# Current and New Treatments of Photodamaged Skin

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## ABSTRACT

Patients with photodamaged skin need guidance in selecting treatment plans that optimize outcomes, minimize downtime, and reduce adverse effects. The gold standard among cosmeceuticals is the topical retinoids, such as tretinoin. A topical formulation of folic acid and creatine appears to be a viable treatment option for the treatment of photodamaged skin. The use of specific topical cosmeceuticals in combination with nonablative photorejuvenation is recommended in choosing modalities that address the concerns of the patient. A combination of intense pulsed light (IPL), low-intensity diode light, and biostimulating drugs has been shown to provide results superior to those of IPL alone for photorejuvenation. Photodynamic therapy (PDT) with 5-aminolevulinic acid (5-ALA) is the treatment of choice for type C photodamage. Low-strength 5-ALA (1 to 2%) applied several times, every 10 to 15 minutes, and incubated for 30 to 60 minutes with 550 to 630 nm, 530 to 1200 nm, or 570 to 1200 nm light activation improved hyperpigmented lesions, skin smoothing, and skin elasticity with high patient satisfaction. The use of 0.5% liposome-encapsulated 5-ALA spraying has been shown to be an alternative to 20% 5-ALA in a cream base in patients undergoing photorejuvenation. Adipose-derived stem cells and their derived secretory factors may have potential as treatments of photodamage.

**KEYWORDS:** Cosmeceutical, photodamage, photorejuvenation, photodynamic therapy

This review focuses on recent advances in the treatment of photodamage by cosmeceuticals and photodynamic therapy (PDT). It will also emphasize the use of multiple modalities in the treatment of photodamage. Actinic keratoses (AKs) are a separate topic and discussed only to a limited extent. The term *photorejuvenation* originally described a series of four to six treatments with intense pulsed light (IPL)[1–3] but in this review will refer to the use of laser or light-based modalities to improve the appearance of the clinical manifestations of photoaging.

## COSMECEUTICALS

### Retinoids

The gold standard among cosmeceuticals is the topical retinoids,[4] such as tretinoin (all-*trans* retinoic acid), whose safety and efficacy in repairing photodamaged skin are well documented.[4,5] Tretinoin inhibits UV-induced upregulation of matrix-degrading metalloproteinase, thus reducing collagen loss in photodamaged skin. Double-blinded, multicenter studies show that tretinoin improves fine wrinkling, mottled pigmentation, skin

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laxity, and roughness, and histologic studies show that tretinoin increases epidermal thickness, decreases melanin content, improves the dermoepidermal junction, and improves keratinocyte ultrastructure.[4] Retinol, or vitamin A, is often found in antiaging creams and is converted in the body to the more biologically active tretinoin.[4] Retinol may be less irritating to the skin than prescription retinoids.[6] Multicenter studies also show that tazarotene, a new retinoid, improves fine wrinkles and reduces mottled pigmentation.[7]

Topical isotretinoin (13-*cis*-retinoic acid) improves actinic lentigines and fine wrinkles but may accomplish this only after conversion in the body to tretinoin.[5] In a recent randomized, double-blinded study, 10- and 20-mg dosages of oral isotretinoin given three times per week for 3 months safely increased the amount of collagen fibers, reduced the number of elastic fibers, and improved skin texture, the depth of wrinkles, and skin color on photodamaged skin. Traditional therapies for photodamage (retinoids, β-hydroxy acids, vitamin C, vitamin E, laser procedures) act by increasing the production of collagen but do not alter the accumulation of deposited elastotic material, as isotretinoin does.[8]

Vitamin C plays an important role in the production of collagen in the skin. As a water-soluble antioxidant that can quench free radicals, topical vitamin C may protect against UVB-induced erythema, reduce UV-induced wrinkling, and enhance the photoprotective effects of sunscreens.[4] Vitamin C also inhibits tyrosinase, decreases melanogenesis, and may inhibit elastin biosynthesis in fibroblasts.[6] Two studies have shown the clinical benefits of vitamin C on human subjects. Fitzpatrick and Rostan[9] reported clinical improvement in perioral and cheek wrinkles in 10 patients after 3 months of treatment with a vitamin C complex formulated in a gel. The authors also presented evidence of increased grenz zone collagen and increased mRNA for type I collagen in patients treated with the formulation. In their double-blind, placebo-controlled study, Humbert and co-workers[10] treated 19 subjects with a vitamin C preparation (5%) for 6 months. The treated sites showed significant improvement in wrinkling, hydration, glare, and brown spots, and biopsy specimens revealed an alteration in dermal elastic fibers.

