

Photodynamic therapy: Basics and new directions for clinical applications

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Polymers in Medicine, ISSN 0370-0747 (print), ISSN 2451-2699 (online)

Polim Med. 2025;55(2):145–151

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Funding sources

None declared

Conflict of interest

None declared

Received on May 30, 2025

Reviewed on June 27, 2025

Accepted on June 10, 2025

Published online on December 19, 2025

Abstract

Photodynamic therapy (PDT) remains a developing modality in cancer treatment. It is a minimally invasive approach that employs a photosensitizing drug, activated by light, to induce localized cytotoxic effects. Initially introduced in oncology, PDT has proven effective for cancers such as skin malignancies and head and neck tumors, while sparing surrounding healthy tissue. Beyond oncology, its use has expanded to dermatology, ophthalmology and dentistry, and it shows promise in the management of chronic inflammatory conditions, pediatric nephrology and emerging applications in cardiovascular and neurodegenerative diseases. Despite persistent challenges such as limited light penetration, advances in photosensitizers and integration with technologies including immunotherapy and polymeric nanocarriers underscore PDT's potential as a versatile tool in precision medicine. Recent studies suggest that PDT can also modulate the tumor microenvironment (TME) and stimulate anti-tumor immune responses, thereby enhancing its therapeutic impact. Consequently, it is increasingly being investigated in combination with other treatment modalities to overcome resistance and improve patient outcomes.

Key words: photodynamic therapy, polymers, photosensitizing effect

Cite as

Popiel-Kopaczyk A, Kręcicki TS, Kozieł R. Photodynamic therapy: Basics and new directions for clinical applications. *Polim Med.* 2025;55(2):145–151. doi:10.17219/pim/208132

DOI

10.17219/pim/208132

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Highlights

- Photodynamic therapy (PDT) provides targeted, minimally invasive cancer treatment, achieving tumor control while sparing surrounding healthy tissues.
- Applications of PDT extend beyond oncology, with growing evidence supporting its use in dermatology, ophthalmology and neurodegenerative disorders.
- Next-generation photosensitizers and nanocarriers improve PDT efficacy, enabling deeper light penetration and advancing its role in precision medicine.
- PDT reshapes the tumor microenvironment and enhances immune response, increasing effectiveness when combined with immunotherapies and other treatment modalities.

Introduction

Photodynamic therapy (PDT) is a contemporary, localized approach for treating tumors and precancerous conditions. The technique selectively targets diseased tissues while sparing adjacent healthy structures, often resulting in superior cosmetic outcomes compared with conventional therapies. It involves administering a photosensitizer that preferentially accumulates in tumor cells; upon activation by light, it triggers cytotoxic reactions that lead to cell death. A major advantage of PDT is its selectivity: photosensitizers accumulate preferentially in tumor cells, thereby increasing safety for patients.^{1,2} In clinical practice, PDT is primarily employed in dermatology,³ urology,⁴ ophthalmology,⁵ and gynecology,⁶ for both oncological and non-oncological conditions. Its applications in cardiology, neurosurgery and orthopedics are less frequent. It is also used in the management of age-related macular degeneration (AMD) and other ocular diseases.⁷ Research into its potential for treating coronary diseases, leukemias and transplant rejection prevention is ongoing. The forgotten approach of PDT, i.e., photodynamic antimicrobial chemotherapy (PACT), has been intensively developed in recent years.⁸ Similarly to PDT, PACT involves phototoxic reactions activated by visible or ultraviolet light, activating photosensitizers, primarily porphyrin-based. It is often recently used to neutralize viruses, drug-resistant bacteria, yeasts, and parasites. Moreover, PACT is successfully applied in dentistry, e.g., in treating caries and gingivitis, as well as for plaque removal. Thus, PDT procedures find a broad application in various neoplastic and non-neoplastic diseases, with relatively good patient comfort.

In recent years, the versatility and precision of PDT have attracted growing interest in the context of personalized medicine. Ongoing research explores the combination of PDT with nanotechnology and immunotherapy, enhancing both its specificity and therapeutic efficacy. Moreover, new generations of photosensitizers are being developed to optimize light absorption, improve tumor selectivity and reduce systemic toxicity. These advances could help overcome current limitations, such as poor light penetration into deep tissues. As such, PDT continues to evolve

as a promising, multi-faceted modality in modern clinical practice, with the potential to reshape treatment paradigms across diverse medical disciplines.

