PFENNINGER & FOWLER'S

Procedures for Primary Care

THIRD EDITION

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CHAPTER 60

PHOTODYNAMIC THERAPY

Greta McLaren

The history of photodynamic therapy (PDT) dates back to the early 1900s. Various chemicals, acting as photosensitizers, were found to have cytotoxic effects on specific types of cells after absorption into the cell when followed by activation with light in the presence of oxygen. The principle of PDT is currently used medically to treat various dermatologic conditions, connective tissue disorders, and malignancies. This chapter reviews the various dermatologic conditions, both medical and cosmetic, that can be treated in the office setting using topical PDT. Both U.S. Food and Drug Administration (FDA)–approved applications as well as "off-label" applications are discussed.

PDT using the topical photosensitizer 5-aminolevulinic acid (ALA-PDT) as a procedure to treat various dermatologic conditions has been gaining popularity over the past decade among dermatologists and primary care physicians alike. The procedure received FDA approval in 1999 for the treatment of minimally to moderately thick actinic keratoses of the face and scalp. However, multiple off-label uses have been investigated and found to be safe and effective. Some of the more common off-label treatment protocols that can be performed in the office setting include the treatment of acne, photodamage, sebaceous gland hyperplasia, and hidradenitis suppurativa. Extensive research regarding the "off-label" use of ALA-PDT in the treatment of nonmelanoma skin cancers, including basal cell carcinoma and Bowen's disease, has been published. However, these topics are not covered in this chapter. Please refer to the Bibliography for more information on these subjects (e.g., Gilbert, 2007).

The most common form of ALA used by physicians in the United States is *20% 5-ALA* (Levulan Kerastick; Dusa Pharmaceuticals, Inc., Wilmington, Mass). This photosensitizing chemical has the unique property of being absorbed by the outer layer of the skin and being taken up selectively by cells undergoing rapid turnover. As a result, this procedure allows for the targeting of rapidly reproducing, unhealthy, sun-damaged, precancerous, and cancerous skin cells.

The mechanism by which ALA-PDT works is as follows: once applied to the skin and allowed to incubate and be absorbed, ALA is converted to a potent photosensitizer (PS), protoporphyrin IX (PpIX). When exposed to oxygen and light of various wavelengths, PpIX reacts to produce a cytotoxic effect (singlet oxygen) on the targeted cells. The absorption peaks for PpIX show a maximum peak at 409 nm, with lesser peaks at 509, 544, 584, and 635 nm (Fig. 60-1). Higher fluencies (light energy) are needed for the lesser peaks, although the deeper penetration at the longer wavelengths may have an added benefit.

$$O_2 + PS + \text{light} \rightarrow \text{singlet oxygen (which destroys the target)}$$

ALA-PDT used off label in the treatment of acne vulgaris works in two ways: (1) destruction of *Propionibacterium acnes*, the bacterium associated with the disorder; and (2) shrinkage of the oil glands with less production of oil as a result. The procedure is considered an alternative to isotretinoin (Accutane), with results in some

In the presence of ALA, *P. acnes* makes a large amount of photosensitive porphyrins, increasing its photosensitivity. The pilosebaceous unit itself selectively accumulates the photosensitizer, PpIX. Light application again produces a chemical reaction that in turn kills the bacteria and also causes involution of the sebaceous gland.

A second PDT photosensitizer, *methyl aminolevulinate* (Metvix, Galderma Laboratories, Paris; and PhotoCure AS, Oslo), has been FDA approved as second-line therapy for the treatment of nonhyperkeratotic actinic keratoses of the face and scalp not amenable to conventional therapy. Despite FDA approval, however, Metvix has not yet been launched in the U.S. market.

