Photoaging is a chemical reaction that occurs when skin is exposed to UV light. Premature skin aging occurs when this reaction disrupts the balance between normal collagen formation and degradation. For example, within minutes of UV exposure to the skin, epidermal growth factor, IL-1, and tumor necrosis factor α receptors activate and produce proteolytic enzymes responsible for degrading collagen. Degraded collagen accumulates in the dermis from UV radiation, which antagonizes neocollagenesis. Histologically, abnormal elastic fibers accumulate in the papillary dermis of sun-damaged skin. Compared to naturally aged, sun-protected skin, photoaged skin has a thicker, rougher, and coarser clinical appearance with mottled pigmentation. Lentigines and diffuse irreversible hyperpigmentation often appear as secondary effects of UV-induced hyperplasia of melanocytes. Additionally, alterations in cutaneous microvasculature, such as regression of small blood vessels and neoangiogenesis, result in telangiectases.

The substantial adverse effects and downtime associated with ablative laser resurfacing techniques have created a niche for alternative skin rejuvenation modalities. Photodynamic therapy (PDT) has emerged as an efficacious treatment option for patients seeking a more noninvasive means to repair photodamaged skin. Photodynamic therapy, a process whereby a photosensitizer and light source in the presence of molecular oxygen selectively destroy a targeted cell, has been explored in combination with various light sources. Treatment paradigms for the off-label use of PDT for photodamage (ie, fine or coarse lines, skin roughness, telangiectases, sallowness) have been established. Recently, the generalizability of PDT has started to change, as the idea of creating safe and effective protocols in darker skin types has just begun to be broached. The minimal side effects and radically reduced incubation times associated with the procedure have made PDT an attractive option for the cosmetic patient.

1999, the US Food and Drug Administration approved this agent in combination with light (ALA-PDT) for the treatment of actinic keratoses. Since then, PDT has been studied off label for aesthetic and cosmetic applications. This article will review the mechanism of action of PDT and its molecular effects on photodamaged skin as well as the latest clinical trial literature (2006–present) in which various light and laser sources have been successfully employed for the off-label indication of photorejuvenation.

MECHANISM OF ACTION
Photodynamic therapy is a process whereby a photosensitizer and light source, in the presence of molecular oxygen, selectively destroy a targeted cell. In the United States, ALA and methyl aminolevulinate (MAL) are available for use as photosensitizers. They are metabolized to protoporphyrin IX (PpIX) when applied topically, and free radicals are produced when PpIX is irradiated with visible light, causing injury to various metabolically active cutaneous targets, such as pilosebaceous units or hyperproliferative keratinocytes. An esterified derivative of ALA, MAL is considered to be more lipophilic than ALA and has an increased penetration of and higher specificity for PpIX induction in hyperplastic lesions, including precancerous cells. In addition, there is evidence that MAL may provoke less pain during PDT than ALA.

The absorption spectrum of PpIX enables the availability of a wide range of electromagnetic radiation options in the visible spectrum. The major absorption peak for ALA, known as the Soret band, is best activated by narrowband blue-light lamps that have an associated 410- to 420-nm wavelength range. However, several other small absorption peaks, known as Q-bands, can be manipulated through the use of a variety of lasers and light sources, such as pulsed dye lasers (PDLs), intense pulsed light (IPL) sources, and red-light sources. The deeper-penetrating wavelengths associated with PDL and IPL have an added photothermal effect of reaching thermal target chromophores such as vessels, pigment, and collagen to enhance the cosmetic possibilities.

MOLECULAR EFFECTS OF PDT ON PHOTOAGING
Few studies have quantitatively examined the cellular and molecular changes that occur in the epidermis and dermis after PDT in photodamaged skin. Utilizing a 3-hour application of ALA followed by PDL therapy to focal areas of photodamaged forearms, Orringer et al.15 showed that ALA-PDT enhances dermal remodeling, even after just 1 treatment cycle. Immunohistochemical analysis of serial biopsy specimens taken at baseline and at various times after treatment revealed that epidermal proliferation was stimulated (more than a 5-fold increase, P < 0.05), epidermal thickness was increased (more than a 1.4-fold increase, P < 0.05), and upregulation of collagen was produced (more than a 2.65-fold increase of procollagen I messenger RNA, P < 0.05; more than a 3.32-fold increase of procollagen III messenger RNA, P < 0.05).

