Photodynamic Therapy: Occupational Hazards and Preventative Recommendations for Clinical Administration by Healthcare Providers

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Abstract

Objective: Photodynamic therapy (PDT) as a medical treatment for cancers is an increasing practice in clinical settings, as new photosensitizing chemicals and light source technologies are developed and applied. PDT involves dosing patients with photosensitizing drugs, and then exposing them to light using a directed energy device in order to manifest a therapeutic effect. Healthcare professionals providing PDT should be aware of potential occupational health and safety hazards posed by these treatment devices and photosensitizing agents administered to patients. **Materials and methods:** Here we outline and identify pertinent health and safety considerations to be taken by healthcare staff during PDT procedures. **Results:** Physical hazards (for example, non-ionizing radiation generated by the light-emitting device, with potential for skin and eye exposure) and chemical hazards (including the photosensitizing agents administered to patients that have the potential for exposure via skin, subcutaneous, ingestion, or inhalation routes) must be considered for safe use of PDT by the healthcare professional. **Conclusions:** Engineering, administrative, and personal protective equipment controls are recommendations for the safe use and handling of PDT agents and light-emitting technologies.

Introduction

PHOTODYNAMIC THERAPY (PDT) IS A CLINICAL PROCEDURE that uses a combination of a photosensitizing drug and application of a specific wavelength of light to activate that drug in order to cause selective damage to an unwanted target tissue within a patient. The basic steps of PDT include: (1) administering a photosensitizing drug (a chemical capable of inducing a photodynamic reaction that transfers energy from light to the tissue) to the patient, (2) waiting sufficient time for the local or systemic uptake of the drug, and (3) then irradiating the treatment area on or within the patient to trigger the phototoxic reaction.

Photosensitizing agents can be administered topically via a cream application or systemically through a subcutaneous or intravenous injection. Once administered to the patient, the length of uptake depends upon the specific photosensitizing drug, and typically occurs within 6–48 h. After sufficient uptake time has passed, a specific wavelength of

light is applied to the affected area for a short period of time. The dose of light, or quantity of energy administered to the patient and absorbed by the photosensitizing agent in a volume of tissue, is dependent upon: (1) the light fluence rate (a measurement of radiant energy incidence per second, which is a unit of power per unit of light expressed in watts per square meter, or W/m^2 , where $1 W = 1 J/s$), (2) the molar extinction coefficient of the photosensitizer (a measurement of how strongly a given chemical absorbs light at a particular wavelength), and (3) the photosensitizer concentration in the region of treatment.¹ Many devices have been developed to deliver light to the afflicted area, including lasers, arc lamps, fluorescent light sources, and light-emitting diodes (LEDs).

PDT has played a substantial role in the treatment of dermatological maladies such as non-melanoma skin cancer, actinic keratinosis, and cutaneous lesions.^{2,3} In addition, applications of PDT have been used in cases of macular degeneration;⁴ treatment of periodontal diseases;⁵ treatment of oral leukoplakia,⁶ oral cancer,⁷ and cervical,⁸ endobronchial,⁹

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esophageal,¹⁰ bladder,¹¹ gastric,¹² head and neck,^{13,14} brain,¹⁵ and other solid tumors from diverse organs.³ In cancer treatment, the effectiveness in each circumstance varies greatly, mainly because of the inability of photosensitizing drugs to preferentially distribute to tumor regions.¹⁶ Development of new PDT technologies requires new and/or improved photosensitizing drugs that specifically localize to tumor cells, as well as development of new methods of administering the correct wavelength and dose of light to the targeted tissues.

Whereas only a handful of treatment methods are currently approved by the United States Food and Drug Administration (FDA), there are many in the developmental phase.¹⁶ PDT holds tremendous potential for clinical applications of treating cancer, but the safe delivery of such procedures must be evaluated to ensure the protection of healthcare professionals. During the experimental phases of new treatment development, patient safety has not yet been fully assessed, and the hazards posed to research personnel remain unclear.

A given PDT method is developed for patient-specific applications with proper photosensitizer and energy dosing. A healthcare professional may treat numerous patients during a given work shift, thereby compounding the combined exposure duration. This potential risk necessitates the development of appropriate procedures and protocols to ensure that both photosensitizer agent and directed light source exposure periods for healthcare providers are maintained within acceptable limits.

