Chapter 7

Nurses and Pharmacists in Interdisciplinary Team of Health Care Providers in Photodynamic Therapy

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Abstract

Background: The modern treatment is based on wide cooperation between diverse representatives of medical professions. The photodynamic therapy is a noninvasive method of treatment both neoplastic diseases and miscellaneous noncancerous illnesses. It is complementary and competitive in some way to various traditional treatment techniques, including chemotherapy, radiotherapy, and surgery. This review emphasizes the significance of collaboration between specialists engaged in research, development, and practical use of photodynamic therapy.

Methods: A literature search of electronic bibliographic databases and scientific publishers was performed. The relevant literature was analyzed to identify articles on the involvement of nurses, pharmacists, physicians, and other representatives in photodynamic therapy treatment.

Results: In the photodynamic therapy, the overall success is not only dependent of a single unit. Coordinated actions of representatives possessing expertise in various fields of medical, and natural sciences are necessary both during joint research, development, and during the course of the photodynamic therapy treatment in clinics.

Conclusions: The effective interaction between professionals and the division of responsibilities at different stages of therapy can guarantee the successful treatment. During therapy, the most important role belongs to the patient who is responsible for acting in accordance with schedules elaborated by physicians, nurses, and pharmacists.

Keywords: hospital pharmacy, nursing, photodynamic therapy, photosensitizer, treatment

1. Introduction

Photodynamic therapy (PDT) is a low-invasive therapeutic method, which allows the selective destruction of diseased tissue. This is complementary to various traditional treatment techniques, including chemotherapy, radiotherapy, and surgery. It is used for the treatment of both neoplastic diseases and miscellaneous noncancerous illnesses. Although many ancient civilizations utilized phototherapy, it appeared again as the treatment procedure in the last century [1–3]. It seems that the success of this particular treatment procedure depends on both the further development of novel photosensitizers and light sources as well as schemes of cooperation between specialists and an interdisciplinary team. **Figure 1** presents the professions of which expertise is essential for photodynamic therapy and which are able to undertake various actions to increase the effectiveness of treatment.

PDT is based on a multi-stage procedure, and its success depends upon a number of procedure components. In addition, successful treatment requires the cooperation of an interdisciplinary team of specialists belonging to different fields of medical sciences: physicians, nurses, and

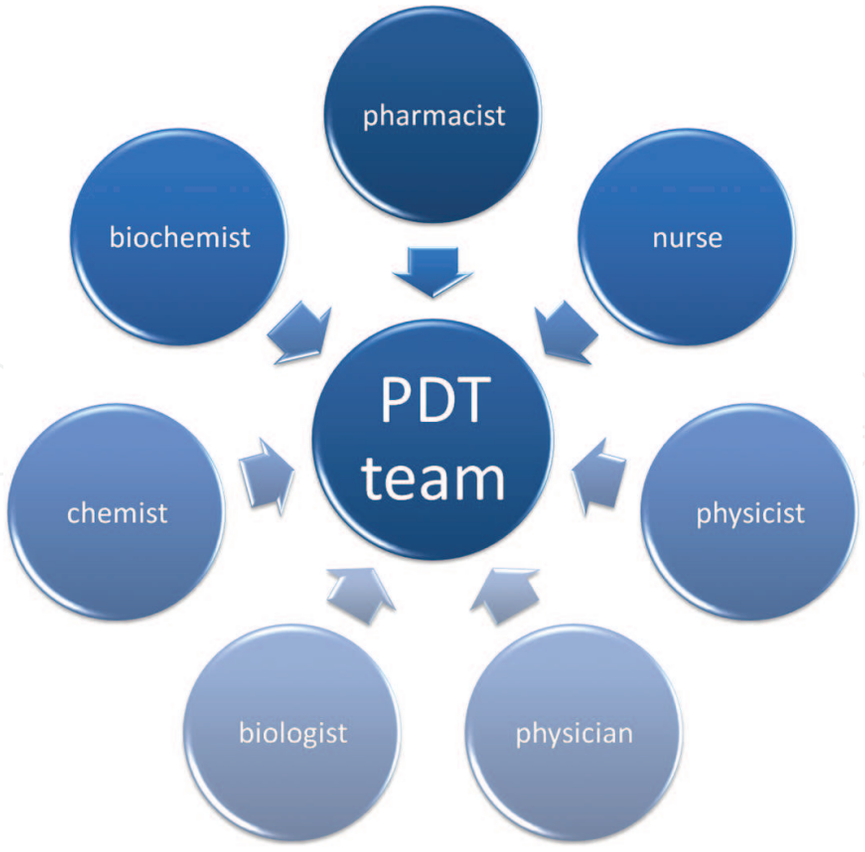

Figure 1. Professionals indispensable for carrying out PDT, based on Ref. [4].

