Hydroquinone, azelaic acid and kojic acid all act as tyrosinase inhibitors.

Monotherapy for Melasma

While the current trend is toward combination therapy for melasma, a variety of monotherapies have proven useful in its management over the years. Hydroquinone has been the standard of topical therapy of melasma for over 50 years. It blocks melanogenesis by competitive inhibition of tyrosinase which prevents the conversion of dopa to melanin. It may also inhibit DNA and RNA synthesis, degrade melanosomes and destroy melanocytes[3,6,15]. In the US, hydroquinone is sold over-the-counter (OTC) in concentrations up to 2%. Prescription-strength hydroquinone is generally 3%-4%, although higher concentrations can be obtained through compounding pharmacies. Typically 4-6 weeks are required before a response is visible. Hydroquinone can be irritating, particularly at higher concentrations. Its most feared side effect is the development of exogenous ochronosis, a chronic, disfiguring sooty pigmentation of the face, characterized by articulated, ripple-like pigmentation of the face. Histologically, collagen and elastin fibers degenerate leading to the characteristic ochronotic deposits in the dermis[3,6].

Although hydroquinone has been used as monotherapy, it is generally combined with other agents for improved efficacy. For example, several products combine hydroquinone with glycolic or salicylic acid, antioxidants such as vitamins C or E and/or sunscreen. The most frequently used formulation is based on a depigmenting formulation proposed by Kligman and Willis in 1975[16]. It combined hydroquinone 5%, tretinoin 0.1% and dexamethasone 0.1%. Other investigators have substituted different corticosteroids and have modified the concentrations of tretinoin and hydroquinone.

Table I. **Goals of Melasma Therapy**

- Retard Proliferation of Hyperactive Melanocytes
- Inhibit Formation of Melanosomes
- Promote degradation of melanosomes
- Protect Skin From UV Radiation

Tretinoin has been found to be effective as monotherapy. Like glycolic acid and topical steroids, it accelerates cell turnover in the epidermis, thereby reducing the amount of time cells have to acquire pigment[16]. In a small series, Kimborough-Green and co-workers found that 73% of African Americans with melasma were improved or much improved following 40-weeks of treatment with 0.1% tretinoin versus 46% of controls. Statistically significant lightening was first noted at 24 weeks and side effects were minimal[17]. However, use of tretinoin monotherapy at concentrations of 0.05% and 0.1% is frequently associated with dermatitis and post-inflammatory hyperpigmentation (PIH). An additional advantage of tretinoin in a depigmenting regimen is its beneficial effect on photodamage.

Topical corticosteroids are usually not used as monotherapy to treat melasma although they do have their own skin bleaching action[18]. They likely act by suppressing secretory metabolic products from melanocytes without causing their destruction. When used with caution, topical corticosteroids can be useful to reduce irritation in Hispanic and Asian patients whose skin is especially sensitive. Drawbacks to their use as monotherapy for melasma include the typical adverse events associated with topical corticosteroids on the face including the development of telangiectasia, acneiform eruptions, and skin atrophy. Patients receiving topical corticosteroids should be monitored for the development of side effects every 2-4 weeks. If adverse events are encountered, the steroid concentration should be decreased.

Other monotherapies that have been used with some success in melasma include azelaic acid, a naturally occurring dicarboxylic acid synthesized by the yeast *Malassezia furfur* from lipids in the skin. It has been used widely in the treatment of acne. It is a weak competitive inhibitor of tyrosinase in vitro with antiproliferative and cytotoxic effects on melanocytes. In a study of dark-skinned patients with facial hyperpigmentation, azelaic acid 15% and 20% combined with glycolic acid was as effective as 4% hydroquinone[19]. The patients receiving azelaic acid had a slightly higher rate of local irritation. Azelaic acid is currently being used sequentially with super-potent topical steroids. A review of recent studies of the use of azelaic acid in

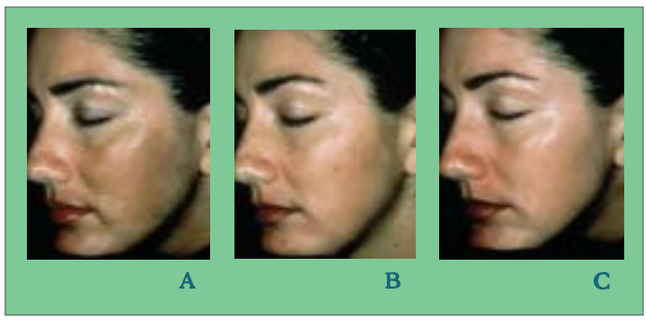

Figure 3A. Hispanic Patient at Baseline of Triple-Combination Cream Therapy
Figure 3B. Hispanic Patient at 4 Weeks of Triple-Combination Cream Therapy
Figure 3C. Hispanic Patient at 8 Weeks of Triple-Combination Cream Therapy