Photosensitizers

Photosensitizers are dyes that initiate physicochemical reactions when exposed to light of a specific wavelength. In PDT, the radiation used falls within the visible spectrum (400–700 nm). Tissue penetration depends on both wavelength and energy, increasing with longer wavelengths at a constant intensity. Blue and green light, with shorter wavelengths, penetrate up to approx. 2 mm, whereas red light (>600 nm) can reach depths beyond 3.5 mm.^{9,10} However, light energy decreases substantially in deeper tissue layers, limiting the photodynamic effect. For this reason, photosensitizers that absorb light at longer wavelengths are preferred to improve penetration into deeper structures. Most currently available photosensitizers absorb at approx. 630–650 nm, a range often referred to as the “therapeutic window.” Natural pigments such as hemoglobin also absorb light and thereby restrict penetration. To be effective, an ideal photosensitizer must satisfy several criteria^{9,11,12}:

- Retention in tissue for at least several hours;
- An absorption spectrum distinct from naturally occurring pigments in the body;
- Minimal side effects;
- High efficiency in generating singlet oxygen or radical oxygen species.

Hematoporphyrin derivatives (HpDs) are the most widely used first-generation photosensitizers and only partially fulfill the criteria for an ideal agent. Hematoporphyrin, first described by Lipson et al. in 1961, was the earliest photosensitizer applied in PDT and later received U.S. Food and Drug Administration (FDA) approval. When administered intravenously at a dose of 2 mg/kg body weight, HpD accumulates in tumor tissue within 48–72 h but persists in the body for 6–8 weeks, leading to prolonged photosensitivity. Hematoporphyrin derivatives are activated by red light at 630 ± 3 nm.¹³ The purified form of this compound was commercialized as Photofrin and has been

widely used in clinical practice (<https://photofrin.com/>).¹³ Other groups of photosensitizing agents include cyanines and phthalocyanines,^{14,15} chlorins¹⁶ and bacteriochlorins, as well as naturally derived compounds such as curcumin, hypericin and riboflavin.⁹

Procedure and basic mechanisms of PDT

Photodynamic therapy involves several stages: photosensitizer administration, cellular accumulation, irradiation, induction of cytotoxic reactions, and subsequent wound formation. The first step is administration, during which the patient receives a photosensitizer that penetrates tumor cells. Over the next several hours, the photosensitizer accumulates selectively within tumor cells, preparing the tissue for light activation. The tumor site is then irradiated with light at a wavelength corresponding to the absorption spectrum of the photosensitizer, typically applied for about 10 min per site. This irradiation triggers cytotoxic reactions in which reactive oxygen species (ROS) and free radicals are generated within tumor cells. The treatment is followed by localized wound formation and subsequent healing, with the affected area typically resolving over several weeks and leaving minimal scarring.²

Photodynamic reactions can proceed through distinct mechanisms, and 3 principal pathways of PDT-induced effects on tumor tissue have been described. In the Type I mechanism, photosensitizers react with acceptor molecules to generate radical species. In the Type II mechanism, triplet-state photosensitizers interact directly with molecular oxygen, producing singlet oxygen.¹⁷ The Type III mechanism is associated with stimulation of the immune response against cancer cells.¹⁸ Following PDT, tumor cells may undergo cell death – through apoptosis, necrosis or other regulated pathways – triggered by photodamage to intracellular compartments such as mitochondria, lysosomes or the endoplasmic reticulum.¹⁹

Clinical applications of PDT

Photodynamic therapy has evolved into a versatile treatment modality with applications extending well beyond its original focus on oncology. Its expanding clinical utility – from inflammatory conditions to pediatric nephrology – offers an increasingly attractive area of investigation for both clinicians and researchers. Recent advances in PDT have focused on improving photosensitizer delivery and combining the technique with chemotherapeutics, antibodies or other adjuvant agents.^{6,20} Importantly, PDT can be applied in 2 main directions: the treatment of oncological and non-oncological diseases.