Lasers and light sources capable of emitting wavelengths of light that correspond to the absorption peaks for PpIX (see Fig. 60-1) are possible sources for activation of ALA. The activating light source for ALA approved in the FDA protocol for the ALA-PDT procedure is the *BLU-U*, a 417-nm wavelength light manufactured by Dusa Pharmaceuticals. Multiple other light and laser sources noted under the "Equipment" section of this chapter have been found to be effective in activating ALA. Devices such as intense pulsed light (IPL) or pulsed-dye laser (PDL) can be synergistic in that not only are they capable of activating ALA, they are able to target other chromophores such as hemoglobin or melanin. As a result, these devices can simultaneously activate ALA and treat telangiectases and solar lentigines, thereby enhancing the cosmetic result for photodamaged skin. This procedure using a PDL or IPL source is often referred to as *photorejuvenation with ALA*.

INDICATIONS

FDA Approved

Actinic keratoses, mild to moderate thickness.

Off-Label Use

- Acne vulgaris
- Acne rosacea
- Cosmetic photorejuvenation
- Sebaceous hyperplasia
- Hidradenitis suppurativa
- Nonmelanoma skin cancers
- Actinic cheilitis
- Warts

CONTRAINDICATIONS

Absolute

- Pregnancy
- Breast-feeding (not studied)
- Planned sun exposure within 48 hours

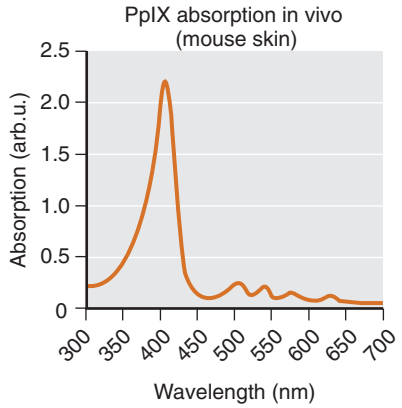


Figure 60-1 The absorption peaks for protoporphyrin IX (PpIX). (Courtesy of Dusa Pharmaceuticals, Inc., Wilmington, Mass.)

Relative

- Seizure disorder
- Diabetes
- Photosensitizing drug use
- Tobacco use

EQUIPMENT

- Acetone and 4 × 4 gauze for skin preparation
- Microdermabrasion machine *(optional)*
- 20% 5-ALA (Levulan Kerastick)
- BLU-U (417 nm), ClearLight (405 to 420 nm; Lumenis, Ltd., Yokneam, Israel), Omnilux Blue Light (415 nm; Photo Therapeutics, Inc., Carlsbad, Calif), PDL (585 or 595 nm), broad-band light source or IPL (410 to 1200 nm)
- Zimmer chiller *(optional)*

PATIENT SELECTION AND PRECAUTIONS

- Photodynamic therapy with ALA can be used on all skin types, Fitzpatrick I through VI, if indicated, using one of the previously noted light devices. Photorejuvenation using an IPL or PDL should be reserved for patients with skin types I through IV only. Patients with *darker skin types* (Fitzpatrick IV and above) are more susceptible to *postinflammatory hyperpigmentation (PIH)* after this procedure. These patients should be well informed of the potential risk of PIH before undergoing the procedure. For the first PDT treatment in skin types IV and above, a shorter incubation time should be considered. The incubation time for subsequent treatments may be gradually increased in 15-minute increments if tolerated (Table 60-1). It is prudent in these patients to take prophylactic measures by prescribing a skin-lightening agent such as hydroquinone 4% gel or cream 2 weeks before and up to 4 weeks after the procedure when treating skin types IV and above.
- The *side effects* and potential downtime with this procedure vary significantly from patient to patient. Some of the more common side effects are *erythema, swelling, peeling, crusting, dryness, and discomfort*. As a general rule, the amount of target tissue present, such as the prevalence of actinic keratoses or severity of acne, along with the length of the incubation period will determine the amount of downtime and side effects.
- *Retinoid use* before the procedure may enhance the results but will also increase the downtime. For better predictability of downtime and side effects, retinoids can be discontinued 1 to 2 weeks before the procedure, unless the enhanced effect, with its potential increased severity of downtime, is desired and discussed with the patient during the consultation.
- ALA-PDT should not be performed on patients who have used *isotretinoin (Accutane) within the previous 6 months*.
- The use of *photosensitizing drugs, including tetracyclines*, must be taken into consideration when performing this procedure. It is acceptable to continue the medication during the treatments; however, the incubation time of ALA is decreased by 15 minutes on the initial treatment to determine if increased side effects due to photosensitivity are likely to occur.
- The discomfort and nerve irritation that may occur with ALA-PDT may stimulate a *herpes simplex virus recurrence* in patients with a history of cold sores. Antivirals should be used prophylactically to prevent this potential side effect in such patients.