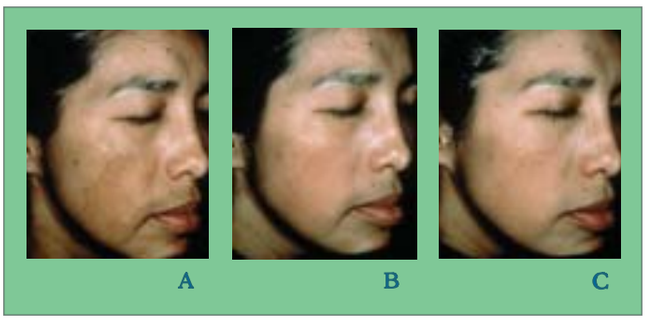

Figure 4A. Hispanic Patient at Baseline of Triple-Combination Cream Therapy
Figure 4B. Hispanic Patient at 4 Weeks of Triple-Combination Cream Therapy
Figure 4C. Hispanic Patient at 8 Weeks of Triple-Combination Cream Therapy

melasma showed good-to-excellent clinical responses in 73%-65% of patients who were treated for 6 months[20].

Kojic acid is derived from the fungus, aspergillus oryzae. It inactivates tyrosinase by chelation of copper. Melanocytes treated with kojic acid become nondendritic and melanin content decreases. Although it is effective at concentrations of 1%-4%, it has a high sensitizing potential and can cause irritant contact dermatitis[6,21].

Combination Therapy for Melasma

The original combination therapy for melasma was that developed by Kligman and Willis in 1975[16]. It consisted of 5% hydroquinone, 0.1% tretinoin and 0.1% dexamethasone in a hydrophilic ointment. Other similar formulations were developed using different concentrations of tretinoin or different corticosteroids. However, these combinations, made at compounding pharmacies were not standardized, unstable and prone to oxidation. The first triple-combination topical therapy to receive FDA approval for the treatment of melasma (Tri-Luma® Cream) contains hydroquinone 4%, tretinoin 0.05% and fluocinolone acetonide 0.01%. The latter is a low potency Class VI fluorinated steroid.

This triple-combination takes advantage of the additive and synergistic effects of the three components first noted by Kligman and Willis[16]. Tretinoin-induced irritation may facilitate the penetration of hydroquinone and also overrides the atrophy-promoting and anti-mitotic effects of the corticosteroid component while the corticosteroid appears to antagonize stratum corneum thinning and to reduce retinoid-induced irritation, thus improving tolerability. Figures 3A-C and 4A-C show the results obtainable in a Hispanic and an Asian patient with the triple-combination therapy beginning with baseline and up to 8 weeks of therapy.

In two multicenter studies that enrolled 641 patients with mild-to-moderate facial melasma, 28% achieved complete clearing in 8 weeks while 78% achieved complete or near-complete clearing in 8 weeks[22]. The triple-combination cream was also compared with dyads consisting of two of its constituent components. Table 2 shows the rates of complete clearing at 8 weeks for each of the treatment dyads versus those that were obtained with the triple-combination cream.

The triple-combination cream was well tolerated. Treatment-related adverse events at week 8 consisted largely of erythema, desquamation, burning, dryness and pruritus. The incidence of possible steroid-related adverse events was also relatively low. Only one patient (in the hydroquinone+ fluocinolone acetonide group) developed skin atrophy. Most instances of telangiectasias were mild and occurred in patients who had them before enrolling in the trial (Table 3).

A 12-month, open-label continuation study was conducted to assess the long-term safety of the triple combination formulation, but investigator and patient assessments of efficacy were also collected[23]. A total of 797 patients were enrolled, including 569 patients who continued from the initial 8-week controlled clinical trial. Those who continued were patients who had achieved complete or near-complete clearing of their melasma or those who had not achieved satisfactory clearing. The latter group received once-daily treatment with the triple-combination cream and were followed at monthly intervals until they had achieved a satisfactory response or lack of response was demonstrated and treatment was terminated. They were followed every two months while off treatment. The patients who had achieved a complete or near-complete response in the initial trial were followed every two months and retreated as necessary when melasma reappeared. All patients used a broad-spectrum sunscreen with SPF 30 during the trial whether on or off treatment.

