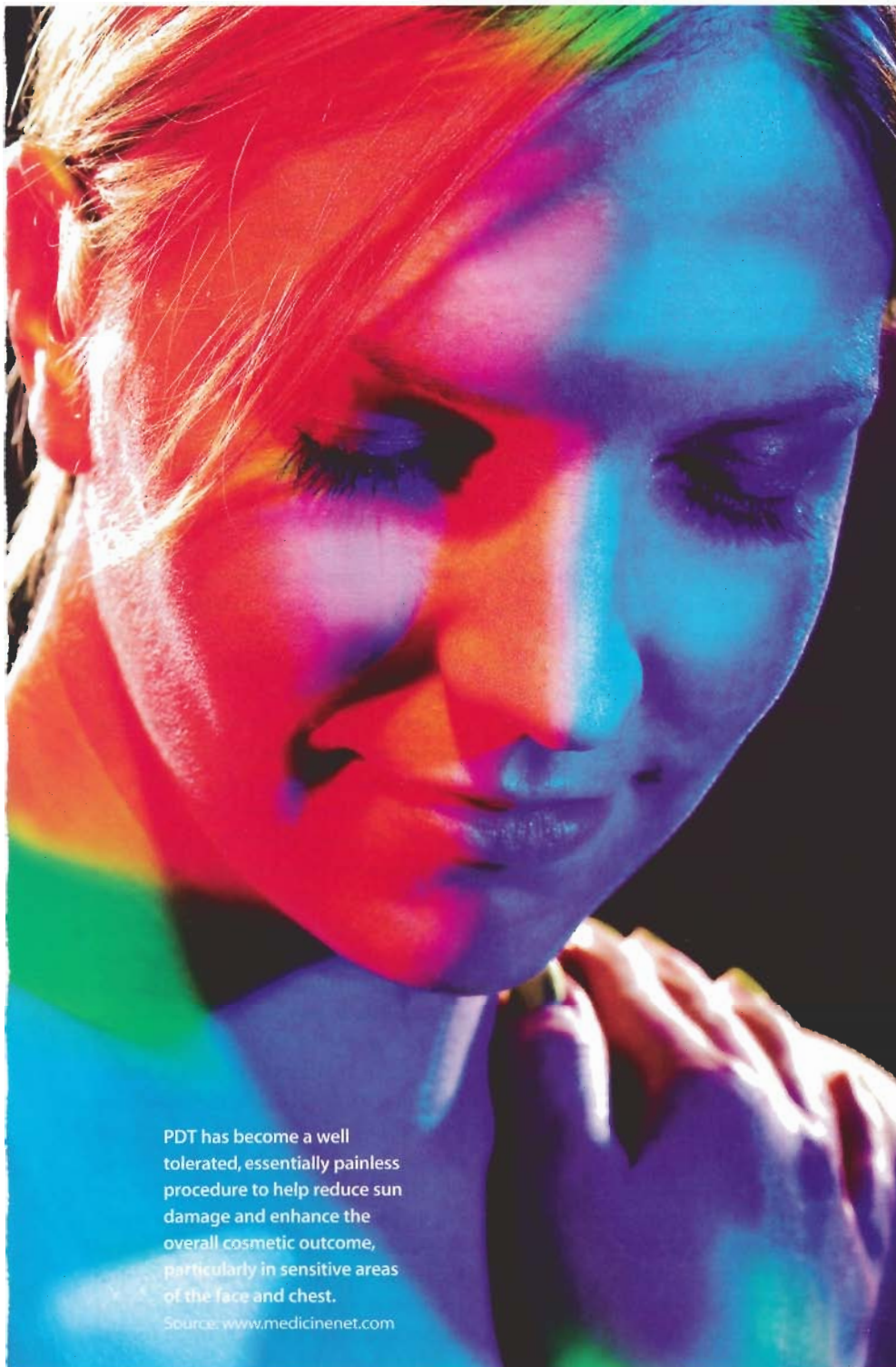


Making Strides in Photodynamic Therapy

BY DANIEL BAROLET, MD



PDT has become a well tolerated, essentially painless procedure to help reduce sun damage and enhance the overall cosmetic outcome, particularly in sensitive areas of the face and chest.

Source: www.medicinenet.com

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PDT has several clinical applications, making it an excellent choice for treating various skin conditions.

In dermatologic circles, photodynamic therapy (PDT) is a popular weapon in the physician's arsenal against benign and malignant dermatological conditions. PDT involves using photochemical reactions mediated through the interaction of photosensitizing agents, light and oxygen.

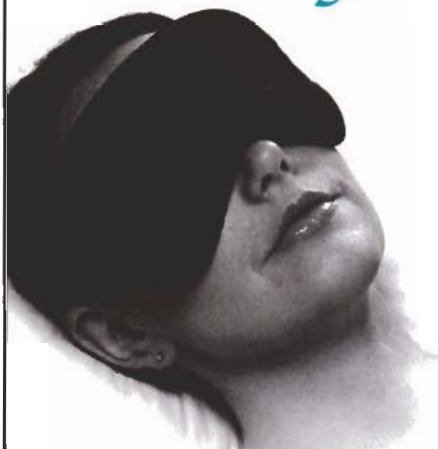
With PDT, physicians selectively treat abnormal cells while preserving the normal structures. We can achieve this dual selectivity by directing the light source on the lesional tissue. Because photosensitizers are preferentially accumulated in hyperproliferative/abnormal tissues, we can minimize damage to adjacent healthy structures. This selectivity accounts for PDT's safety and efficacy.