The purpose of this review is to summarize and present the published literature pertaining to photodynamic therapy hazards and their control, to understand the types of and extent to which these hazards exist, to inform the medical community about these hazards, and to prioritize the methods of control that may be implemented in clinical or research settings. A literature search was performed for photodynamic therapy hazards in the United States National Library of Medicine and the National Institutes of Health's PubMed database with combinations of search terms that included, but were not limited to, photodynamic therapy, phototherapy, photosensitizer, lamp, laser, ultraviolet, infrared, burn, injury, skin, eye, technician, nurse, physician, exposure, and hazard. The reference lists of key publications identified in our search were systematically evaluated to locate additional studies relevant to photodynamic therapy hazards. This review was limited in scope to occupational hazards for healthcare professionals, and did not specifically address patient safety literature.

The results of our literature search revealed a lack of publications that specifically document the potential hazards to healthcare staff who perform PDT procedures. Further, incidence rates of occupational injuries suffered during PDT events are not easily obtainable, as there are no central reporting systems to catalog such injuries. The Manufacturer and User Facility Device Experience online database hosted by the FDA, is a voluntary reporting system aimed at cataloging incidents involving medical devices. Although not its primary purpose, this database sometimes logs occupational injury related incidents. A search of this database for events categorized under product codes relevant to PDT devices between 1990 and 2012 yielded a total result of 50 incidents.¹⁷ Of these, 41 incidents documented patient injuries

caused by treatment, 4 incidents documented device malfunction, and 3 incidents indicated injury to technicians. Two of the occupational incidents documented crushing injuries suffered by staff while moving equipment, not during procedures. The other occupational incident was the case of a physician assistant with history of epilepsy, experiencing a seizure ~30 min after conducting a PDT procedure; however, it was unknown whether the PDT procedure caused the seizure.

The lack of reported incidents is not altogether surprising, as hospital staff have historically underreported accidents, including such occupational injuries as needle sticks and musculoskeletal disorders, for fear of an unsupportive administrative response.¹⁸ One report, specific to exposures to ultraviolet radiation of shortwave wavelengths in surgical suites, found that healthcare staff did not recognize the radiation of an exposure hazard, and lacked specific training on hospital procedures aimed to protect against such exposure.¹⁹ As PDT is an emerging technique, the risks for operators are poorly characterized to date; however, opportunities for potential exposure will continue to grow as applications of PDT increase. Potential occupational hazards of PDT include the exposure of workers to: (1) photosensitizing drugs, either during the preparation of the agent or the administration of the agent to patients, and (2) non-ionizing radiation from the light source employed during the treatment. Here, we discuss the potential health effects from exposure to these chemical or physical agents and employ the occupational hygiene hierarchy of control strategies for minimizing exposures and lowering workplace risk.

Photosensitizing Agents

Theoretically, the optimal photosensitizing agent would be a single, pure compound with a molar extinction coefficient between 600 and 800 nm, have no toxicity without light exposure, and possess a relatively rapid clearance from normal tissues to minimize side effects.³ Most photosensitizing agents cannot meet all of these criteria. Rather, final drug development is dependent upon maintaining a balance between optimal photoreactivity and biological absorption properties of the compound that, when combined with the light treatment, offers the most clinically effective outcome with the lowest level of side effects experienced. Few FDA-approved photosensitizing drugs have reached the market;²⁰ however, alternative photosensitizing agents in development demonstrate strong promise for PDT treatment. Implications for occupational exposure safety issues have yet to be determined for any of these additional agents.

Toxic photochemical effects can potentially occur once chromophores within tissues absorb a given wavelength of light. This energy absorption mediates the formation of an electronically excited state of the chromophore molecule, allowing it to undergo either a chemical transformation and/or interaction with biomolecules present within the targeted tissue. The molecular interactions may then lead to chemical changes of both molecules or to a transfer of energy to the other biomolecules. These interactions lead to the formation of chemical radicals and reactive oxygen species, which have the potential to initiate the photodynamic effect. Upon photoexcitation, chromophores undergo intersystem crossing and produce free radicals and singlet oxygen, and thus become photosensitizers.²¹

Hematoporphyrin derivative (HPD), porfimer sodium

Porfimer sodium (Fig. 1) (sold under the tradenames Photofrin®, Photosan®, Photogem®, and Photohem®) is by far the most common photosensitizing agent used in clinical PDT applications.²² Porfimer sodium is administered intravenously at a dose of ~ 2 mg/kg. Forty to 50 h following injection, illumination of the tumor area is achieved with a laser system capable of a stable power output at a wavelength of 630 ± 3 nm. The laser is applied to the tumor location via a fiberoptic diffuser that is passed through the operating channel of an endoscope/bronchoscope. Light dosing between 130 J/cm of diffuser length and 300 J/cm of diffuser length is typically employed; the dose used is dependent upon a number of factors, most notably the disease type being treated. A second light application at 50 J/cm of diffuser length is sometimes given 96–120 h after injection.