## α-Hydroxy Acids

α-Hydroxy acids (AHAs) include glycolic, lactic, malic, citric, and other acids. These agents increase type I collagen mRNA and hyaluronic acid in the dermis and epidermis.[11] They also make skin appear smoother by reducing adhesion of keratinocytes and increasing cellular turnover in the stratum corneum.[4,6] Lactic and glycolic acids are commonly found in cosmeceuticals. AHAs act as humectants and improve stratum corneum barrier function[6] and enhance the beneficial effects of tretinoin.[12] AHAs may be combined with hydroquinone (34%) to treat dyschromia associated with photodamage.[11]

## Growth Factors

Growth factors comprise biologically active compounds such as cytokines, which regulate a variety of cellular activities.[11] It is well known that growth factors are necessary for wounds to heal. Transforming growth factor (TGF)-β, for example promotes collagen synthesis,[13] enhances wound strength, promotes the formation of granulation tissue, enlarges regenerated dermis, and stabilizes the dermoepidermal junction.[4,14] In a study reported by Fitzpatrick and Rostan,[14] subjects applied a cytokine cocktail gel twice daily to the face for 2 months. The gel contained the cytokines vascular endothelial growth factor, hepatocyte growth factor, interleukins 6 and 8, platelet-derived growth factor, granulocyte colony-stimulating factor, and TGF-β. Improvements were observed in the periorbital area (12.2%), texture (14.1%), wrinkle depth (36.2%), epidermal thickness (30%), and grenz zone collagen (37% increase). Amorphous clumping of elastic fibers was reduced, and the number of fine branching fibers was increased.[4] TGF-β1 obtained from cultured fibroblasts is currently found in cosmeceuticals.[6]

Kinetin, a plant growth factor, has been shown in vitro to inhibit the morphologic and biologic changes as human fibroblasts age. Kinetin also may have antioxidant properties and has been included in several antiaging formulations. An uncontrolled study showed that kinetin application for 24 weeks improved skin roughness by 60%, mottling by 27%, and facial wrinkling by 13%.[11] A major advantage of kinetin over retinoids or AHAs is that irritation of skin is minimal.[11]

## Peptides

Peptides are among the newest ingredients to enter the cosmeceutical market. These chains of amino acid sequences may promote cellular processes that stimulate the production of collagen. The peptide sequence glycine, proline, hydroxyproline for example, is found on type I procollagen and is part of the feedback regulation of collagen synthesis. This pentapeptide is currently in cosmeceutical products that have been shown in clinical testing to improve the appearance of skin.[15]

Peptide complexed with copper, a trace element required for wound healing, are believed to improve skin firmness and texture, fine lines, and hyperpigmentation.[15] Copper is a cofactor of the superoxide dismutase, an antioxidant, and of lysyl oxidase, an enzyme necessary for production of collagen and elastin. Copper also downregulates MMPs (matrix metallo propenase) and reduces collagenase activity.

### Pigment Lighteners

Cosmeceuticals used to lighten pigment are also useful in making skin tone more uniform. Hydroquinone inhibits the activity of tyrosinase, the enzyme necessary for melanin biosynthesis. Hydroquinone may be combined with AHAs, retinol, vitamin C, and topical steroids.[16,17] Other pigment-lightening agents have been reviewed.[6,16]

### Folic Acid and Creatine

Folic acid plays an important role in DNA synthesis and repair and in cellular turnover, and creatine has been linked to DNA protection. Because folic acid penetrates human skin and creatine is involved in DNA protection, Knott and colleagues[18] treated skin models (in vitro) and the skin of human subjects (in vivo) with a topical formulation of folic acid and creatine. The results showed greater skin regeneration in treated versus untreated controls in the in vitro study and greater epidermal turnover in treated versus vehicle controls in the in vivo study. Compared with untreated control areas, the formulation-treated areas showed greater protection of DNA from UV light, increased firmness of skin, and reduced wrinkle volume. The authors concluded that the topical formulation of folic acid and creatine is a viable treatment option for the treatment of photodamaged skin.

### Other Cosmeceuticals

Cosmeceuticals also include vitamins A and B, α-lipoic acid, coenzyme Q-10, and idebenone, which protect against photodamage, inflammation, and carcinogenesis to varying degrees.[6] A recent double-blind, randomized, placebo-controlled trial[19] showed that oral green tea polyphenols did not improve clinical or histologic photoaging parameters after 2 years of use. Estriol preparations have been shown to improve wrinkle depth, elasticity, pore size, and skin firmness. Combinations are also effective. A cream of estrogen and glycolic acid has been shown to increase skin thickness more than either product alone.[11]

## COMBINATION TREATMENTS

A combination treatment in this review is considered a treatment that includes at least two separate and unrelated modalities, such as a light or laser device combined with daily application of creams. Rokhsar and colleagues[4] recommend the use of specific topical cosmeceuticals in combination with nonablative photorejuvenation on the basis of anecdotal studies that suggest that cosmeceuticals and laser rejuvenation enhance results and maintain improvement. Practitioners should first determine what aspects of photoaging are of the greatest concern to the patient, and then choose modalities that address these concerns. Selection of an appropriate combination should consider, for example, that improvement in skin texture with nonablative laser therapy is comparable with that achieved with topical retinoids, growth factors, vitamin C, and possibly α-hydroxy acids, and that improvement in dyschromia and telangiectasia is superior to that achieved with cosmeceuticals. In a patient with mild to moderate dyschromia and mild to moderate textural changes, for example, cosmeceuticals that normalize pigment and lasers that improve pigment, vessels, and texture would be appropriate choices.