To produce a therapeutic or cosmetic effect, we administer a photosensitizing agent by one of several routes: topical, oral or intravenous. The agent is then converted to protoporphyrin IX (PpIX), an endogenous potent photosensitizer that accumulates in the tissue. The second step involves activating the PpIX in the presence of oxygen and light within a specific range of wavelengths. PpIX thereafter converts to biomolecules—singlet oxygen or radicals—that damage the target tissue without harming the surrounding structures.

Different Photosensitizers

Many photosensitizer families are in clinical use or under investigation. A photosensitizer should have the following characteristics: It should have maximum absorption at the wavelength of light used, offer a good penetration and even distribution throughout the target

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area and demonstrate a high selectivity to abnormal tissues.¹

To date, physicians have used topically active agents, such as 5-aminolevulinic acid (ALA) and the methyl ester of ALA, methyl-5-amino-4-oxopentanoate (MAL). These topical vehicles penetrate the stratum corneum to reach the target area and increase the endogenous synthesis of PpIX. Of the two, MAL seems to penetrate the skin more quickly and deeply. It rapidly achieves the maximum in intracellular protoporphyrin concentration, which leads to a shorter incubation time—three hours—compared with ALA, which takes four to six hours.²

Light Sources

In PDT protocols, various wavelengths of light in the visible spectrum (400 nm to 700 nm) and near-infrared radiation (NIR) (700 nm to 1000 nm) have been used. Wavelengths include blue (400 nm to 470 nm), green (470 nm to 550 nm) and red (630 nm to 1000 nm) light.

For best effects, the wavelength should allow optimum penetration of light in the skin. In general, the longer the wavelength (up to 850 nm), the deeper its penetration into tissues.^{3,4} Depending on the tissue type, the penetration depth is less than 1 mm at 400 nm, 0.5 mm to 2 mm at 514 nm, 1 mm to 6 mm at 630 nm and maximal at 700 nm to 800 nm. The wavelength also should be within the absorption spectrum of PpIX. The absorption peaks of PpIX are within the visible/NIR spectrum and permit illumination with various light colors/wavelengths.⁵

Red light can be used successfully for deeper localized target tissues (e.g., sebaceous glands), and blue light may be useful for treating skin conditions located in the epidermis, such as actinic keratoses. Blue light also photo bleaches any residual protoporphyrin IX (PpIX) in the epidermis, thereby reducing post-treatment photosensitivity.

Several light sources have been used in cutaneous clinical applications studies of PDT, including incoherent lamps (xenon and halogen lamps), lasers (pulsed dye, argon), intense pulse light (IPL) and light-emitting diodes (LED).

Lasers and IPL have a downside, how-

ever. They may induce peak power effects, such as tissue hypoxia, thermal diffusion in the dermis, photo bleaching of the photosensitizer before photoactivation and simultaneous micro-injuries in the dermis. This sometimes is desirable when trying to get rid of blood vessels and lentiginos in photodamaged skin.

An LED source, on the other hand, avoids thermal peak power effects on the photosensitizer. It also can cover larger surfaces than lasers and is available in multiple wavelengths that meet the absorption peak spectrum of PpIX.

No single light source is ideal for every possible dermatological indication. We must base our choice of a light device and specific wavelength on the intended clinical application, as well as on the number and size of the lesions.

Clinical Applications

PDT has several clinical applications, making it an excellent choice for treating the following conditions:

Actinic keratoses. This premalignant condition is most common in fair-skinned people who are frequently exposed to the sun. It's characterized by thick, scaly or crusty patches of skin. Some of these precancers progress to squamous cell carcinoma, so they need to be treated.

Researchers are continually assessing the optimal wavelength of light to use with actinic keratoses (AK). Most studies have been conducted with red wavelengths. However, blue light and green light also are effective because AK lesions are mainly located in the epidermis.^{6,7} ALA and MAL are approved for use in Europe, New Zealand, Australia, Canada and the United States. ALA is primarily indicated for hyperkeratotic AK and MAL, for nonhyperkeratotic AK of the face and the scalp in immunocompetent patients.

Basal cell carcinoma. As the most common form of skin cancer, basal cell carcinoma (BCC) is rarely life-threatening. But if left untreated, it can be disfiguring. It also can produce local destruction and cause bleeding. Moreover, large and longstanding tumors may metastasize into regional lymph nodes and surrounding tissues and bones. Hence, these lesions must be treated readily.

Current evidence suggests that topical ALA and MAL-PDT are effective treatments for superficial BCC, with superior healing and cosmesis than cryotherapy.⁷⁻⁹ PDT therapy, however, appears to be less effective for nodular BCC. For nodular BCCs, surgical excision remains the treatment of choice. Using PDT to treat superficial and/or nodular BCC is approved in Europe, New Zealand and Australia.