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pharmacists, but also at certain stages: chemists, physicists, biophysicists, and biologists [4]. Many advantages resulting from cooperation between laboratory and clinical researchers have been raised by Sieroń and Kwiatek [5], who summarized laboratory and clinical research on PDT and photodynamic diagnosis (PDD) in Poland. Benefits resulting from cooperation between various specialists have been noted for several years of PDT treatment in Brazil, stressing that the cooperation between specialists helps to improve the results and the quality of treatment. The patient potential for PDT treatment in Brazil needed to be initially assessed by the physician, nurse, and a physicist. The role of nurses is of great importance in this system, as they participate in the PDT procedures and have the closest contact with patients. Each case is discussed by specialists in order to assess potential benefits and consequences of therapy [4]. Researchers implementing the photodynamic therapy in patients with lung cancer have described an effective collaborative team consisting of a surgeon, oncologist, nurse, and pharmacist. For each patient, they elaborated the so-called schedule of photodynamic therapy. As light delivery requires special skills, during PDT treatment the presence of a "laser specialist" was found necessary [6].

The nurse's role in PDT treatment of patients is apparent and for example might be given a procedure utilized in the treatment of patients with neovascular (wet) age-related macular degeneration which was summarized in excellent review by Rich et al. [7]. Moreover, Collins and Garner stressed at least two points when nurse-pharmacist cooperation would be beneficial for patient in PDT therapy: (i) in the planning of PDT therapy before the patient arrives in the acute care environment, (ii) and in the prevention of medication being exposed to light and its dilution before administration [6].

On the one hand, access to PDT is often insufficient. On the other hand, operating costs would be astronomical for each hospital. Therefore, a mobile PDT unit designed to be put into operation by the Yorkshire Laser Centre is the solution to this problem. This unit allows more patients to benefit from PDT treatment. The personnel in such units consist of a driver/technician, a PDT physician, a nurse or a carer, and coordinator [8].

2. Photodynamic reaction

The legitimacy of the established interdisciplinary team justifies the photodynamic reaction mechanism, which is the basis of PDT. It is well known that PDT is a suitable combination of three components: the drug—photosensitizer, light, and oxygen. Photosensitizer is a drug, which, when introduced to the body, accumulates in the tissue. Drugs used in PDT treatments belong to different chemical classes and are of different structures and properties. After the tissue has been irradiated with light in an appropriate wavelength and intensity, the photosensitizer is activated. Reactive oxygen species are generated, which effectively causes apoptotic or necrotic death of the diseased tissues [9–11].

Photosensitizer and light are both necessary for PDT. After parenteral or topical application, photosensitizers are mainly present in cancer cells and also to some extent in surrounding healthy tissue (**Figure 2**). The subcellular localization of the photosensitizers in cells embraces various organelles including plasma membranes, endoplasmic reticulum, mitochondria,

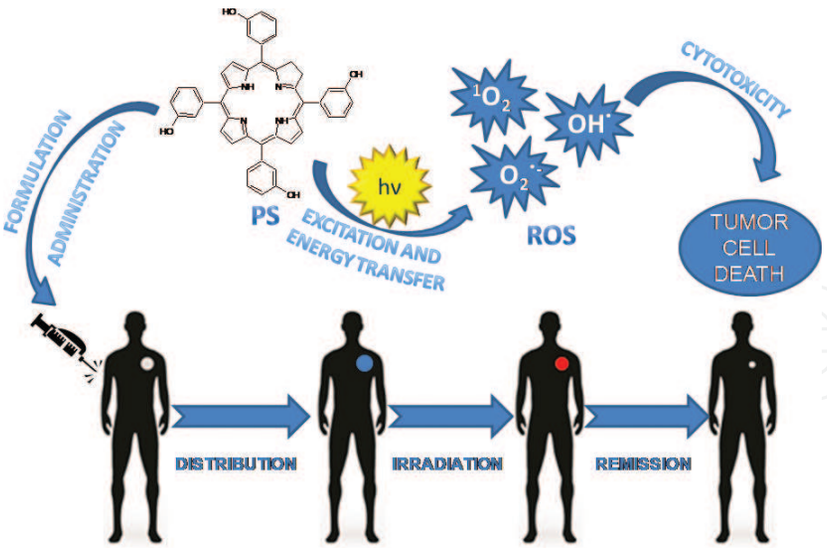

Figure 2. Mechanism of photodynamic reaction and photodynamic therapy.