Oncological applications

Photodynamic therapy is well established in the treatment of a variety of cancers, including skin malignancies (e.g., basal cell carcinoma (BCC), squamous cell carcinoma (SCC) and actinic keratosis), as well as head and neck cancers, esophageal cancer, bladder cancer, and lung cancer.^{13,17} In oncological protocols, PDT primarily employs broad-spectrum red light, with typical therapeutic doses ranging within 100–150 J/cm² at an intensity of 100–200 mW/cm².¹⁹ The mechanisms of PDT involve the selective accumulation of photosensitizers in malignant tissues, followed by light activation that triggers cytotoxic reactions leading to cell death, vascular damage and local inflammation, while sparing surrounding healthy tissue. This selectivity not only reduces treatment-related morbidity but also improves cosmetic outcomes, reinforcing confidence in PDT's clinical efficacy.¹⁹ Selectivity can be further enhanced through the use of nanocarriers to optimize photosensitizer delivery or by conjugating photosensitizers with antibodies that target specific cell populations.^{17,18}

Non-oncological dermatological and inflammatory conditions

- In dermatology, PDT has been employed to manage^{21,22}:
- Psoriasis: PDT modulates immune responses and reduces keratinocyte proliferation.²³
 - Acne vulgaris: PDT with 5-aminolaevulinic acid (ALA) or methyl aminolevulinate targets sebaceous glands and reduces *Cutibacterium acnes* load.²⁴
 - Vitiligo: PDT procedure promotes melanocyte regeneration through photomodulation.²⁵
 - Chronic ulcers: photodynamic therapy enhances wound healing by reducing microbial load and stimulating angiogenesis.
 - Recurrent palmar and plantar warts caused by human papillomavirus (HPV) infection.²⁶

It is also used in several non-oncological disorders, with lower PDT doses in the range of 10–40 J/cm² and intensity of 50–70 mW/cm².²¹ Similar PDT doses have shown promise in treating inflammatory diseases due to their ability to reduce pro-inflammatory cytokines and modulate immune responses.²⁷ This procedure can be effectively used in:

- Rheumatoid arthritis: Experimental studies suggest that PDT can reduce joint inflammation and synovial hyperplasia.
- Periodontitis and gingivitis, where this method is applied in dental settings: PDT targets biofilms and resistant bacteria, improving oral health outcomes.
- Inflammatory bowel disease (IBD): Early-stage research indicates its potential in managing localized intestinal inflammation.

Applications in pediatric diseases

In pediatrics, PDT is emerging as a potential therapeutic approach to address conditions involving inflammation, infections or dental disorders²⁸:

- Nephrology and urinary tract infections (UTIs): PDT can serve as an adjunct to antibiotics, targeting multidrug-resistant bacterial strains and reducing recurrent infections in children.^{29,30}
- Renal fibrosis: Studies indicate that PDT may inhibit fibroblast proliferation and collagen deposition, which are central to chronic kidney disease (CKD) progression. The potential of PDT in managing CKD offers a ray of hope for future therapeutic approaches.³⁰
- Dentistry: PDT's immunomodulatory effects could potentially attenuate systemic inflammation associated with glomerular diseases.³¹

Ophthalmological disorders

Photodynamic therapy, as a highly precise technique, has also found important applications in ophthalmology, where it is commonly employed for^{5,7}:

- Age-related macular degeneration: PDT slows the progression of neovascularization and is primarily indicated for the wet form of the disease, which is characterized by abnormal blood vessel growth and may lead to vision loss.
- Non-AMD choroidal neovascularization: PDT is also used to manage neovascularization unrelated to AMD.
- Central serous chorioretinopathy (CSCR): PDT reduces retinal detachment and fluid accumulation.
- Choroidal hemangioma: PDT with verteporfin has been applied as a targeted treatment option.
- Diabetic retinopathy: PDT minimizes angiogenesis and preserves visual acuity.