An early example of combination therapy was reported by Trelles and colleagues,[20] in which the authors nonablatively rejuvenated the faces of 25 women with "adjunctive pretreatment micropeel" followed by IPL and a regimen of nutritive and antipigmenting creams between IPL treatments. The goal of the combination was to enhance the clinical effects of IPL and improve satisfaction in patients with different skin types and photodamage conditions.

Adjunctive epidermal treatment consisted of a light mechanical micropeel before IPL irradiation and, between treatment sessions, application of calendula-based hydrating and nutritive cream and a moisturizing cream with avocado and mosquette rose oils twice a day, and glycolic acid and kojic acid antipigmenting cream at night. Patients were given five IPL treatments at 1-week intervals and a sixth treatment 4 weeks after the fifth treatment.

Eight weeks after the first treatment, 19 subjects rated improvement as fair to very good while the remaining six improved little or not at all. Adverse effects were not observed. Although this was not a controlled study, the authors contended that the pretreatment micropeel removed the poorly organized stratum corneum (which would reduce reflection of IPL, thus improving penetration of the energy) and helped the epidermis to regain a youthful appearance.

Fournier and colleagues[21] used blue (405 to 420 nm) and near-infrared light (850 to 890 nm) in combination with glycolic acid peels and topical vitamin C to rejuvenate skin. The aim was to evaluate the combination of the anti-inflammatory action of blue light and the enhancement of blood and lymphatic circulation provided by the infrared light. One group of patients ($n = 20$) (group A) received light-based treatment twice weekly for 4 weeks in which irradiation was preceded by application of standard glycolic acid superficial peel. Patients also applied vitamin C cream nightly for 4 months and a neutral hydrating cream every morning. The second group ($n = 7$) (group B) received the same peel and topical regimen but did not receive the light treatment. Patient satisfaction was higher in group A. Using digital patient photographs, an independent observer noted 65% of

patients improved in skin radiance, 80% on pore size, and 20% on rhytides 4 months after the final treatment. In group B, the observer noted no improvement in skin radiance, pore size, and rhytides. Patient-assessed improvements were similar. The authors concluded that the addition of the blue-IR light treatment greatly enhanced the results obtained by the glycolic acid peel and vitamin C regimen.

Mezzana[22] recently compared a combination of IPL, low-intensity diode light, and biostimulating drugs with IPL alone for photorejuvenation in 100 subjects aged 35 to 65 years and with varying degrees of photodamage. The light device was an Epi C (Espansione Marketing, Centergross-Funo [BO], Italy), a source for both IPL and low-intensity diode light with interchangeable lamps, and the biostimulation drugs were a mixture of vitamin C, low-weight hyaluronic acid, and β-glucan (HCG 2000; Mavi Sud Apprillia, Italy). The "triple-therapy" group ($n = 60$) received seven sessions of IPL and nine sessions of low-intensity diode light with biostimulation drugs, and the monotherapy group ($n = 40$) received seven sessions of IPL alone. Drugs (5 mL) were injected 5 minutes after exposure to diode light during each of the nine sessions. Injections were superficial and into the deep dermis at multiple facial sites spaced 1 to 2 cm apart. Both treatment groups showed favorable improvement in hyperpigmentation and telangiectasia. For skin texture and firmness, improvement was positive in 70% of triple-therapy patients and only 30% of monotherapy patients. Patient satisfaction was higher in the triple-therapy group. Side effects were limited to redness (12 to 18 hours) for both treatment groups and ecchymosis in the triple-therapy group.