These findings of increased collagen production are in keeping with the results of a pilot study by Marmur et al.16 that examined via electron microscopy the ultrastructural changes produced by ALA applications followed by exposure to a noncoherent IPL source. The authors reported that changes in epidermal thickness and collagen upregulation were qualitatively similar to those described in response to topical tretinoin therapy. Therefore, ALA-IPL may provide retinoid-like benefits to the appearance of the skin, with these changes likely occurring more rapidly than with topical retinoid therapy.

It should be noted that immunostaining for p53, a marker of photodamage, did not show a decrease following ALA-PDT treatment in the Orringer et al.15 study. Additionally, this study’s 3-hour incubation time is substantially longer than the 60-minute incubation period that is generally utilized. Also, the photodamaged skin of the forearm may have varying wound-healing properties in comparison to the face where PDT procedures typically are conducted.

PDT WITH IPL SOURCES
Intense pulsed light has a broad spectrum of wavelength activation (515–1200 nm), which has been shown to independently improve telangiectases and irregular pigmentation. It also is effective as an adjunct to PDT by precisely targeting the Q-bands of PpIX to initiate the phototoxic reaction. Intense pulsed light affords a deeper penetration into the red and near-infrared range, allowing for photothermal activation of various chromophores that further improve skin texture, diminish pigmentation, and decrease overall redness and telangiectases.

When PDT was initially approved by the US Food and Drug Administration for the treatment of actinic keratoses, ALA solution was applied to the skin 14 to 18 hours before irradiation with a light source. Phase 2 trials showed an 88% clearance of actinic keratoses when 2 long incubation treatments were administered, and more than 94% of trial participants also noted an improvement in skin texture after treatment; however, drawbacks such as stinging and burning during therapy and itching, erythema, and edema after therapy made this treatment regimen unattractive to the majority of dermatologists.

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In response, several groups began to investigate the use of shorter incubation times with ALA-PDT, and a 1-, 2-, or 3-hour incubation period was discovered to be just as efficacious in clearing actinic keratosis as the initial 14 to 18 hours of incubation. Similar results were reported regarding the effectiveness of the abbreviated incubation time and photorejuvenation. The first split-face clinical study using 3 treatments at 1-month intervals of short-contact ALA-PDT with IPL versus IPL alone was conducted by Gold et al in 2006. The percentage of improvement in the combined treatment side was greater than the control for all facets of photodamage (eg, crow’s feet, tactile skin roughness, mottled hyperpigmentation, telangiectases); however, the authors failed to report if this difference was statistically significant.

More recently, there have been 2 major studies investigating the use of PDT with IPL for photorejuvenation in Asians with Fitzpatrick skin types III and IV (Table). Current ablative photorejuvenation options carry such substantial side-effect profiles (eg, postinflammatory hyperpigmentation and prolonged downtime) that utilization in this patient population is limited. A split-face study of 24 participants comparing ALA-IPL to IPL alone showed that the global photodamage score (50% vs 13%; P = .005), fine lines (71% vs 33%; P = .009), and coarse wrinkles (50% vs 13%; P = .005) were significantly better on the combined treatment side. For safety, ALA solution 5% was used in this study in contrast to the 20% solution that is most often utilized in clinical trials. The IPL energy fluences used were close to half of those used in studies conducted on white participants. Even though satisfactory results were obtained, postinflammatory hyperpigmentation did occur in 2 participants, though satisfactory results were obtained, postinflammatory hyperpigmentation did occur in 2 participants, while the use of MAL in Europe historically has been paired with red light. Recently, a split-face trial was conducted in 18 participants who were randomized to treatment with either MAL–red light or MAL–blue light after microdermabrasion and illumination with PDL and IPL. Overall, MAL-PDT was found to be equally effective using red light versus blue light with no differences in categorical photodamage measures, including wrinkles, pigmentation, erythema, or clearance of actinic keratoses. Only 2 participants reported mild discomfort with red-light illumination; no participants experienced discomfort resulting from blue-light exposure.