Photodynamic therapy is widely used in ophthalmology, most commonly with verteporfin as the photosensitizer. It selectively targets choroidal vascular abnormalities, inducing occlusion of affected vessels. Initially, it was extensively applied at full-dose verteporfin for the treatment of neovascular age-related macular degeneration (nAMD). However, when vascular endothelial growth factor (VEGF) receptor inhibitors were detected, the clinical approach has shifted toward other chorioretinal disorders, including central serous chorioretinopathy, polypoidal choroidal vasculopathy and choroidal hemangioma.³²

Emerging applications in cardiovascular and neurological diseases

Research on PDT is also expanding into novel fields. In atherosclerosis, photodynamic activation of porphyrins has been investigated for targeting atherosclerotic plaques and improving vascular health.^{33,34} In neurodegenerative diseases, PDT-mediated clearance of amyloid plaques

is being explored as a potential therapeutic approach for Alzheimer's disease.³⁵

It was noted that cardiovascular disorders are among the leading causes of death worldwide. Photodynamic therapy can be used to treat atherosclerotic cardiovascular disease (ACD), and the photosensitizing agent should have a specific affinity for macrophages, which are crucial in the development of atherosclerosis.³³ Available studies indicate that PDT using indocyanine green (ICG) is a promising approach for the prevention of restenosis³⁶ and the treatment of atherosclerosis.³⁷

Photodynamic therapy has also shown potential in the field of neurodegenerative diseases. Studies have demonstrated that nano-photosensitizers, such as core-shell azobenzene-spiropyran structures on gold nanoparticles, can inhibit tau protein aggregation in neural cells and promote dendritic growth in neuronal cells.³⁸

Advantages of PDT in multisystem diseases

The localized action of PDT, which spares surrounding healthy tissues and produces minimal systemic effects, makes it particularly suitable for delicate pediatric populations and chronic inflammatory conditions. Furthermore, its adaptability to different photosensitizers and light sources broadens its potential for application across diverse pathologies. Table 1^{21–24,30,32,34,39–47} provides a structured overview of PDT applications and their clinical relevance. Porfimer sodium, a first-generation photosensitizer, is extensively used in oncology. In contrast, ALA and methyl aminolevulinate (MAL), both second-generation photosensitizers, are more commonly applied in dermatology.³⁹ Verteporfin is predominantly used in ophthalmology for conditions such as AMD.⁵ Additionally, emerging applications in inflammatory and pediatric conditions remain under experimental investigation, with ongoing efforts focused on developing optimized photosensitizers.

Photodynamic procedures with polymeric nanocarriers

Recently, PDT protocols have preferably used encapsulated photosensitizers to target cancer cells more precisely.⁴⁷ One of the most applied types is polymeric nanocarriers,⁴⁸ such as PEGylated micelles (PEG – polyethylene glycol micelles), poly(lactic-co-glycolic acid) (PLGA) or chitosan nanoparticles, dendrimers, and stimuli-responsive polymersomes, which are increasingly explored to overcome the pharmacokinetic and selectivity barriers that still limit classical PDT.⁴⁹ When we encapsulate hydrophobic photosensitizers, these biodegradable carriers protect them from early degradation, prolong systemic circulation, and favor passive accumulation within cancer tissue by the enhanced-permeation-and-retention effect, and simultaneously enhancing photo-dependent cytotoxicity.

Table 1. Diseases treated with photodynamic therapy (PDT) and commonly used photosensitizers

Disease/condition	Clinical application	Photosensitizers	Light wavelength	Reference
Oncological applications				
Skin cancers (BCC, SCC)	treatment of localized tumors with excellent cosmetic outcomes	Photofrin, Metvixia (MAL), ALA	630–650 nm (red light)	21, 22, 39
Head and neck cancers	ablation of tumors in hard-to-reach areas	Photofrin	630 nm	40
Esophageal cancer	localized destruction of malignant tissues	Photofrin	630 nm	41
Lung cancer	treatment of early-stage or non-resectable tumors	Photofrin	630 nm	42, 43
Non-oncological applications				
Psoriasis	modulation of immune response and keratinocyte proliferation	MAL, ALA	630–650 nm	23
Acne vulgaris	targeting sebaceous glands and <i>Cutibacterium acnes</i>	ALA	400–450 nm (blue light)	24
Age-related macular degeneration	neovascularization inhibition	Verteporfin	689 nm (infrared)	34
Central serous chorioretinopathy	fluid accumulation reduction	Verteporfin	689 nm (infrared)	32
Periodontitis and gingivitis	bacterial biofilm reduction in dental applications	Toluidine blue, Methylene blue	630–700 nm	44
Inflammatory conditions				
Rheumatoid arthritis	reducing joint inflammation	photosensitizers under development	experimental range	45
IBD	reducing localized intestinal inflammation	photosensitizers under development	experimental range	46
Pediatric nephrology				
Urinary tract infection	targeting multidrug-resistant bacteria	photosensitizers under development	experimental range	47
Renal fibrosis	mitigation of fibroblast proliferation	photosensitizers under development	experimental range	30