In this study, IPL improvements were greater in telangiectasias and pigmented lesions than in skin texture, in contrast with Weiss and colleagues,[23] who achieved skin textural improvement in 83% of patients. The rationale for using low-intensity diode light was based on previous studies that showed increased fibroblast proliferation induced by light emitting diode (LED) and low-power irradiation; the effects of low-power laser irradiation on cell growth and procollagen synthesis of cultured fibroblasts; the use of various wavelengths of light to increase growth factor secretion from cultured macrophages; and that the authors might use different wavelengths of low-intensity diode light to stimulate endothelial proliferation and macrophage activation.[22]

Regarding the mixture of biostimulation drugs, previous studies show that ascorbate derivatives suppress the effect of UV light on fibroblasts and keratinocytes and stimulate collagen synthesis; low-molecular-weight hyaluronic acid modulates protein synthesis in fibroblasts and collagen proliferation; and β-glucans boost immune responses, have antioxidant properties, and stimulate collagen synthesis in the dermis.[22]

## PHOTODYNAMIC THERAPY

The use of PDT for the treatment of skin conditions is based on the work of Kennedy et al,[24] who showed that topical 5-aminolevulinic acid (5-ALA; 20%) could photosensitize target lesions on the skin, and that light of the appropriate wavelength could be used to activate the 5-ALA–induced photosensitive compounds that would destroy the cells in which these compounds are produced.[25]

Recent studies suggest that PDT with 5-ALA or methylaminolevulinate (MAL) photosensitizing agents may improve the appearance of wrinkles and fine lines, telangiectasias, and photodamage.[26] Photosensitizing agent is applied to the target area and permitted to incubate for a specified time. During the incubation period, 5-ALA, for example, penetrates rapidly proliferating cells of photodamaged skin more rapidly than undamaged skin, conferring selectivity to the technique. 5-ALA enters the heme biosynthetic pathway of the epidermis and is converted to protoporphyrin IX (PpIX), the only photosensitive intermediate in this pathway.[27] When enough PpIX has accumulated in the target tissue, the area is exposed to wavelength(s) of light absorbed by PpIX, resulting in the production of free radicals such as singlet oxygen, a metastable intermediate that destroys cells.[27]

IPL alone has been widely used for photorejuvenation. Investigators have since shown that for the treatment of photodamaged skin, 5-ALA PDT provides greater improvement than IPL alone[3,28–30] and the pulsed dye laser alone,[31] and that clinical improvement with 5-ALA PDT and IPL activation correlates with ultrastructural evidence of improvement.[30] Zane and colleagues,[32] using echocardiography to evaluate skin thickness, showed that PDT with MAL photosensitizing agent incubated for 3 hours and activated with red light improved photoaging, mottled hyperpigmentation, fine lines, roughness, and sallowness, but did not improve deep wrinkles, telangiectasia, facial erythema, and sebaceous gland hypertrophy. That same year, Ruiz-Rodrigues and colleagues[33] showed improvement in fine lines, tactile roughness, and skin tightness after treatment with MAL PDT. Dover and colleagues,[3] in their prospective, randomized, controlled split-face study of 5-ALA PDT with IPL versus IPL alone, showed that improvement in global score for photoaging, mottled pigmentation, and fine lines was greater with 5-ALA PDT with IPL than with IPL alone, but improvements in tactile roughness and sallowness did not differ between the two modalities, suggesting that results with 5-ALA and MAL under the stated conditions are roughly comparable for photoaging, pigmentation, and fine lines.

Consensus panel members for the use of 5-ALA PDT in dermatology have recommended at least three 5-ALA PDT sessions spaced 2 to 4 weeks apart for photorejuvenation and suggest that 5-ALA PDT may be

part of a standard five-treatment IPL regime for photorejuvenation.[27] The treatment of photodamaged skin is an off-label use, as 5-ALA PDT is FDA cleared only for the treatment of nonhypertrophic AKs.

5-ALA has been used successfully for skin rejuvenation in a facial plastic surgery practice. Zakhary and Ellis[25] apply 5-ALA to the target area, incubate for 3 hours, and irradiate the target tissue with a 532-nm diode-pumped, frequency-doubled Nd:YAG laser. The long 5-ALA incubation time and diode-pumped laser maximize 5-ALA penetration depth and activation of PpIX. The green 532-nm energy is absorbed by oxyhemoglobin and melanin, permitting treatment of abnormal vascular structure and pigmented lesions such as keratoses, lentigines, and ephelides.

## EXAMPLE OF COMBINATION TREATMENT

The following is a general protocol followed in our office. Ideally, a combination treatment plan does not rely on cost. If it does, we begin by addressing the issues of greatest concern to the patient. For example, if a patient has AKs, lentigines, telangiectasia, wrinkles, and facial laxity, we pretreat the entire face with topical tretinoin daily and imiquimod (Aldara; Graceway Pharmaceuticals, Bristol, TN) twice weekly to enhance the response to 5-ALA PDT with IPL. This begins the treatment for the AKs. Patients usually apply numbing cream to the target area just before coming to the office for their first 5-ALA PDT session. When the patient arrives, the target area is degreased by scrubbing with acetone or rubbing alcohol immediately before applying 5-ALA. We incubate 5-ALA (Levulan; Dusa Pharmaceuticals, Wilmington, MA) for 1 hour and activate with IPL followed by 3 minutes exposure to blue light. The patient has 4 days of downtime with edema and scabbing with this procedure. Patient faces are photographed under standard conditions before and after each treatment.