Solutions of porfimer sodium alone are neither eye nor dermal irritants. However, because of its potential to induce photosensitivity, porfimer sodium could possibly be an eye and/or skin irritant in the presence of bright light. For healthcare personnel tasked with preparing or administering porfimer sodium, it is imperative to avoid contact with the eyes and skin. Photofrin typically takes 4–6 weeks to clear the body;²³ therefore, if accidental eye or skin exposure occurs, the exposed person must be protected from bright light sources (e.g., powerful lamps or sunlight) for several weeks.²⁴

Verteporfin

Verteporfin (Fig. 2), known by the trade name Visudyne®, is used in the PDT treatment of ophthalmic maladies such as age-related macular degeneration, pathologic myopia, and histoplasmosis, as well as pancreatic and skin cancers.³ Verteporfin is administered to the patient via intravenous infusion for 10 min. The activation of verteporfin is accomplished with light from a nonthermal diode laser of 689 nm wavelength 15 min after the start of the infusion. The recommended light dose is 50 J/cm² at an intensity of 600 mW/cm² administered over 83 sec. Verteporfin is supplied as a lyophilized dark green cake and must be reconstituted with sterile water. The solution is administered via injection, and safe sharps handling precautions should be followed.

Aminolevulinic acid (ALA)

ALA (Fig. 3), known by the trade name Levulan®, is administered as a 20% topical solution intended for direct application to lesions diagnosed as actinic keratoses. Photodynamic therapy with ALA for actinic keratoses involves the application of the product to the target lesions, followed by a 14–18 h uptake period. After sufficient uptake time, illumination of the target lesions is performed with blue light (417–432 nm) using the BLU-U® Blue Light Photodynamic Therapy Illuminator. A 1000 sec (16 min, 40 sec) exposure is required to provide the recommended 10 J/cm² light dose. Preparations of ALA contain alcohols (ethanol and isopropanol) and are intended for topical use only. Applications to the eyes or to mucous membranes should be avoided.²⁵

Methyl aminolevulinate (MAL)

MAL (Fig. 4), known by the trade name Metvixia®, is a topical cream used for the PDT treatment of non-hyperkeratotic actinic keratoses. MAL is administered directly to skin lesions. The treatment cream contains emulsifying agents, emollients, chelating agents, and preservatives, and the manufacturer recommends nitrile gloves be worn when applying and removing the cream. (Further discussion of personal protective equipment [PPE] is provided in the Exposure Controls section.) The uptake period for MAL is ~ 3 h, and subsequent illumination of the lesions is performed with red light within a narrow spectrum at ~ 630 nm. Light treatment is accomplished with the Aktelite® CL128 lamp, which is equipped with 128 individual LEDs. A light dose of 37 J/cm² is recommended with the lamp placed 50–80 mm from the skin, with typical exposure for 7–10 min.²⁶

m-Tetrahydroxyphenylchlorin (mTHPC)

Currently, one of the most promising next generation photosensitizers is mTHPC (Fig. 5), known by the tradename Foscan®. This drug is approved in Europe and is used in most of the world, but has not been approved by the FDA because of patient safety concerns about its ability to produce photoburns in patients.²⁷ mTHPC is administered

FIG. 1. Hematoporphyrin derivative (HPD), porfimer sodium.

FIG. 2. Verteporfin.

intravenously, and requires an uptake period of 4 days before illumination treatment. The tumor is irradiated with laser light of 652 nm wavelength. Foscan® is one of the most potent photosensitizers produced to date, and treatments require small drug doses (as low as 0.1 mg/kg body weight) and small light doses (as low as 10 J/cm²).¹⁶ mTHPC distributes itself throughout the body, making the recipient's skin and eyes extremely photosensitive for ~15 days after administration. In the unlikely event that any mTHPC is exposed to direct skin contact when the injection is administered, the worker is recommended to protect the exposed area from light for at least 3 months.²⁸

Experimental therapies

PDT research continues to evolve, as novel photosensitizers (such as porphyrin derivatives²⁹) and new delivery pathways (such as nanoparticle-based PDT³⁰) continue to be studied. These novel materials and approaches offer hope of

FIG. 3. Aminolevulinic acid (ALA).