This study utilized multiple illumination devices, making it difficult to compare red LED to blue light in a head-to-head comparison. The blue light source (417 nm) targeted the Soret band, while the red LED and PDL took advantage of the porphyrin peaks at 630 nm and 690 nm, respectively. The broadband IPL is likely to target numerous peaks along the PpIX spectra. The authors speculated that activating the photochemical reactions along multiple peaks of the porphyrin curve may increase the effectiveness of MAL-PDT and lead to superior clinical results. Additionally, PDL targets the chromophore hemoglobin within vessels, thereby reducing erythema. Also, via selective photothermolysis, IPL targets both melanin and vessels, leading to improvement in pigmentation, erythema, and telangiectases. Lastly, combining IPL and PDL can lead to synergistic dermal changes, likely due to fibroblast stimulation and subsequent collagen synthesis.
### Outcome of Controlled Studies Using PDT for the Treatment of Photoaging

<table>
<thead>
<tr>
<th>Reference</th>
<th>Light Source (Parameters)</th>
<th>Photosensitizer (Incubation Time)</th>
<th>Split Face</th>
<th>Participants, n/Treatments, n</th>
<th>Treatment Area (Fitzpatrick Skin Type)</th>
<th>Follow-up Period</th>
<th>Results</th>
<th>Side Effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Xi et al²⁷</td>
<td>IPL (520 nm, 17–20 J/cm²)</td>
<td>ALA (1 h)</td>
<td>Yes</td>
<td>24/3</td>
<td>Face (types III and IV)</td>
<td>1 mo</td>
<td>Combination treatment showed significant improvement in global photodamage score ($P = .005$), fine lines ($P = .009$), and coarse wrinkles ($P = .005$)</td>
<td>Moderate erythema, prolonged erythema, edema, and PIH (more intense in the combined treatment side)</td>
</tr>
<tr>
<td>Kosaka et al²⁸</td>
<td>IPL (500–670 nm and 870–1400 nm, 23–30 J/cm²)</td>
<td>ALA (2 h)</td>
<td>Yes</td>
<td>16/3</td>
<td>Face (types III and IV)</td>
<td>3 mo</td>
<td>Noticeable improvements on both sides of face; reduction in the photoaging score did not significantly differ</td>
<td>Mild to severe pain, burning sensation, or erythema in all ALA-IPL participants</td>
</tr>
<tr>
<td>Gold et al²⁶</td>
<td>IPL (550 nm, 34 J/cm²)</td>
<td>ALA (1 h)</td>
<td>Yes</td>
<td>13/3</td>
<td>Face (types I–IV)</td>
<td>3 mo</td>
<td>Combined treatment showed more improvement for crow’s-feet, tactile skin roughness, mottled hyperpigmentation, and telangiectases</td>
<td>Erythema and edema on both sides of the face</td>
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<thead>
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<th>Reference</th>
<th>Light Source (Parameters)</th>
<th>Photosensitizer (Incubation Time)</th>
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</tr>
</thead>
<tbody>
<tr>
<td>Sanclemente et al²⁹ (2011)</td>
<td>Red light (635 nm, 37 J/cm²)</td>
<td>MAL (3 h)</td>
<td>Yes</td>
<td>48/2</td>
<td>Face (N/A)</td>
<td>1 mo</td>
<td>Combined treatment showed significant improvement ($P = .0000$) in global photodamage, fine lines, coarse lines, mottled pigmentation, tactile roughness, and sallowness</td>
<td>Combined treatment showed significantly ($P = .0000$) more pain, erythema, edema, desquamation, and vesiculation</td>
</tr>
<tr>
<td>Clementoni et al³⁰ (2010)</td>
<td>Microneedling pretreatment + broadband pulsed light (560 nm, 19–22 J/cm²) + red light (630 nm, 75 J/cm²)</td>
<td>ALA (1 h)</td>
<td>No</td>
<td>21/1</td>
<td>Face (types II and III)</td>
<td>6 mo</td>
<td>Significant improvement ($P &lt; .05$) in global photodamage, fine lines, mottled pigmentation, sallowness, tactile roughness, and telangiectases</td>
<td>All participants had fine desquamation that terminated by 7 d posttreatment</td>
</tr>
<tr>
<td>Issa et al¹ (2010)</td>
<td>Red light (635 nm, 37 J/cm²)</td>
<td>MAL (2 h)</td>
<td>No</td>
<td>14/2</td>
<td>Face (type III)</td>
<td>6 mo</td>
<td>Improvement in texture, firmness, wrinkle depth, and skin coloration; statistically significant ($P = .008$) increase in collagen fibers</td>
<td>Majority of adverse effects were classified as mild</td>
</tr>
<tr>
<td>Ruiz-Rodríguez et al³¹ (2008)</td>
<td>Red light (635 nm, 37 J/cm²)</td>
<td>MAL (1 h vs 3 h)</td>
<td>Yes</td>
<td>10/3</td>
<td>Face (types II and III)</td>
<td>2 mo</td>
<td>3 h: moderate improvement of skin tightness, fine wrinkles, and tactile roughness</td>
<td>3 h: erythema and edema, scaling</td>
</tr>
</tbody>
</table>

