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Biophotonics and Photodynamic Therapy: Emerging Optics-Based Treatments for Eye Conditions

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Abstract

Background: Ophthalmic medicine is increasingly leveraging the precision of light-based technologies for diagnosis and treatment. Biophotonics, the interaction of light with biological systems, and Photodynamic Therapy (PDT), a light-activated treatment, represent paradigm shifts in managing complex eye diseases. These provide targeted approaches with fewer adverse effects compared to conventional treatments.

Aim: The aim is to synthesize current evidence and technological advances in the years between 2013 and 2025 about the use of biophotonics and PDT to treat a range of ocular pathologies, from AMD to corneal disorders and oncological pathologies.

Methods: A narrative literature review was performed using PubMed, Scopus, and Web of Science. Search terms included "ophthalmic biophotonics," "photodynamic therapy," "verteporfin," "corneal cross-linking," "retinal imaging," and "light-guided therapy."

Results: The evidence confirms the established role of PDT in treating neovascular AMD and central serous chorioretinopathy. Significant refinements are noted toward the optimization of PDT parameters ("half-dose," "half-fluence") to enhance safety. Novel applications of PDT are emerging, such as in corneal neovascularization and ocular tumors. Simultaneously, biophotonic techniques, including two-photon microscopy and optogenetics, are entering the clinical arena from the research domain, providing unprecedented diagnostics at the cellular level and vision restoration strategies.

Conclusion: Biophotonics and PDT represent the cornerstone technologies in current ophthalmology. Their evolution to more selective, personalized, and combination treatments promises an improvement in therapeutic outcomes and further extension of the frontiers of eye diseases that can be treated. Future integration with AI and nanotechnology will continue to cement their leading role in the revolution of ophthalmic care.

Keywords: ophthalmic biophotonics, photodynamic therapy, age-related macular degeneration, corneal cross-linking, verteporfin

Introduction

By its very nature, the human eye is an organ exquisitely designed to interact with light. Therefore, it becomes all the more befitting that ophthalmology has emerged as one of the pioneering fields that work with the properties of light, not only for diagnosis but also for therapeutic intervention (Age-Related Eye Disease Study 2 (AREDS2) Research Group, 2013). Optics, photobiology, and medicine converged to create a new era of precision treatments, including most prominently biophotonics and photodynamic therapy. These novel methods constitute a radical departure from conventional surgical and pharmacological interventions, offering an unprecedented degree of spatial and biological specificity. Utilizing the interaction of light with tissue, treatments can be delivered in a targeted manner to preserve delicate ocular structures while effectively managing disease (Schmidt-Erfurth & Pruente, 2007).

Biophotonics describes a wide range of technologies using light as a means of understanding

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and manipulating biological processes (Figure 1). In ophthalmology, this includes advanced imaging modalities such as OCT angiography, adaptive optics, and multiphoton microscopy, which offer non-invasive, high-resolution views of the microstructure of the retina and cornea (Ahn, 2025). Beyond diagnostics, biophotonics also includes therapeutic applications such as CXL, which uses UVA light to strengthen the cornea, and laser therapies for glaucoma and posterior capsular opacification (Bousquet et al., 2018). Photodynamic Therapy is a more narrow term referring to therapy in which a light-sensitive drug photosensitizer is administered that is selectively absorbed by target cells and illuminated with a specific wavelength of light. Light activation initiates a photochemical reaction that generates cytotoxic reactive oxygen species, leading to local and controlled destruction of pathological tissues, such as the abnormal blood vessels characteristic of neovascular AMD (Cabrera et al., 2019).