If cost is not an issue, we pretreat with Vitalize Peel (Skin Medica, Carlsbad, CA) and then treat with 5-ALA PDT with IPL activation followed by Fraxel Laser (Solta, Hayward, CA) for fine lines, wrinkles, and, if present, acne scars, all over a 4- to 6-week period. We repeat the entire sequence (or parts of it) to achieve effacement of wrinkles. Treatment stops when all the desired end points, including tissue tightening, are achieved.

Posttreatment care consists of ice packs, sun avoidance for 24 to 48 hours, analgesia if necessary, moisturizers, and topical aloe. For crusting, we instruct patients to soak the treated area in a solution of white vinegar in cool water, and then to apply a water-based emulsion (Biafine; OrthoNeutrogena, Langhorne, PA) and skin care lotion (Elta; Swiss-American Products Inc., Carrolton, TX). Makeup may be used when crusts and denuding are resolved. We recommend discarding old jars of makeup to avoid infection.

If skin laxity is severe, we use a radiofrequency device (Thermage, Hayward, CA); when telangiectasias are severe, the vascular laser devices (Apogee, Cynosure,

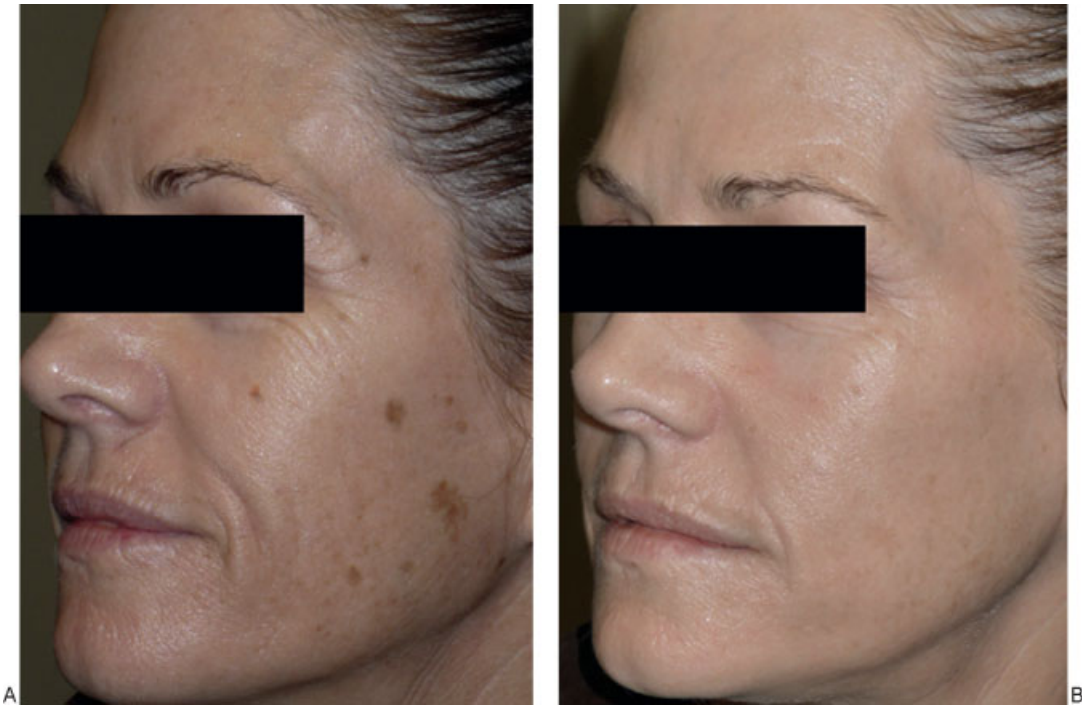


**Figure 1** A 47-year-old woman (A) with sun damage before treatment and (B) 2 weeks after (1) pretreatment with topical antioxidants, (2) 5-ALA PDT with activation by IPL and exposure to blue light for 3 minutes, and (3) microdermabrasion 2 weeks later. 5-ALA incubation was 1 hour. (Photographs courtesy of Ava T. Shamban, M.D.)

Inc., Westford MA and V Beam, Candela Corporation, Wayland MA) work well.

Clinical examples are shown in Figs. 1–3.