UTIs – urinary tract infections; IBD – inflammatory bowel disease; BCC – basal cell carcinoma; SCC – squamous cell carcinoma; MAL – methyl aminolevulinate; ALA – aminolevulinic acid.

Available studies highlight additional advantages when nanocarrier surfaces are functionalized with antibodies, peptides or small-molecule ligands that actively direct the photosensitizer toward overexpressed cancer biomarkers.⁵⁰ At the same time, pH-, redox- or light-cleavable polymer shells allow on-demand release precisely at the tumor target site. Beyond effective drug transport, polymeric platforms provide space to co-load oxygen carriers, immune adjuvants or chemotherapeutics, creating multifunctional “all-in-one” nanoreactors that synergize PDT with diagnostics, immuno- or chemotherapy.^{51,52} Early pre-clinical studies already report superior tumor regression and reduced skin phototoxicity compared with free photosensitizers, underlining the clinical promise of polymer-based nanotechnology in both oncological and inflammatory indications.

Limitations

Despite its wide-ranging clinical potential, PDT is limited by shallow light penetration, lack of standardized treatment protocols and the prolonged photosensitivity

caused by some photosensitizers. Additionally, many of its emerging applications remain experimental and require further clinical validation to confirm their safety and efficacy.

Conclusions

Photodynamic therapy has evolved into a highly versatile and innovative treatment modality, extending beyond its oncological origins. This technique utilizes the selective activation of photosensitizers through light exposure to induce cytotoxic effects, exhibiting significant efficacy in targeting malignancies while preserving adjacent healthy tissue. Over time, the selectivity and minimally invasive characteristics of PDT have established it as a valuable asset in various clinical fields.

Initially a foundational approach in the management of conditions such as skin cancers, head and neck tumors and internal organ malignancies, PDT has broadened its applications to include dermatological conditions, such as acne and psoriasis, as well as ophthalmological disorders, particularly AMD and diabetic retinopathy. Additionally,

its immunomodulatory properties facilitate the treatment of chronic inflammatory diseases, including rheumatoid arthritis, periodontitis and IBD. There is emerging potential for PDT in pediatric nephrology, addressing UTIs, alleviating inflammation in nephrotic syndrome and mitigating renal fibrosis.

Recent research also highlights the promise of PDT in treating cardiovascular diseases, particularly atherosclerosis, and neurodegenerative conditions, including Alzheimer's disease, thereby expanding its clinical applications. The localized application of PDT minimizes collateral damage to healthy tissues, enhancing its value in sensitive areas such as the eyes or specific areas in pediatric disorders. Its low systemic toxicity ensures patient safety, while its adaptability allows for integration across diverse medical disciplines ranging from oncology to dentistry.

However, PDT is not without challenges. Limited light penetration restricts its efficacy to surface or near-surface lesions, necessitating the development of advanced photosensitizers with improved selectivity and deeper tissue penetration. Additionally, standardized treatment protocols are required to optimize outcomes across a wide range of diseases. Future research should prioritize next-generation photosensitizers and explore combinations with other therapies, such as immunotherapy or nanotechnology, to overcome current limitations and extend PDT's potential.

In conclusion, PDT represents a cutting-edge, minimally invasive treatment that connects traditional methods and modern precision medicine. Its success in oncology and other fields has paved the way for diverse applications, including inflammation management and pediatric nephrology, underscoring its multidisciplinary potential. With advancements in photosensitizer technology and light delivery systems, PDT is poised to play an increasingly significant role in medical practice. By addressing its current challenges and fostering interdisciplinary collaborations, PDT holds the promise of unlocking new therapeutic possibilities and improving patient outcomes across a wide spectrum of diseases.

Use of AI and AI-assisted technologies

Not applicable.

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