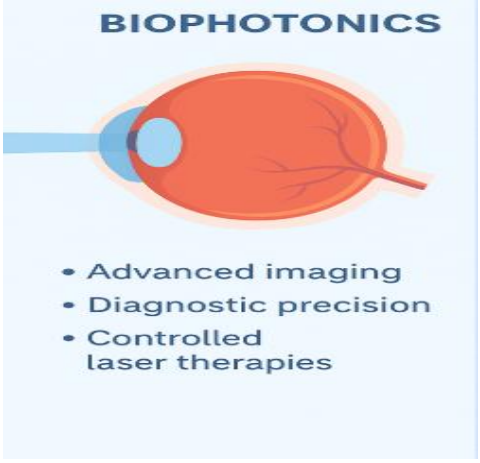

Figure 1. Overview of Biophotonics and Photodynamic Therapy in Ophthalmology

This narrative review aims to comprehensively synthesise the existing evidence and technological developments between 2013 and 2025 on the use of biophotonics and PDT in the management of a wide range of ocular disorders. The review will outline the established applications of these treatments, describe new uses supported by emerging evidence, and discuss innovative trends positioned to transform ophthalmic treatment paradigms. It is expected that through examination of the principles of, indications for, and future directions of these optics-based therapies, this review will highlight their transformative potential in preserving and restoring vision worldwide.

Basic Principles of Photodynamic Therapy in the Eye

The efficacy of PDT depends on the interaction between a photosensitizing agent, light of an appropriate wavelength, and tissue oxygen. The sequence of events involves a well-defined series of steps leading to its therapeutic specificity. First, a photosensitizer is administered systemically, usually via intravenous injection. In ophthalmology, verteporfin, a benzoporphyrin derivative, has been the most widely used agent. The drug then circulates and accumulates preferentially in metabolically active tissues, such as the rapidly proliferating endothelial cells of choroidal neovascular membranes in neovascular AMD or in hyperproliferative cells in tumors. This selective retention is a key factor in achieving targeted therapy while sparing the surrounding healthy retina and choroid (Altamirano et al., 2020).

The second element is the drug-light interaction. Following a time interval that allows for maximum differential accumulation of the photosensitizer in the target tissue, usually 15 minutes for verteporfin, a non-thermal laser light with a wavelength corresponding to the peak absorption of the drug, 689 nm for verteporfin, is exposed to the lesion via a slit lamp or a laser indirect ophthalmoscope. The light has to have adequate energy and power to pass through the ocular media and activate the drug without creating thermal injury (Al-Torbak, 2012).

The third critical factor is the presence of molecular oxygen. The photosensitizer, after light activation, reaches an excited state and transfers energy to the surrounding oxygen molecules, thereby producing very reactive and cytotoxic singlet oxygen and other ROS. Such an oxidative burst is confined to the area of illumination and to the immediate vicinity of the photosensitizer; thus, the site of damage is highly localized. Three major mechanism-of-action components have been described: (1) direct cytotoxicity against endothelial cells, inducing apoptosis; (2) neovascular endothelium damage, promoting thrombosis and occlusion of the abnormal vessels; and (3) anti-inflammatory and immunomodulatory effects contributing to long-term suppression of angiogenesis. Such a multifaceted mechanism allows PDT to achieve vascular closure and regression of pathological structures with remarkable precision (Mirshahi et al., 2024). Figure 2 visualizes the essential steps of ophthalmic PDT. This mechanism underlies PDT's role in treating neovascular AMD, CSCR, ocular tumors, and emerging indications.

Established Clinical Applications: From AMD to CSCR

The most well-established and foundational use of PDT in ophthalmology is in the management of neovascular or "wet" AMD. For many years, verteporfin PDT represented the gold standard of treatment, based on the landmark TAP and VIP studies. PDT showed a significant ability to stabilize vision and decrease the risk of severe vision loss in patients with predominantly classic subfoveal CNV (Nguyen et al., 2021). The introduction of anti-VEGF agents, however, has shifted the primary treatment paradigm for neovascular AMD due to their far

superior efficacy in improving vision; still, PDT retains an important niche role. It is more commonly used today in combination therapy for those cases poorly responsive to anti-VEGF monotherapy, for certain specific subtypes of CNV-like polypoidal choroidal vasculopathy, or as a strategy to decrease the high treatment burden imposed by intravitreal injections (Lin et al., 2025).