PATIENT EDUCATION AND POST-TREATMENT GUIDELINES

Because of the potential severity of side effects and reactions to this procedure, an initial consultation with the patient by a physician with a full explanation of the potential risks, downtime, and side effects is recommended. Once ALA is applied and absorbed in the skin, it may remain reactive to sunlight for the next 24 to 48 hours, regardless of cleansing after the application. It is therefore imperative that patients understand the need to *avoid sunlight*, both direct and indirect, for a minimum of 48 hours after the procedure. An educational handout and informed consent should be reviewed with the patient during the initial consultation.

PROCEDURE

1. Baseline photographs are always helpful.
2. Review consent form and post-treatment guidelines with the patient.
3. Review the history to note any contraindications or use of photosensitizing drugs.
4. Note any cold sore risk and prescribe antivirals if indicated.

TABLE 60-1 Levulan Incubation Time for ALA-PDT Treatment

Area	Treatment Number	Fitzpatrick Skin Type	Disease Severity	Occlusion	Time (in minutes)
Face/scalp	First	I–III	Mild to moderate	No	60
	Second–Fifth	I–III	Same as above	No	60–90*
	First	I–III	Moderate to severe	No	30
	Second–Fifth	I–III	Same as above	No	45–60*
	First–Fifth	IV–VII	All	No	30–45
Chest, back, arms or legs	First–Fifth	I–III	Mild to moderate	Yes	120
	First–Fifth	I–III	Moderate to severe	Yes	90–120
Chest, back	First–Fifth	IV–V	All	Yes	60–90
	First–Fifth	VI	All	Yes	60

5. Cleanse and prepare the skin with either a vigorous acetone scrub or microdermabrasion.
6. Crush the Levulan Kerastick according to directions and shake the solution for 3 minutes.
7. Protect the patient's eyes and mouth with petrolatum ointment or gauze and apply the Levulan solution to the treatment area (face, neck, chest, back, arms, hands, or legs). Areas with more severe disease may be treated with a second coat of Levulan.
8. Incubate to allow for sufficient absorption of the Levulan depending on area, disease severity, and skin type (see Table 60-1).
9. Areas other than the face and neck, such as chest, back, hands, arms, and legs, require longer incubation times for sufficient absorption of the Levulan. If treating these areas, occluding the area with cellophane (kitchen plastic wrap) and tape will enhance the absorption and decrease the incubation time required (see Table 60-1).
10. When significant acne and or photodamage is present or if the patient has a darker skin type and is at risk for PIH, consider a shorter initial incubation time. Gradually increase incubation times with subsequent treatments, depending on tolerance. Do not exceed a 30-minute incubation time in Fitzpatrick skin type VI because of the increased risk of PIH in these patients (see Table 60-1).
11. Wash the treated area with a gentle cleanser and water after incubation, before starting the light treatment.
12. Activate the Levulan by exposing the treated area to a light source. Narrow-band blue light, IPL, PDL, and light-emitting diode light that falls within the required wavelength absorption spectrum for PpIX (see Fig. 60-1) are all possible sources for activation of Levulan. The operator should use the chosen device in accordance with the individual device's operating protocol. If using the BLU-U light alone, the exposure time is approximately 15 minutes. The recommended energy for the Omnilux 415-nm light, according to the manufacturer, is 48 J/cm^2 for 20 minutes. However, this energy setting can cause significant discomfort, so start with a setting of 24 J/cm^2 for 20 minutes. Energy settings can always be increased. For significant photodamage, actinic keratoses, or deep cystic acne, use IPL at 25 to 45 J/cm^2, depending on the skin type and cooling mechanism, followed by additional exposure using blue light (410 to 417 nm) at 10 to 48 J/cm^2 for 3 to 8 minutes, depending on the energy settings used.
13. Apply a gentle moisturizer or Aquaphor.
14. Inform the patient that the redness and swelling will likely intensify over the next 48 hours. The patient should use a hat or umbrella and sunscreen to guard against any sun exposure for the next 48 hours.
15. Patients appreciate a follow-up by phone or office visit in 24 to 72 hours.
16. To help prevent PIH, prescribe a lightening agent such as hydroquinone 4% cream for darker skin types (IV to VI) once the skin is fully recovered.
17. When IPL with ALA is used for sebaceous gland hyperplasia, at a 7- to 10-day follow-up, hyfrecate the majority of the lesions still present. After two to three treatments with ALA-PDT, there is a significant reduction in the number of newly occurring lesions.