FIG. 4. Methylaminolevulinate (MAL).

utilizing highly selective drugs that can localize specifically to tumor areas and/or which can be activated by different wavelengths of light.³¹ Although these experimental approaches offer tremendous promise for the future of PDT treatment, caution must be used in the application of technologies that have not yet undergone thorough risk assessments.³²

Light Sources

PDT requires the illumination of tissue with specific wavelengths of light to induce the phototoxic effect of the photosensitizing agent. Hemoglobin and melanin molecular absorption of energy occurs at wavelengths of ~600 nm and below, whereas water molecular absorption of energy occurs at ~950 nm. Additionally, whereas longer wavelengths provide deeper tissue penetration than shorter wavelengths, the longer wavelengths have insufficient energy to initiate a photodynamic reaction. Photosensitizers that excite in the region between 600 and 900 nm are generally considered to be the most ideal; however, some photosensitizers excite at wavelengths outside of this range and are clinically useful.

Both eye and skin injuries may occur from overexposure to high intensity light radiation; however, it is extremely

FIG. 5. m-Tetrahydroxyphenylchlorin (mTHPC).

important to avoid hazards to the eye because of the potential for loss of vision caused by retinal injury. The two mechanisms of biological effect that may lead to adverse outcomes as tissues absorb radiant energy are thermal and photochemical effects. Thermal damage occurs when the rate of light energy released by thermal deactivation is more rapid than thermal diffusion, inducing a rise in tissue temperature.

Given the wide range of wavelengths employed in PDT treatment, there are many devices and light sources used in PDT, and no one light source is ideal for all treatment regimes, even when using the same photosensitizer.^{3,33} The light source selected must be chosen based upon the following criteria: (1) properties of the photosensitizer absorption, (2) the disease being treated, (3) the location within the body to be treated, (4) the area/volume of the tissue to be treated, (5) the cost of the device, and (6) the size of the device to be used.³ The efficacy of PDT depends upon the complex dosimetry of total light energy, light exposure time, and light delivery mode.

Lasers

Lasers are the most commonly used light source for PDT because of their ability to produce high intensity monochromatic light in targeted regions.¹ Diode lasers, which are small, cost effective, and simple to install and use, are now being specifically designed for PDT use.³ Risk of physical injury posed by lasers can include burns to skin or ignition of other materials that may contact laser beams, eye injury from directed or reflected laser energy that enters the eye, and electrocution or burns from power supplies and electronics.³⁴ Direct or reflective skin and eye contact are the most important hazards posed to healthcare professionals involved with PDT treatment, whereas electrical hazards from power supplies would present the greatest risk to engineers performing maintenance on the devices. Specific thermal effects that may arise from overexposure of non-ionizing radiation sources (most often associated with class 4 laser sources that have sufficient power to induce thermal damage, see Table 1) include injury to the retina, lens, cornea, or skin.

Another potential mechanism of biological effects is photomechanic (or photoacoustic) damage, which occurs when light energy is transferred to tissues more rapidly than the mechanical relaxation of the tissue. Intense pulsed lasers have sufficiently high fluence rates and short laser pulses (<1 ns) which may induce tissue disruption by shear forces or by cavitation (i.e., formation and implosion of liquid cavities), resulting in the photomechanic damage.²¹

Ultraviolet (UV) lamps

UV radiation, or electromagnetic radiation in the wavelength range of 100–400 nm, is often used in dermatological PDT treatments.³⁵ Many PDT lamps emit high levels of UV, usually in the UVA range (315–400 nm), but also sometimes in the UVB region (280–315 nm) of the spectrum. UV PDT lamps have high potential for causing overexposure to healthcare workers, because often the dose administered to patients is in excess of occupational exposure limits.³⁶ Photochemical effects can include UV photokeratoconjunctivitis (also known as welders' flash), UV cataract, UV erythema, and skin cancer associated with UVA and UVB exposure.³⁷