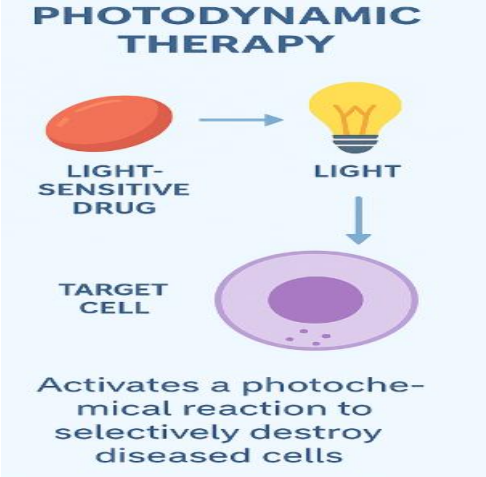

Figure 2. Mechanism of Photodynamic Therapy in Ocular Disease

Another major indication where PDT has shown outstanding results is in Central Serous Chorioretinopathy. Central serous chorioretinopathy is a serious detachment of the neurosensory retina resulting from leakage originating from the retinal pigment epithelium, with associated, often subtle, choroidal vascular hyperpermeability underneath (van Dijk et al., 2023; Rabiolo & Bandello, 2020). PDT, with commonly utilized reduced fluence or half-dose verteporfin protocols, has resolved the fluid beneath the retina and restored lost vision in chronic or recurrent cases. The proposed mechanism of action is selective choriocapillaris and RPE therapy that decreases choroidal hyperpermeability, allowing the RPE pump function to recover (Iacono et al., 2019). Indeed, after the PLACE trial, half-dose PDT gained its place as superior to laser photocoagulation or observation for chronic CSCR, definitively cementing it as the first-line treatment in many centers (Altınel et al., 2021).

Besides these two main indications, PDT has an established role in the management of ocular tumors, especially circumscribed choroidal hemangiomas. These are benign vascular tumors that may cause exudative retinal detachments with loss of vision. PDT induces thrombosis and involution of the hemangioma, with rapid resolution of subretinal fluid and improvement of function. The precision provided by this modality allows the treatment of lesions close to the fovea or optic nerve, where conventional laser or radiation therapy would carry a higher risk of collateral damage (Shields et al., 2020).

Corneal Cross-Linking: A Biophotonic Revolution in Corneal Stability

While PDT treats posterior segment diseases, another biophotonic innovation has transformed the approach to corneal diseases, especially keratoconus and post-LASIK ectasia. CXL is a minimally invasive surgical procedure that arrests the progression of these ectatic diseases by enhancing the biomechanical stiffness of the corneal stroma. The standard Dresden protocol involves the application of riboflavin (Vitamin B2) as a photosensitizer to the de-epithelialized cornea, followed by irradiation with UVA light (370 nm) at a specific irradiance for 30 minutes (Sarac et al., 2018).

A photochemical reaction is the biophotonic principle involved. Under UVA exposure, riboflavin acts as a photosensitizer, absorbs photons, and transitions to an excited triplet state. In the presence of ambient oxygen, it forms ROS, mainly singlet oxygen. These ROS cause the formation of additional covalent bonds, or cross-links, between adjacent collagen fibrils and proteoglycans within the corneal stroma. The corneal rigidity and resistance to enzymatic digestion increase significantly, thereby effectively stabilizing the cornea and preventing further bulging and thinning. The success rate of CXL in arresting the progression of keratoconus is more than 95% in many studies, and for this reason, CXL has become the standard of care all over the world (Hovakimyan et al., 2012).

The technology has since evolved with the development of "epi-on" or transepithelial CXL techniques, aiming at maintaining the integrity of the corneal epithelium to minimize postoperative pain, risk of infection, and healing time. Other approaches, such as accelerated CXL protocols using higher irradiance for shorter periods, are also being refined to optimize the efficiency of the treatment and patient comfort. Its application is also expanding beyond keratoconus, showing promise in treating infectious keratitis by strengthening the corneal tissue and due to its antimicrobial photodynamic effect, and also in managing bullous keratopathy (Iacono et al., 2020).

Emerging Applications and Novel Photosensitizers

The success of PDT in its established domains has spurred research in novel applications and the development of next-generation photosensitizers. One promising area is the treatment of corneal neovascularization, which impairs vision and causes cosmetic concerns (Yoon et al., 2019). Preclinical and early clinical studies have demonstrated that PDT with verteporfin or other agents can cause regression of pathological corneal vessels with minimal damage to adjacent transparent cornea and thus presents a potential alternative to steroid therapy or fine-needle diathermy (Sarma et al., 2023).