## NEW DEVELOPMENTS IN PHOTODYNAMIC THERAPY

The mechanism by which PDT improves the signs of photoaging may be associated with an increase in the production of type I collagen, such as that seen with the use of IPL and both 5-ALA and MAL.[34] The cellular and molecular changes associated with 5-ALA PDT with PDL activation have recently been reported in detail.[35] Orringer and colleagues, in their 25-patient study with 3-hour incubation of 5-ALA, assessed levels of Ki67, a marker of epidermal proliferation; cytokeratin 16, a marker of epidermal injury; p53, a marker of photodamage (p53); and markers of collagen production (prolyl 4-hydroxylase, heat shock protein 47, and type I procollagen) in the dermis of the forearm.[35] These markers were quantified in biopsy samples at baseline and at various time points after treatment by

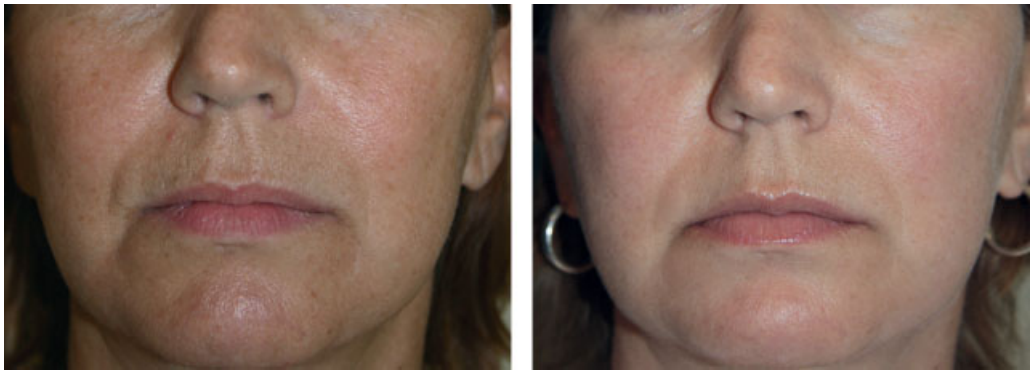

**Figure 2** A 51-year-old woman (A) with rosacea before treatment and (B) 3 months after (1) pretreatment with topical antioxidants, (2) 5-ALA PDT with activation by IPL, 595-nm pulsed dye laser, and blue light, and (3) resurfacing with fractional $CO_2$ laser (Active Fx/Deep Fx; Lumenis, Santa Clara, CA) 2 weeks later. 5-ALA was incubated 1 hour. (Photographs courtesy of Ava T. Shamban, M.D.)

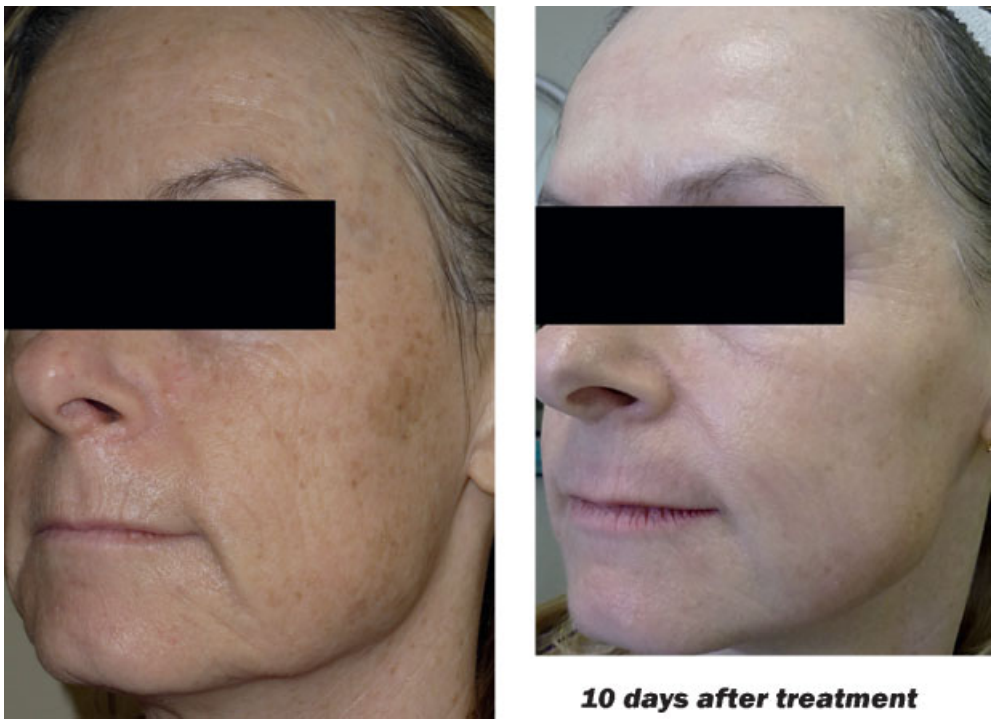


**Figure 3** A 56-year-old woman (A) with skin laxity before and (B) 10 days after (1) pretreatment with topical antioxidants, (2) 5-ALA PDT with activation by IPL and exposure to blue light for 3 minutes, and (3) resurfacing with fractional $CO_2$ laser (Active Fx/Deep Fx; Lumenis). 5-ALA was incubated 1 hour. (Photographs courtesy of Ava T. Shamban, M.D.)

immunohistochemical analysis, reverse transcriptase–polymerase chain reaction, or enzyme-linked immunosorbent assay. All markers were significantly elevated after treatment, indicating that 5-ALA PDT with PDL activation stimulated epidermal proliferation, increased epidermal thickness, produced epidermal injury, and upregulated production of type I and type III collagen, all of which were associated with improved appearance of the skin.