The triple combination cream was used for an average of 6.8 months. There were 415 patients who were treated for at least 180 days and 92 who were treated for 360 days. The majority of

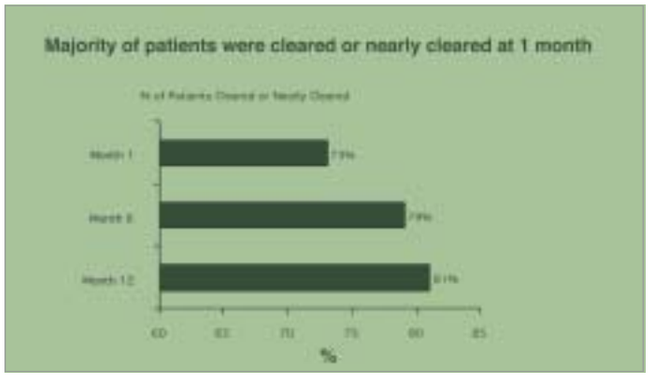

Figure 5. Triple-Combination Cream Long-Term Efficacy Results[23]

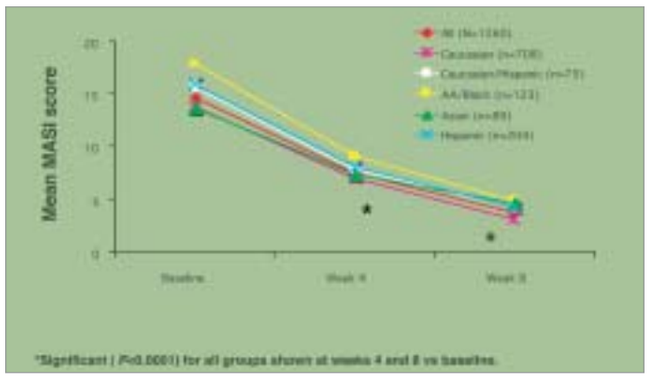

Figure 6. Overall Mean MASI Score by Race/Ethnicity[2]

the patients received two or more treatment courses. Some were retreated as early as one month. As in the original clinical trial, application-site erythema and desquamation were the most commonly reported adverse events. Most of the treatment-related adverse events were mild and transient and did not lead to study discontinuation. The incidence of treatment-related side effects was very low. The incidence of telangiectasia was 4% in the 92 patients with at least 360 days of treatment. All cases of telangiectasia were mild, and 15 of 23 had improved or resolved by study end while 8 were unchanged. The incidence of skin atrophy and acne were 0.6% and 8%, respectively in all 797 patients in the long-term study.

The triple-combination cream produced a highly significant reduction in MASI (Melasma Area and Severity Index) scores. This effect was consistent across all study groups for overall scores, darkness scores and homogeneity scores. Figure 5 shows the long-term efficacy results obtained in this study. At

Table 2. **Complete Clearing of Melasma Up To and Including Week 8[22]**

Triple-Combination Therapy	Tretinoin+ Hydroquinone	Tretinoin + Fluocinolone Acetonide	Hydroquinone + Fluocinolone Acetonide
28.6%	10.1%	1.9%	3.1%

Table 3. **Summary of Treatment-Related Adverse Events at Week 8[22]**

No of Pts With Adverse Event (%)	RA+HQ+FA N=161	RA+HQ N=158	RA+FA N=161	HQ+FA N=161
Erythema	66 (41)	69 (44)	26 (16)	41 (25)
Desquamation	61 (38)	97 (81)	40 (25)	6 (4)
Burning	29 (18)	36 (23)	33 (20)	5 (3)
Dryness	29 (18)	21 (13)	23 (14)	5 (3)
Pruritus	18 (11)	34 (22)	12 (7)	5 (3)
Atrophy	0	0	0	1 (6)
Total	102 (63)	126 (80)	104 (65)	55 (34)

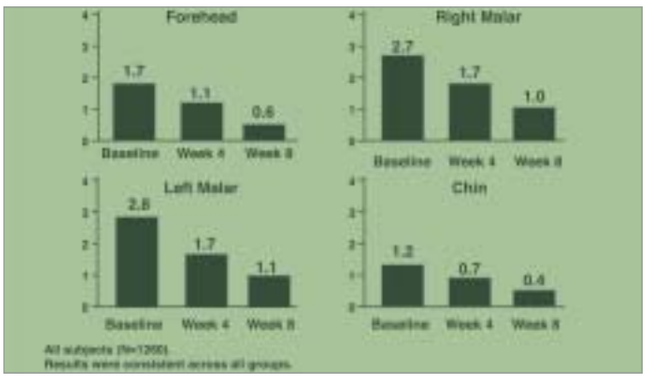

Figure 7. Mean MASI Darkness Score by Region[2]