Complications

- *PIH* is a potential complication of this procedure. If this occurs, prescribe a combination cream of hydroquinone 4%, tretinoin 0.05%, and fluocinolone acetonide 0.01% to be used once or twice daily for up to 8 weeks. Microdermabrasion every 2 weeks may also be added.
- Sun exposure in the first 48 hours may result in *blistering, severe* phor, and frequent follow-up visits to monitor for infection are recommended.
- *Infection* is rare but can occur. If impetigo occurs, mupirocin (Bactroban) topical ointment or cephalexin 500 mg twice daily may be prescribed for 7 to 10 days. If herpes simplex virus infection occurs, antivirals such as acyclovir should be prescribed.
- Also see some of the common after-effects noted previously.

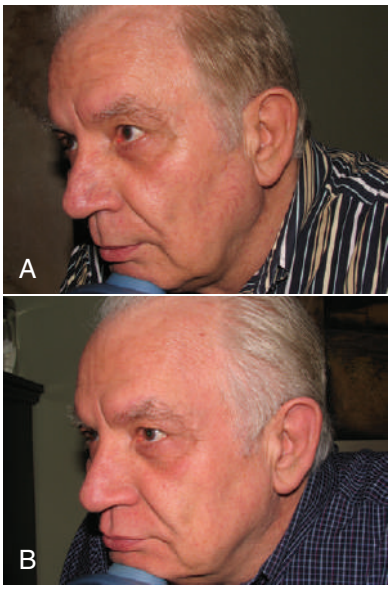


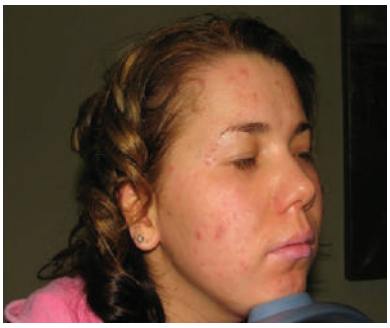
Figure 60-2 **A,** Photodamage before treatment. **B,** Photodamage after three photodynamic therapy treatments with intense pulsed light and BLU-U.

Postprocedure Management

Avoiding sun exposure and keeping the treated area moist are essential. Aquaphor is a preferred healing ointment. To soften any significant crusting, apply wet gauze soaked in a solution of one teaspoon of vinegar to one cup of water. This may be applied for 10 minutes three times daily.

Results

With three to five photorejuvenation treatments with ALA-PDT (60-minute incubation time) in combination with IPL followed by BLU-U for 3 minutes (Fig. 60-2A and B); or with three to five acne treatments with ALA-PDT (60-minute incubation time) and BLU-U exposure alone for 15 minutes (Figs. 60-3 and 60-4), the patient satisfaction rate is very good.



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