Most studies of 5-ALA PDT have been performed with 20% 5-ALA. As stated earlier, Lowe and colleagues[24] used 5% 5-ALA for 30 minutes and 633-nm light emitting diode for activation to reduce fine lines and improve skin softness in six patients, Serrano and co-workers[34] evaluated the effectiveness and safety of even lower strength 5-ALA (1 to 2%) and activated with 550 to 630 nm, 530 to 1200 nm, or 570 to 1200 nm light for the treatment of photoaging ($n = 8$), acne ($n = 12$), and vitiligo ($n = 6$). Low-strength 5-ALA was used to minimize phototoxic reactions and adverse effects and to reduce patient discomfort during treatment.

Serrano and colleagues, rather than apply 5-ALA only once before activation, applied 5-ALA several times, every 10 to 15 minutes, and incubated for 30 to 60 minutes. They treated patients three to four times at 3- to 4-week intervals. They also pretreated their target areas with salicylic acid chemical peel to increase 5-ALA penetration during the short incubation periods. After the final treatment, hyperpigmented lesions were reduced in 90% of patients, skin smoothing and elasticity were improved in all patients, and satisfaction was high in 88% of patients.

Adverse effects in these studies were reported as minimal and transitory. In general, erythema, mild edema, and sensations of burning, itching, or stinging are common in areas treated by PDT. The most undesirable side effect is photosensitivity, which may last several days in the treated areas. To minimize this effect, physicians instruct patients to avoid exposure to sun for 24 hours after treatment.[34] Yet, the frequency and severity of erythema and edema after PDT may be significant, even when photosensitizing agent incubation time is reduced.[37] For example, Dover and colleagues[3] reported intense erythema and edema in half of their patients treated with 5-ALA (20%) PDT with IPL activation compared with 15% of patients treated only with IPL alone. In the study of Alster and colleagues,[28] erythema persisted for 1 to 4 days, and desquamation and blistering lasting for 2 to 4 days only on the 5-ALA (20%) PDT side of the faces.

To overcome these disadvantages, Bjerring and colleagues[37] investigated the use of 0.5% liposome-encapsulated 5-ALA spraying as an alternative to more highly concentrated 20% 5-ALA in a cream base in patients undergoing photorejuvenation. Concentration of the accumulating PpIX was monitored during spraying by quantifying fluorescence in the skin of the target area before 5-ALA application and at various time points during the incubation period. Spraying was stopped when the fluorescence had increased over baseline by at least 2 FluoDerm units.

In their 37-patient, split-face study, Bjerring and colleagues sprayed both sides of the faces with 0.5% 5-ALA. When skin fluorescence had reached at least 2 FluoDerm units (~1 hour, spraying at 5-minute intervals), one side of the sprayed face received a single pass of a 530- to 750-nm wavelength band, a double pulse of 2.5 milliseconds duration spaced by 10 milliseconds, and a 6 to 7 J/cm$^2$ fluence. The wavelength band included only the 580-nm and 635-nm absorption peaks of PpIX. The other side of the face received three passes at a lower fluence (3.5 J/cm$^2$), longer pulse duration (30 milliseconds), and a wavelength band of 400 to 720 nm, which encompassed five PpIX absorption bands (407, 505, 540, 580, and 635 nm) rather than two. The two different IPL conditions were chosen so the authors could compare the effects of their standard photorejuvenation protocol (530 to 750 nm) for type I photorejuvenation and wrinkle reduction with results obtained using settings to show the effects due to PDT alone. The reductions in periorbital and perioral wrinkles were comparable on both sides of the face and were equivalent to those using 20% 5-ALA in previous studies[3,28] in which IPL was used for activation. Side effects were also reduced compared with those previously reported.

In addition to showing that 0.5% liposome encapsulated 5-ALA provided results that compared well with those obtained with 20% 5-ALA and with reduced adverse effects, this study showed that it was possible to monitor PpIX accumulation by fluorescence, thus ensuring that penetration of 5-ALA and its conversion to PpIX were consistent among patients and that sufficient PpIX had been produced before the target area was irradiated.