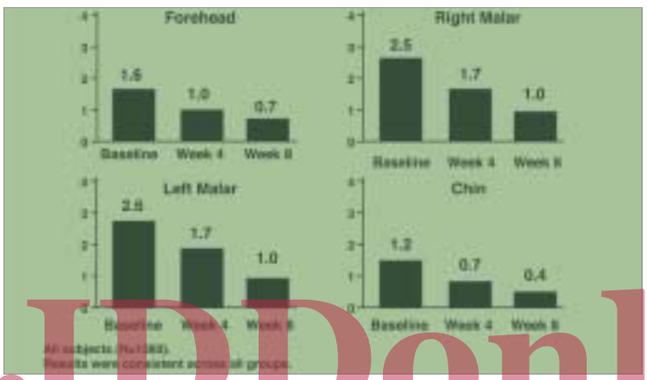

Figure 8. Mean MASI Homogeneity Score by Region[2]

month 1, 73% of the patients were cleared or nearly-cleared. At 6 months, 79% were cleared or nearly cleared while at month 12, 81% had achieved complete- or near-complete clearing. The response time was more rapid with each retreatment so that patients who were retreated required less time to achieve the desired result.

An open-label, community-based phase IV study examined the efficacy and safety, as well as changes in quality of life parameters of 1400 patients with moderate to severe facial melasma[2]. Assessments of melasma severity were made at baseline and at weeks 4 and 8. The overall mean MASI score by race/ethnicity showed a highly significant 75% reduction from 14.68 at baseline to 7.38 at week 4, and 3.64 at week 8 ($P<0.0001$) (Figure 6). The reduction was greater among Caucasians (-78%) and less among Asians (-67%). Improvements in darkness (Figure 7) and homogeneity (Figure 8) scores were similarly dramatic across all study groups. On Global Assessment, 30% of all patients were clear or almost clear by week 8.

The triple-combination cream [Tri-Luma® Cream] demonstrated a favorable safety profile in the intent-to-treat population of 1290 patients. The most common adverse events were erythema and desquamation and >99% were mild or moderate in severity. Of the possible corticosteroid-related adverse events,

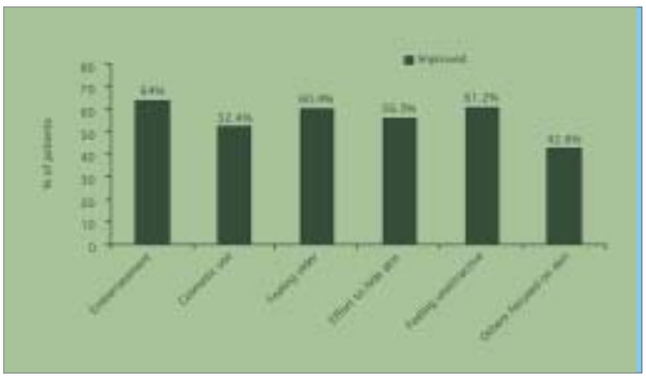

Figure 9. QOL Indices in Self-Perception Categories: All Subjects[2]

atrophy did not occur in any patient. The incidence of telangiectasia was <2%, and, in some cases, these lesions were pre-existing (Table 4)[22].

All subjects showed significant improvements in self-perception categories including "embarrassment," "cosmetic use," "feeling older," and "feeling unattractive" (Figure 9). Melasma's impact on quality of life has traditionally been under-appreciated by the medical profession yet it has been significant to many melasma patients, especially those from cultures where beauty and flawless skin are highly important.

Procedural Therapy

Chemical peels act in melasma by removing melanin. There are numerous options for chemical peels. Including 30%-35% trichloracetic acid (TCA) peels + hydroquinone, 20%-70% glycolic acid, 48% free glycolic acid + 30% TCA, modified Jessner's solution with hydroquinone + kojic acid—the so-called "Miami peel," and 20%-30% salicylic acid peels. It is important to note that while higher concentrations can be used in white skin, Hispanics, blacks and Asians require lower concentrations. Mild glycolic acid or salicylic acid peels will give good results in these patients while avoiding the risk of causing PIH.

Peels can be used as adjuvants or for enhancement as well as in recalcitrant cases. For example, in one study, 40 Indian patients with epidermal melasma received either a modified Kligman's formula (5% hydroquinone, 0.05% tretinoin and hydrocortisone acetate 1% in a cream base) plus serial glycolic acid peels or the modified Kligman's formula alone[24]. While both groups showed significant decreases in MASI scores from baseline to 21 weeks, the group receiving the combination treatments showed a statistically significant trend towards greater and more rapid improvement ($P<.001$).