TABLE 1. LASER HAZARD CLASSES⁴⁵

Class	Considerations
1	Is incapable of producing damaging radiation levels during use.
1M	Is incapable of producing hazardous exposure conditions during normal operation unless beam is viewed with an optical instrument.
2	Emits in visible portion of spectrum and eye protection provided by aversion response.
2M	Emits in visible portion of spectrum and eye protection provided by aversion response but potentially hazardous if viewed with optical aids.
3R	Potentially hazardous under some direct and specular reflection viewing condition if the eye is appropriately focused and stable, but the probability of injury is small. The laser will not pose a fire hazard or diffuse-reflection hazard.
3B	May be hazardous under direct and specular reflection viewing conditions, but is normally not a diffuse reflection or fire hazard.
4	Is a hazard to the eye or skin from the direct beam, and may pose a diffuse reflection or fire hazard

The current classification was revised in 2002; however, many older laser systems may be classified using the older system (e.g., I, II, IIIa, IIIb, IV).

Intense pulsed lights (IPL)

Intense pulsed light (IPL) devices use flashlamps and computer-controlled capacitor banks to produce pulsed polychromatic light of high intensity in wavelengths from 250 to 1400 nm. Using band-pass filters to block UV and infrared (IR) wavelengths, IPLs can be limited to specified wavelengths, making the IPL device a versatile piece of equipment that can effectively tailor treatments to patients. Depending upon the particular device, the pulse duration can be set in the millisecond (ms) range, and the combination of particular wavelengths, pulse durations, pulse intervals, and fluences facilitates the treatment of a wide spectrum of skin conditions.³⁸ An IPL device is different from a monochromatic laser in that it inherently emits a broadband spectrum. The wide emission spectra are useful for the treatment of numerous skin lesions, as skin chromophores, such as oxyhemoglobin or melanin, exhibit broad absorption spectra. To date, there are no consensus performance standards applicable to the operation of IPL systems. However, as these devices emit high-radiant exposures that are comparable to lasers, they have the potential to cause substantial damage to eyes and skin, and should be treated with similar precautions.³⁹

LEDs

LEDs are alternative light sources with relatively narrow spectral bandwidths and high fluence rates.³ These devices are an optimal illumination source for PDT because of their small size, high light output, and low energy requirements.⁴⁰ LEDs emitting visible light do not directly emit UV and IR radiation, but do include the blue light wavelength

(400–500 nm) that has raised exposure concerns.²¹ Blue light wavelengths are known to induce retinal damage (photoreinitis) and have been implicated in the development of age-related macular degeneration.⁴¹ Blue-light injury can result from viewing either a high intensity light for a short period of time or from a low-dose exposure for an extended period of time.⁴²

Occupational Exposure Prevention and Control

Chemical exposure

Occupational exposure limits (OELs) for chemicals in the workplace are not usually developed for pharmaceutical agents such as photosensitizing drugs, often because of the incomplete characterization of adverse health outcomes.⁴³ However, other chemicals used in the preparation of treatments may possess exposure limits from some standards-setting organizations, such as the Permissible Exposure Limits (PELs) from United States Occupational Safety and Health Administration (OSHA) or the Threshold Limit Values (TLV®) from the American Conference of Governmental Industrial Hygienists (ACGIH). Hazardous ingredients of the drug preparation are available from the manufacturer either on the product label and/or the material safety data sheet (MSDS).

Although PELs and TLVs have not been established for PDT drugs, an important consideration to be taken into account regarding worker exposure is the difference between the drug's pharmacokinetics in patients for whom the drugs are intended and the healthy workers administering the drugs who may become unintentionally exposed. The photosensitizer drug is most often effective for patients whose homeostasis mechanisms have been compromised and who are able to metabolize the drug effectively. The drug designers take advantage of this relatively rapid clearance so that PDT treatment may be performed soon after administration. Side effects for the patients become minimal because of the short clearance times. The data for the clearance on healthy patients is limited because of the ethical consideration of putting healthy individuals at risk of exposure with no potential benefit from that exposure. More in this regard will have to be gleaned from the collection of reports of humans accidentally exposed to the compounds.

Non-ionizing radiation exposure

TLVs for non-ionizing radiation have been developed by the ACGIH⁴⁴ and by the International Commission on Non-Ionizing Radiation Protection (ICNIRP).³⁶ The radiometric measurement radiance ($\text{W}/\text{cm}^2\text{sr}$) describes the brightness of a source, or the amount of light emitted by a source, whereas irradiance (W/cm^2) describes the power density on a receiving surface.^{21,37} Radiant exposure (J/m^2) is the photobiological dose of radiant energy.⁴⁵ The OELs developed by these agencies take into account the biological effectiveness of the non-ionizing radiation to cause harm across many wavelengths for the duration of exposure to the target tissue.