Bowen's disease. Bowen's disease (BD) is a neoplastic skin disease, considered either as an early stage or intraepidermal form of squamous cell carcinoma in situ. BD typically presents as a gradually enlarging, well demarcated erythematous plaque with an irregular border and surface crusting or scaling. BD occurs predominantly on sun-exposed areas of skin.

ALA and MAL induce good clinical responses in BD.^{6,7} PDT is certainly one of the best clinical approaches to BD because the lesions are often large; a surgical approach may produce extensive scarring. MAL is approved in Europe, New Zealand

and Australia for treating BD when surgical excision is considered less appropriate. It is not approved in the United States for this indication.

Photoaging. Photoaging refers to skin damage from prolonged, lifetime exposure to ultraviolet radiation. It's associated with morphological changes, including rhytides, furrows and telangiectasia.^{10,11}

Several studies have shown that PDT with ALA and MAL has positive effects on photo-damaged skin. Physicians have obtained photorejuvenation effects mainly with red and blue light.¹² The exact mechanism of action is not well known, but increased collagen synthesis occurs after treatment.¹³ Although PDT with ALA and MAL can be used for photoaging, it's not currently approved by regulatory agencies, including the FDA.

Acne vulgaris. This skin disease is associated with hypercornification of the pilosebaceous duct, increased sebum production, colonization with *Propionibacterium acnes* and an inflammatory response. Patients can present with noninflamed whiteheads and black-

heads, seborrhea, inflamed papules, pustules and nodules, which may be followed by atrophic or hypertrophic scarring.

PDT with ALA and MAL is now used off-label to treat acne. Patients experience significant clinical improvement. In fact, with various light devices and wavelengths, they see a decrease in sebum production and sebaceous gland size post-treatment.¹⁴ Given that sebaceous glands are often located in the mid-dermis, red light might be a better choice to target these structures. The exact frequency and number of sessions required are unknown.

In general, PDT with ALA and MAL are well tolerated with occasional mild and transient side effects. Local sensations of burning, pruritus and stinging are also commonly reported during light exposure and, sometimes, for hours after treatment. Local erythema and edema at the treatment site also are seen. Cutaneous photosensitivity may occur, and we can handle this by protecting the area with clothing and avoiding sunlight. Postinflammatory

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hypopigmentation and hyperpigmentation also may occur. Blistering, suppuration and erosion indicate phototoxicity and may take up to eight weeks to heal, with local crusting, scaling and pruritus.

Before selecting PDT as a treatment modality, be sure to review potential contraindications, which include cutaneous sensitivity, porphyria, allergy to Pp or to components of the topical agent. Be cautious when treating pregnant women or children. We have limited information about using PDT in these populations. So we should not take unnecessary risks.

With PDT, we can noninvasively target therapy and locally irradiate involved areas. We also can generate excellent cosmetosis with minimal discomfort and adverse affects. This is a distinct advantage of this modality. Another big advantage of PDT is that the photosensitizer doesn't interact directly with DNA, but instead interacts with oxygen in tissue. Essentially, we are using light and drugs to make singlet oxygen, which leads to selective necrosis/apoptosis of targeted cells.

Several issues will play a role in the future of PDT. Among them is the light source. Using an LED source avoids the thermal peak effect on the photosensitizer, a problem we typically encounter with thermal technologies, such as IPLs and pulsed dye lasers. LED technology clearly allows us to progressively activate the photosensitizers.

In addition, the wavelength specification is key to matching selective absorption peaks of the photosensitizer. We should use a wavelength with a narrow spectral band that reaches deeper dermal structures. In fact, a dual-wavelength LED (red and blue) device optimizes PDT results by activating the photosensitizer deep at the target structure.

We also should consider the potential key role in the skin absorption of the photosensitizer. The challenge rests in reaching deeper in the skin for enhanced clinical effect in the

dermis. The entire photon delivery method, before and during PDT, could hold part of the answer for more effective treatments.


Not only can LED sources be used to stimulate a photosensitizer, but high-powered infrared LEDs can prepare the skin before treatment. Researchers have used a new pre-PDT method to increase in situ conversion of 5-ALA to PpIX. PDT experimentation is limited, however, because only two photosensitizers are cleared: Levula™ and Metvix.™ But promising agents are in the industry pipeline.

Clearly, PDT presents an interesting array of treatment strategies for physicians, and the future looks quite promising for this modality. ■

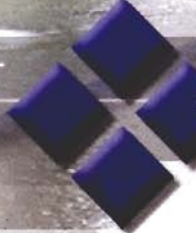
For a list of references, go to www.advanceweb.com/healthyaging and click on the references toolbar.

DANIEL BAROLET, MD, conducts research activities in his own Skin Optics Research Laboratory (RoseLab) affiliated with McGill University in Montreal, Canada. A pioneer in laser dermatology, Dr. Barolet contributed to several technological innovations pertaining to photoepilation, photorejuvenation, LED therapy and PDT.


Disclosure: Dr. Barolet indicates that he holds a patent for a health care product or category of products named in this article.



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