Lasers act in melasma by disrupting melanin granules. While there are several types of lasers which can treat pigmentary abnormalities, their use in melasma is associated with equivocal or negative results, and their use remains controversial. In

Table 4. **Local Tolerance to Treatment: Non-Serious AEs**[22]

No. of Pts with AEs	All Subjects n=1290 16% (205)	African American n=127 12% (15)	Asian n=90 14% (13)	Hispanic n=205 21% (44)	Caucasian n=725 14% (102)	Caucasian/ Hispanic n=76 21% (16)
Erythema	5.7% (73)	3.1% (4)	8.9% (8)	7.8% (16)	3.9% (28)	9.3% (7)
Skin irritation	6.0% (77)	7.1% (9)	3.3% (3)	8.8% (18)	5.4% (39)	6.7% (5)
Dry skin	3.6% (47)	1.6%(2)	2.2% (2)	3.9%(8)	4.1%(30)	4.0%(3)
Atrophy	0	0	0	0	0	0
Telangiectasia	0.6%(8)	0	0	1%(2)	0.7%(5)	1.3%(1)

a study of 10 patients with melasma that was refractory to bleaching creams and chemical peels, full face laser resurfacing was performed using an erbium YAG laser using a fluence of 5.1-7.6 J/cm^2 [25]. There was an initial marked improvement in MASI scores and melanin reflectance spectrometry. However, between weeks 4 and 6 postoperatively, all 10 patients developed PIH which was worse than the initial melasma. All improved following biweekly glycolic acid peels, topical azelaic acid cream and sunscreens. However, the authors warned that the development of PIH necessitates prompt and persistent intervention to reverse it. They note that the use of this laser therapy should be reserved only for recalcitrant melasma.

Nouri and co-workers conducted a comparison study of the combination of pulsed CO_2 laser at 300 mJ/cm^2 versus pulsed CO_2 followed by another pass with the Q-switched alexandrite pigmented dye laser[26]. All 4 patients in the combination therapy group showed complete resolution of melasma within the treatment area. In the CO_2 only group, 2 of 4 patients developed peripheral hyperpigmentation. The authors suggest that this may be due to lower energy at the edges leading to PIH in areas with intact melanocytes. However, in both treatment arms, all patients showed complete resolution of melasma within the treatment area.

Therapeutic Approach in Melasma

The choice of treatment for melasma depends upon the area of involvement and the intensity of pigmentation. The new trend is the use of combination topical therapies as well as the combination of topical therapies plus procedures such as peels. Figure 10 presents a treatment algorithim for the management of melasma according to its severity. Mild melasma can be treated with hydroquinone with or without glycolic acid or with azelaic acid. Moderate melasma can be treated with hydroquinone plus tretinoin or another retinoid such as adapalene [Differin®]. Severe melasma requires treatment with the triple-combination cream [Tri-Luma® Cream]. Chemical peels or microdermabrasion may be helpful in some cases with the caveat that darker complexions should receive relatively gentle chemical peels. In most cases, lasers do not add benefits to treatment and may result in the development of PIH.

Essential for all treatment regimens is maintenance therapy to prevent repigmentation of treated areas. The use of retinoids or azelaic acid in combination with kojic acid, which can be used long-term as a skin bleaching agent plus sunscreens appears to be effective.

Summary

Melasma is generally under-diagnosed and under-treated. Nevertheless, it is a distressing problem for some 5-6 million American women. Currently, there is no standard treatment for melasma so therapy should be individualized according to severity and Fitzpatrick skin type. Epidermal melasma responds to virtually all treatments whereas dermal melasma is more recalcitrant. Until recently, monotherapy was most often used to treat melasma. Bleaching and keratolytic creams have proven to be effective over years of use, but may be irritating. Moreover, there is often a long latency until results are visible. Combination therapy has proven to produce more rapid and significant results, often with fewer side effects. New combination compounds consisting of a retinoid or azelaic acid in combination with a skin bleaching agent such as hydroquinone or kojic acid plus a corticosteroid have a synergistic effect and are the current standard of care for melasma. The only triple-combination treatment [Tri-Luma® Cream] currently approved for use is based on a the original Kligman and Willis formulation. It contains hydroquinone 4%, tretinoin 0.05% and fluocinolone acetonide 0.01% in a cream base. The use of lasers should be reserved only for refractory cases. Because melasma is a chron-

ic relapsing condition, sunscreens are critical to long-term success and maintenance of results.

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