UV radiation

The ACGIH TLV and ICNIRP OEL for broadband UV radiation are identical, and apply to continuous sources for exposure durations > 0.1 sec. The guidelines allow that ex-

posure to the eye and skin be maintained $< 0.003 \text{ J}/\text{cm}^2$ -effective, when the spectral irradiance at the eye or skin surface is mathematically weighted against a hazard sensitivity spectrum from 180 to 400 nm. If the irradiance level is constant, the maximum exposure duration, in seconds, may be found as the ratio of the TLV to the effective irradiance. ACGIH makes special note that the TLV does not apply to individuals who are photosensitive, which would include patients receiving PDT drug therapy or clinical personnel who have been inadvertently exposed to PDT drugs.

Laser radiation

The OELs for laser energy are dependent upon wavelength, duration of exposure, and source type (pulsed vs. continuous lasers, and small vs. extended sources). ACGIH has detailed a number of wavelength-dependent and various parameter-specific correction factors. These factors are biologically based and account for the different hazards of the various wavelengths of lasers. The duration of exposure is a critical factor in determining the OEL; by increasing exposure time, the OEL decreases. Sources may also be classified as small or extended, and the classification is based on the size of the potentially irradiated area on the retina.

Exposure controls

Clinics that utilize a PDT procedure must understand which occupational hazards the specific PDT treatment poses to staff, as well as properly plan and prepare administration of the procedure. American National Standards Institute (ANSI) provides recommendations for the safe use of lasers in healthcare facilities (ANSI Z136.3).⁴⁶ Further, OSHA and the Joint Commission on the Accreditation of Healthcare Organizations (JCAHO) have both been using ANSI standards as recommendation and enforcement criteria in regards to proper operation and maintenance of laser technologies. Appendix B of the Z136.3 standard recognizes that laser and non-laser systems are employed to provide intense, monochromatic light for PDT, and, therefore, that the controls outlined for laser safety should also apply to safe use of these light sources.

The ANSI standards require that the institution using laser devices appoint a Laser Safety Officer (LSO) who manages and administers a laser safety program throughout the facility. The safety program needs to include: (1) detailed written safety policies and procedures, (2) documentation of training of all related personnel, (3) documentation of provisions for laser safety eyewear (operating wavelength normally experienced/exposed to), (4) posted warning signs for laser rooms, and (5) monitoring of periodic maintenance on all lasers. Standalone or healthcare service providers or clinics also have access to these same safety and regulatory agency guidelines, which are available online for reference and guidance. Additional standard operating procedures (SOPs) or protocols may be developed and applied, given the individual circumstances and activities within any given facility. Examples of key criteria recommended for inclusion and selection in a safety program or function would include, but not be limited to, the areas found in Table 2. One or multiple control techniques may be applied to best protect workers from hazards.

TABLE 2. RECOMMENDED CONTROL STRATEGIES FOR PHOTODYNAMIC THERAPY (PDT) TREATMENTS

<i>Control level</i>	<i>Example</i>
Engineering control	<ol style="list-style-type: none"> 1. All windows, doorways, and other open portals to an enclosed facility should be covered or restricted to reduce any escaping non-ionizing radiation. 2. Continuous, pulsed, or repetitive laser radiation for PDT treatments should only be administered using a foot/hand switch that has been engineered to require constant pressure. 3. Use diffusely reflecting materials near the light source. 4. Ensure that light-generating devices are equipped with an emergency kill switch in case of emergency.
Administrative control	<ol style="list-style-type: none"> 1. Ensure that a route for rapid egress by treatment personnel is kept available at all times during the PDT session. 2. An entryway warning system should be used when light source/PDT is in operation. 3. An appropriate laser warning sign should be posted both inside and outside the laser-controlled area. 4. Store or disable light-generating equipment when not in use. 5. Avoid the use of dry materials and/or flammable objects near laser radiation area. 6. Completely train individuals involved with PDT treatments in all aspects of non-ionizing radiation safety. 7. Training of health care providers in all aspects of medical laser or PDT treatments is required when lasers are used for the treatment procedure. 8. Training of all personnel who may require frequent entry into the PDT treatment areas to recognize warning signs and dangers associated with exposure to the light source radiation is required. 9. A Laser Safety Officer must be designated for a facility when lasers are used for PDT treatment. 10. Entry of any personnel not involved with PDT treatment should be restricted when devices are in use.
Personal protective equipment	<ol style="list-style-type: none"> 1. Appropriate protective eyewear must be provided to all personnel, including patients if necessary, within the treatment area. 2. Verify that all eyewear in use is proper protection for the DED wavelength and PDT regimen in use at that particular point in time. Different PDT regimens operate at varying wavelengths, which may require more than one set of eyewear to be available for use depending upon treatment regimens. 3. Appropriate protective garments must be provided to all personnel, including patients if necessary, within the treatment area. 4. Appropriate gloves with compatible materials for use with a given PDT photosensitizer must be worn within the treatment area.