(Continued)
<table>
<thead>
<tr>
<th>Reference</th>
<th>Light Source (Parameters)</th>
<th>Photosensitizer (Incubation Time)</th>
<th>Split Face</th>
<th>Participants, n/Treatments, n</th>
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<th>Follow-up Period</th>
<th>Results</th>
<th>Side Effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Zane et al (2007)</td>
<td>Red light (635 nm, 37 J/cm²)</td>
<td>MAL (3 h)</td>
<td>No</td>
<td>20/2</td>
<td>Face (types II and III)</td>
<td>2 mo</td>
<td>Significant improvement (P &lt; .05) of mottled hyperpigmentation, fine lines, roughness, and sallowness</td>
<td>Erythema, edema, crusting, and erosions</td>
</tr>
<tr>
<td>Ruiz-Rodriguez et al (2007)</td>
<td>Red light (635 nm, 37 J/cm²) + fractional resurfacing</td>
<td>ALA (3 h)</td>
<td>Yes (ALA–red light + fractional resurfacing vs fractional resurfacing alone)</td>
<td>4/2</td>
<td>Perioral (types II and III)</td>
<td>4 mo</td>
<td>Combined treatment showed increased improvement in wrinkles</td>
<td>Combined treatment showed increased erythema, edema, and scaling</td>
</tr>
<tr>
<td>Palm et al (2011)</td>
<td>Microdermabrasion + PDL (690 nm, 10–12 J/cm²) +/− IPL (520 nm, 17–20 J/cm²) + either red light (630 nm, 37 J/cm²) or blue light (417 nm, 10 J/cm²)</td>
<td>MAL (1 h)</td>
<td>Yes (MAL–blue light vs MAL–red light)</td>
<td>18/1</td>
<td>Head and neck (types I–II)</td>
<td>1 mo</td>
<td>No statistically significant differences in signs of photodamage of MAL–PDT with blue light vs red light</td>
<td>Mild erythema resolved by day 7</td>
</tr>
<tr>
<td>Orringer et al (2008)</td>
<td>PDL (595 nm, 7.5 J/cm²)</td>
<td>ALA (3 h)</td>
<td>No</td>
<td>25/1</td>
<td>Forearms (N/A)</td>
<td>6 mo</td>
<td>Stimulation of epidermal proliferation, epidermal injury produced, and upregulation of collagen</td>
<td>None reported</td>
</tr>
</tbody>
</table>

Abbreviations: PDT, photodynamic therapy; IPL, intense pulsed light; ALA, 5-aminolevulinic acid; PIH, postinflammatory hyperpigmentation; MAL, methyl aminolevulinate; N/A not available; PDL, pulsed dye laser.
PDT FOR PHOTOREJUVENATION

Multiple illumination devices also were used in an ALA-PDT trial involving 21 participants; microneedling was followed by red light and broadband pulsed light.30 Microneedle rollers boost cosmesis through collagen induction and increase penetration of topical cosmeceuticals. The roller, which is embedded with stainless steel, solid-bore needles that are 108 μm in width and 300 μm in length, creates numerous transdermal channels to augment topical penetration of ALA. Statistically significant improvement was seen in the global photaging scores at 3 months compared to baseline (P<.05); however, a lack of appropriate controls in this pilot study inhibits extrapolation of the results reported.30

The combination of an ablative device with PDT has been explored by Ruiz-Rodriguez et al13 who treated half of the perioral area in 4 women with fractional resurfacing and ALA–red light PDT in 2 treatment sessions that were 3 weeks apart. Compared to fractional resurfacing alone, the combination treatment showed an increased improvement in superficial wrinkles in 3 participants. Although the power of this pilot study is low, the results affirm that clinical cosmetic results can be synergistically advanced by combining ablative methodologies with PDT.33

CONCLUSION

The technological evolution of PDT has made the procedure a powerful utility for patients seeking noninvasive methods to photorejuvenate the skin. Manipulation of the PpIX absorption spectra with different illumination devices, combination with ablative techniques, and pretreatment of the skin with microdermabrasion or microneedling have augmented the cosmetic efficacy of PDT. The generalizability of PDT also has begun to change, as the idea of creating safe and effective protocols in patients with darker skin types has just begun to be broached. The minimal side effects and radically reduced incubation times associated with this procedure have made PDT an attractive option for the cosmetic patient.

REFERENCES