Research in ocular oncology is focused on the development of more selective and effective PDT

for intraocular tumors such as retinoblastoma and uveal melanoma (Turkoglu et al., 2019). Approaches include the synthesis of photosensitizers that selectively target tumor cells by conjugation to antibodies or peptides that bind to tumor-associated antigens. Second, the use of nanoparticle-based delivery systems is under investigation as a means to enhance the bioavailability and tumor-specific accumulation of photosensitizers, enabling the treatment of larger or more resistant lesions (Carroll et al., 2013).

Another frontier is the application of PDT for infectious keratitis, especially in those caused by drug-resistant bacteria, fungi, or *Acanthamoeba*. Antimicrobial PDT (aPDT) makes use of photosensitizers that bind to microbial cells. Light activation generates ROS that lethally damage microbial membranes and DNA, independent of antibiotic resistance mechanisms. This represents a wide-spectrum, non-antibiotic approach to the management of challenging ocular infections. Early results are encouraging, positioning aPDT as a potential adjuvant or alternative to conventional antimicrobial therapy. The following table summarizes the main clinical applications of PDT and biophotonics in ophthalmology.

Table 1: Clinical Applications of Biophotonics and Photodynamic Therapy in Ophthalmology

Condition	Technology	Mechanism of Action	Clinical Status
Neovascular AMD	Verteporfin PDT	Occlusion of choroidal neovascularization via vascular damage and thrombosis.	Established (combination/refractory cases).
Central Serous Chorioretinopathy	Half-dose/ Half-fluence PDT	Reduces choroidal hyperpermeability and restores RPE function.	First-line for chronic cases.
Keratoconus / Corneal Ectasia	Corneal Collagen Cross-Linking (CXL)	Increases corneal stromal stiffness via UVA-induced collagen cross-linking.	Gold-standard for halting progression.
Circumscribed Choroidal Hemangioma	Verteporfin PDT	Thrombosis and involution of the vascular tumor.	Established, first-line treatment.
Corneal Neovascularization	PDT (e.g., Verteporfin)	Targeted occlusion of pathological corneal blood vessels.	Emerging / Investigational.
Infectious Keratitis	Antimicrobial PDT (aPDT)	ROS-mediated destruction of bacteria, fungi, or parasites.	Emerging / Adjuvant therapy.
Retinoblastoma	Targeted PDT	Selective cytotoxicity to tumor cells using novel photosensitizers.	Preclinical / Early Clinical.

Advanced Biophotonic Imaging: Guiding Therapy with Unprecedented Precision

The therapeutic advances in biophotonics are inextricably linked to parallel progress in diagnostic imaging. High-resolution, non-invasive imaging technologies are crucial for patient selection, treatment planning, and monitoring response (Reinhard et al., 2015). OCT forms the cornerstone, offering the necessary detail of cross-sectional images of the retina. More recently, the development of OCTA has been a game-changer, enabling the visualization of retinal and choroidal vasculature without dye injection. This has become invaluable for the identification of CNV type and activity in AMD, for vascular changes after PDT, and for the assessment of the choroid in CSCR (Kumar et al., 2022).

Adaptive optics imaging takes resolution to a cellular level. By correcting ocular aberrations, AO systems can resolve individual photoreceptors, RPE cells, and white blood cells in the retinal capillaries. In the context of PDT and other therapies, AO thus allows direct assessment of the treatment effects on cellular structures, enabling a much deeper understanding of therapeutic efficacy and potential toxicity. As an example, it can be employed to quantify the loss of RPE cells or cone photoreceptors subsequent to a treatment session, thus guiding future parameter adjustments (Zhang et al., 2019).

Two-photon excitation microscopy, while primarily a research tool, is gaining clinical potential. It enables the imaging of fluorescent molecules deep within tissues with reduced phototoxicity. This technology could be used to visualize, in real time, the distribution and pharmacokinetics of novel photosensitizers within the eye, truly enabling personalized dosing and illumination strategies. Advanced imaging modalities are rapidly moving ophthalmic practice from a mostly subjective field to one guided by quantitative data of high fidelity (Hong et al., 2024).