Administrative controls

Administrative controls are policies or practices that should be implemented to limit personnel from exposure to hazardous agents. Primary administrative control in the case of PDT treatment is the use of SOPs that address the appropriate location of all personnel involved in the treatment area while also requiring all treatment professionals to use appropriate engineering or personal protective controls during the PDT session. Written operating procedures should be obtained from the manufacturer of the light source, and the LSO should be responsible for ensuring that such procedures are updated accordingly. When healthcare providers are implementing new treatment techniques within a clinical setting, it is advised that the treatment staff undertake a practice session in which all aspects of the procedure are performed without operating the light source. During this trial run, personnel may learn where possible hazardous situations may arise, and they will become better prepared for the procedure before it occurs.

Personnel access to areas where PDT treatments are being conducted should be restricted to only those workers whose presence is absolutely necessary to conduct the procedure.

Strict enforceable policies are useful tools for preventing unnecessary exposures. Procedural controls include: (1) adherence to written safety policies and procedures, (2) assignment of a qualified laser assistant (i.e., someone who has been properly trained in safe operations of equipment), (3) maintaining a list of qualified users, (4) requiring storage or disabling the light source when unauthorized operation is a concern, (5) informing staff of the location and proper operation of the emergency stop control of the device, (6) assurance that the light source is only placed in the ready function state when the user is ready to treat the target tissue, (7) use of only diffuse reflective materials or instruments with low reflectance in or near the path of light when possible, and (8) limiting the use of more than one device with floor pedal operation to avoid confusion.

ANSI has established criteria for prevention of eye and skin burn hazards by establishing the nominal hazard zone (NHZ), or area around the laser where the beam intensity exceeds the OEL; areas that are peripheral to the NHZ are considered safe.⁴⁷ The distance of the NHZ can be determined from product literature, direct measurement, or other equivalent assessment elucidated in the ANSI Z136.1 standard. The NHZ for medical lasers is largely dependent on

beam divergence and duration of use, and must be calculated by the LSO for each laser used. This determination is important in assessing both operator and other personnel exposures to laser radiation and to determine appropriate PPE. Within the NHZ, engineering and personal protective controls are to be implemented, and treatment staff are required to comply with other safety policies.

Engineering controls

Implementation of engineering controls is the most effective way to prevent exposure to PDT drug compounds during preparation. Photosensitizing agents, especially those with volatile compounds within the formulation, are best prepared in a laboratory fume hood, designed to ensure capture of volatile compounds and prevent contamination of the work environment. In many clinical settings using light sources, a treatment control area (TCA) can be defined as the room in which the light source is used for PDT procedures and which contains the NHZ. Engineering controls within the TCA typically include barriers, such as walls or curtains that prevent inadvertent laser exposure to persons beyond the treatment area. Within this area, the lasing device should be operated only as part of an interlock system that would immediately shut the instrument down if unprotected personnel enter the area. The requirements of the TCA include posted warning signs at entry locations; these signs are required to cover windows, doorways, or other open portals in such a manner as to reduce transmitted radiation to levels below OELs, and to allow rapid egress or entrance in emergency situations.

Engineering controls can also be integrated into features of the light source device, such as guarded switches (e.g., trigger guard or foot pedal guard), safe accessories (e.g., optical devices that protect from inadvertent viewing of non-ionizing radiation during procedures), and warning labels. Warning signs should be prominently displayed on all entryways to the TCA to warn those entering the area of light source use, and should be covered or removed when the procedure is completed.