This investigation was prompted by an earlier study[38] that had shown that the average skin surface fluorescence induced by the liposome-encapsulated 0.5% 5-ALA incubated for longer than 2 hours did not differ statistically from the average measured skin surface fluorescence observed after 30 minutes incubation of 20% 5-ALA cream. With this new protocol, the risk of posttreatment phototoxicity was reduced because the 0.5% 5-ALA–induced fluorescence returned to normal levels within 8 hours after the end of incubation. In contrast, the 20% 5-ALA–induced fluorescence increased 1.6 to 9 times its level 8 hours after the end of incubation. In other words, the 20% 5-ALA–induced fluorescence continued to increase, even after the cream was removed from the skin, whereas the 0.5% 5-ALA–induced fluorescence decreased and was gone 8 hours after its removal.

## NEW THERAPIES FOR PHOTODAMAGE

### A 3-in-1 Wavelength Light Source

In her 37-patient study, Lee[39] achieved an average 73% improvement in pigmentation, 68% in redness and telangiectasia, and 20% improvement in skin texture 1 month after an average of 5.3 treatments with a cooled sapphire IPL handpiece with adjustable wavelengths (LimeLight; Cutera, Brisbane, CA). The spectral range of the novel device is 520 to 1100 nm. Improvements were based on comparison with untreated (control) sides of the face, neck, chest, arm, hand, and legs. Patient satisfaction was high, and adverse effects were transitory and limited to mild erythema and edema, a warm sensation, and, in patients with pigmentation abnormalities, darkening of lentigines and ephelides.

Unlike other light sources used for the treatment of photodamage, the device in this study permits the user to shift the spectral peaks and range to target either oxyhemoglobin or melanin. The practitioner avoids the cost of having to purchase separate heads to treat vascular or pigmented lesions and can safely treat both light and dark skin. It is also easy to shift among each of the three heads by touching a computerized console without delaying treatment, avoiding the inconvenience of having to change heads. Longevity of clinical benefits remains to be determined.

### Handheld LED

LED therapy has been shown to be effective and safe for the treatment of photodamage.[40] Using a handheld LED device, Sadick[40] achieved visible improvement in facial rhytides in 74% of subjects ($n = 22$) 12 weeks after the final of eight treatments over 4 weeks. Subjects treated themselves, and adverse events were limited to mild facial edema after the initial treatment. At 12 weeks, 73% of subjects rated outcome as either good or excellent, 84% reported improved skin tone, 79% reported improved smoothness, 73% achieved better clarity, 68% achieved greater skin firmness, and 47 reported improved elasticity. Improvement was noticeable at 5 or 6 weeks. Eighty-four percent of subjects rated the device as very easy or extremely easy to use.

The device is designed to use 830- and 633-nm light because previous studies have shown that near-infrared light (830 nm) enhances cellular recruitment, mitosis, and chemotaxis of macrophages, neutrophils, and fibroblasts in the target area, and 633-nm red light increases procollagen synthesis and fibroblastic growth factor synthesis.

### Adipose-Derived Stem Cells

The efficacy of conventional antiaging treatments depends on their ability to induce new collagen synthesis by activating dermal fibroblasts. Adipose-derived stem cells (ADSCs) and ADSC-derived secretory factors, however, have been shown to protect dermal fibroblasts from oxidative stress caused by UVB radiation and chemicals. Data also show that ADSCs and their conditioned media (ADSC-CM) inhibit melanogenesis and stimulate collagen synthesis and migration of dermal fibroblasts during wound healing. Third, injection of lipoaspirate cells (20 to 30% ADSCs) has been shown to increase dermal thickness and to reduce wrinkles. Collectively, these observations indicate that ADSCs and their secretory factors have potential for the treatment of photodamage.[41]

One advantage of this new approach is the availability of large quantities of ADSCs from lipoaspirates. Another is the demonstrated safety, practicality, and effectiveness of stem cells in repairing damaged tissue, because the pathophysiology of photoaging is similar to that of chronic wounds. ADSCs may also have antioxidant effects, and animal studies show that subcutaneous injection of ADSCs reduces UVB-induced wrinkling, increases dermal thickening, and increases dermal content. In addition, ADSC-CM has been shown to increase protein expression of type I collagen and reduce the protein level of matrix metalloproteinases (which degrade collagen) in fibroblasts; the latter may explain the increase in collagen observed in the dermis of animals. Finally, because ADSC-CM inhibits melanin synthesis, it may have potential as a whitening agent.

These stem cell investigations have been conducted in vitro and in animals. The next step is to initiate clinical trials in humans.

## CONCLUSION

Facial aesthetic procedures have become faster and more efficient to meet the growing demands for safe, simple, rapid, and effective treatment modalities. As new technologies become available, facial plastic surgeons will discover new ways to combine them to optimize outcomes and minimize adverse effects in their patients.

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