Future Directions and Integrative Technologies

The future of both biophotonics and PDT in ophthalmology involves greater selectivity, personalization, and integration with other technological frontiers. One very exciting area is that of optogenetics, a technique utilizing gene therapy to express light-sensitive ion channels-opins-in specific

populations of retinal cells. For those patients with end-stage retinal degenerations such as retinitis pigmentosa, where photoreceptors are lost but the inner retinal neurons are preserved, this approach offers a strategy for restoration of light sensitivity. Though still in early clinical trials, it speaks to a radical merger of biophotonics and molecular biology for the restoration of vision (Busskamp et al., 2024).

In this respect, another direction of interest is the combination of PDT with other modes of treatment. As mentioned, PDT combined with anti-VEGF therapy for AMD can leverage the vascular occlusive effect of PDT with the anti-permeability effect of anti-VEGF, potentially leading to more durable treatment responses. Similarly, the combination of CXL with other procedures, such as topography-guided photorefractive keratectomy, is being explored, not only to stabilize the cornea in keratoconus but also to improve visual acuity (Ferrara & Adamis, 2016).

The integration of Artificial Intelligence is also at hand. AI algorithms analyzing multimodal imaging data (OCT, OCTA, fundus autofluorescence) can predict the pattern of disease progression, select the optimal candidates for PDT or CXL, and allow the automated personalization of treatment parameters. This data-driven approach will bring the field closer to precision medicine, where treatments are tailored to an individual's unique disease phenotype.

Finally, nanotechnology is poised to play a transformative role. Nanoparticles can be engineered into versatile platforms for "theranostics"-that is, the combination of therapy and diagnostics. A single nanoparticle could carry a photosensitizer, a contrast agent for enhanced imaging, and a targeting ligand for specific tissue homing. This would enable image-guided PDT, where the same agent is used to visualize the target and then, with a different light source, to treat it with unparalleled precision. The following table summarizes these future directions and the technologies enabling them.

Table 2: Future Directions in Ophthalmic Biophotonics and Photodynamic Therapy

Innovation Area	Description	Potential Impact
Optogenetics	Genetic expression of light-sensitive proteins in retinal cells to restore vision in degeneration.	Vision restoration for currently untreatable blinding diseases.
Nanoparticle-Based PDT	Use of engineered nanoparticles to improve photosensitizer delivery, targeting, and enable theranostics.	Enhanced efficacy, reduced side effects, personalized dosing.
Artificial Intelligence (AI) Integration	AI algorithms for automated image analysis, treatment planning, and outcome prediction.	Precision medicine, optimized treatment parameters, improved accessibility.
Novel Photosensitizers	Development of agents with faster clearance, longer activation wavelengths, and inherent targeting.	Shorter photosensitivity periods, deeper tissue penetration, greater selectivity.
Combination Therapies	Strategic pairing of PDT/CXL with pharmaceuticals (anti-VEGF), gene therapy, or other procedures.	Synergistic effects, reduced treatment burden, improved long-term outcomes.

Conclusion

Biophotonics and photodynamic therapy have forever changed the face of ophthalmic management. From the well-established vision-preserving applications in verteporfin PDT for AMD and CSCR to the structural stabilization offered by corneal cross-linking, these light therapies epitomize the power of targeted, minimally invasive interventions. The field is dynamic, with ongoing research continually refining existing protocols while forging ahead into new frontiers, from combating corneal infections to restoring vision through optogenetics. The convergence of biophotonics with advances in imaging, nanotechnology, and artificial intelligence holds the greatest promise for treatments that will not only be more efficacious but also deeply personalized (Yin et al., 2024).

The eye, a window to the body and an ideal optical medium, will undoubtedly continue to be at the leading edge of this photonic revolution (Spaide et al., 2018). In fact, embracing and further investing in these technologies is of paramount importance as the ophthalmic community pursues its goal of eradicating blindness and improving the quality of life for millions of patients around the world. The future of ophthalmic therapy is not only brighter but more precisely illuminated.

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