PPE

In the case of PDT treatment, PPE should include skin and eye protection from chemicals and non-ionizing radiation. Skin protection from chemicals must take into account adequate coverage, as well as appropriate material to prevent penetration of PDT agents. Personnel should follow manufacturer recommendations for identifying compatible glove materials for the drug in question.

Skin protection for healthcare professionals involved with administering the PDT treatment should include laboratory coats or other clothing that covers as much exposed skin as possible, and that also blocks radiation. Certain factors of clothing that may affect radiation protection include the material, weave, color, stretch, weight, quality, and water content.⁴⁸ Generally, radiation may leak through the mesh of woven fabrics, and often cotton or polyester-cotton blends do not offer consistent radiation protection. One measure of the ability of a fabric to protect against radiation is the UV protection factor (UPF), defined as the ratio of effective UV dose for the unprotected skin to the effective dose to protected skin. A UPF of 10 indicates that 90% of the UV is

absorbed by the material, whereas a UPF of 40 indicates 97.5% absorption. Choosing fabrics with higher UPF ratings may be desirable if uncontrolled exposure to a UV radiation source is anticipated. The use of sunblock cream is considered inadequate for the protection of UV exposure from light sources. An added consideration for PDT procedures using class 4 lasers is the combustibility of clothing. In general, flame-resistant fabrics should be worn when operating medical laser devices.

Protective eyewear should be used for PDT treatments that have the potential to expose workers to direct light radiation. Optical density (OD), the parameter used to catalog the ability of eyewear to effectively reduce the optical radiation exposure, is a base 10 logarithm of the ratio of the unprotected exposure level (usually a measured value) to the permissible exposure level. Therefore, an OD of 1 will have an attenuation of 10, whereas an OD of 6 will have an attenuation of 10^6 .⁴⁸ The recommended levels of attenuation required for a given light source can usually be found in the manufacturer's product literature. Because healthcare providers have to view the patient and the treatment area, the optical filters must both protect against light source radiation and allow sufficient transmission of daylight to enable viewing. To achieve maximal safety for the eyes, it is important to adjust the optical filters of the safety goggles to the radiation source used. The important parameters of the radiation sources are wavelength, pulse duration, intensity, distance and radiant exposure. These parameters of a light source system determine the characteristics of the safety goggles. Each light source requires special safety goggles that are labeled for their use (wavelength range of protection and OD).³⁹

In addition to broadband light sources, safety eyewear for lasers must also be appropriate for the wavelength in use. Safety eyewear must be worn with the use of any class 4 laser device, and most PDT laser devices fall into this laser class. Further, optical safety eyewear are meant only to provide protection from the viewing of an indirect diffusely reflected beam and are not designed for direct intrabeam viewing.⁴⁷ Direct beam viewing, even with the use of safety eyewear, poses an optical hazard to healthcare providers working with laser devices. Light sources using fiberoptics (e.g., diode laser devices) present a special hazard if the fiber were to break during the treatment procedure. Safety eyewear may be required by all personnel in the entire TCA to protect against such an occurrence.

Conclusions

PDT treatments offer a promising future for the treatment of a number of diseases, including different types of cancers, as new photosensitizing drugs and light supply devices are continually created and improved. As PDT treatment evolves, care must be taken to ensure the health and well-being of not only the patient, but also of the healthcare providers and supporting clinical staff members who participate in patient treatment. Adherence to general health and safety principles and proper planning of PDT procedures should help to minimize potential hazards in the workplace and allow continued successful treatment of patients and protection of all healthcare workers involved. When incorporating PDT procedures into the treatment repertoire of a clinic, standard recommendations for safe use

should include, but not be limited to, appropriate engineering, administrative, and PPE controls.

Physical hazards (e.g., non-ionizing radiation generated by the light-emitting device with potential for skin and eye exposure) and chemical hazards (i.e., photosensitizing agents administered to patients with potential exposure via skin, subcutaneous, ingestion, or inhalation routes) must be considered for safe use by the healthcare professional. Clinics that utilize a PDT procedure must understand which occupational hazards the specific PDT treatment poses to staff, as well as properly plan and prepare administration of the procedure. Primary controls strategies must include administrative controls, such as SOPs, engineering controls that capture chemical contaminants or shut off the light emitting device, and PPE that includes skin and eye protection from chemicals and non-ionizing radiation. Adherence to general health and safety principles and proper planning of PDT procedures should help to minimize potential hazards in the workplace and allow continued successful treatment of patients and protection of all healthcare workers involved.

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Author Disclosure Statement.

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