lysosomes, and Golgi apparatus [12, 13]. Up to that point, photosensitizer occurs in an unexcited singlet state which has two electrons with different spins in the low energy orbital. Light is necessary for the activation of the photosensitizer and the induction of the photodynamic reaction [14]. For this reason, the photosensitizer is irradiated with light in an appropriate wavelength generated by precise sources, e.g., diode lasers or, considering the relatively high cost of lasers, the much cheaper, and portable light emitting diodes (LED). Fiber optics, or LED portable arrays illuminating light, are used for various types of cancer, including pulmonary tumors and fit through a bronchoscope or CT-guided needle or catheters [15]. A very important problem to be addressed is the suitable drug-light interval: as the photosensitizer is introduced into the body, and the vascular supply circulates as long as it accumulates in the tumor. Early illumination, after photosensitizer introduction, causes predominantly vascular effects, whereas later illumination favors tumor-cell effect. As a result, the photosensitizer when illuminated is "boosted" from its ground state to a higher energy state singlet-excited state. This state is an extremely short-lived, so an excess of accumulated energy has to be released in two different ways: the first one, which is the basis of PDD, involves the emission of light called fluorescence and corresponding to the relaxation of a molecule from the excited to ground state. The second alternative is an intersystem crossing which undergoes without energy emission and results in the formation of the triplet-excited state of the photosensitizer. Note that the half-life of the triplet-excited state is much longer than that of the singlet-excited state. In this case, photosensitizers can very rarely return to their ground state through the emission of energy called phosphorescence. In the comparison of the singlet and triplet excited states, it can be ascertained that both of them are utilized in photodynamic therapy. However, the contribution of the triplet state is much greater. As the energy is released by the excited photosensitizer, the initiation of the photodynamic reaction processes may result in the formation of reactive oxygen species (ROS) which are known to be toxic to neoplastic cells [12, 16].

The three main types of photodynamic reactions can be identified, among which two are extremely important in PDT. In the first type of reaction, energy from the excited photosensitizer is transferred to an electron or hydrogen atom of a substrate or another molecule and

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anion or cation radicals may be obtained. Afterwards, they interact with the surrounding oxygen which is transformed into toxic oxygenated species. Water molecules are the main target of this attack with a hydroxyl radical and superoxide anion radical formed as the products of the reaction. The mechanism of the second type of photodynamic reaction consists of a reaction of the photosensitizer with molecular oxygen ($^3O_2$) and singlet oxygen ($^1O_2$) formation. As singlet oxygen is thought to play a main role in destroying cancer cells, the type II PDT mechanism is known as an appropriate photodynamic reaction (PDR). Although in both types, I and II, reactions may occur simultaneously, in most cases, one of them is more common, depending on the structure and physicochemical properties of photosensitizers. The newest photosensitizers are designed to generate as much singlet oxygen as possible (preferring type II). There is also another type of photodynamic therapy mechanism called the type III PDT mechanism. However, it is based on the direct interaction of excited photosensitizers, which is toxic to the target cancer cells without oxygen species being involved [12, 15, 17].

The singlet oxygen obtained during PDT is thought to be a very reactive derivative of the oxygen species. It is able to initiate a cascade of molecular effects resulting in the selective destruction of lesions, indirect vascular damaging effects (vascular shutdown), and the influence on immune systems (inflammation induction and other tumor-specific immune reactions) [10]. Its half-life is 40 ns and the range of action is 20 nm [9, 18]. The amount of singlet oxygen species produced by photosensitizers has to be sufficient to destroy even large lesions. The toxic character of radicals and singlet oxygen species results in apoptotic (via signal transduction pathways) and/or necrotic cell death. The destructive influence on the vascular system is a result of vasoconstriction, thrombosis, ischemia or necrosis connected with the singlet oxygen lethal effect to the nearest cells [19].

3. Modern photosensitizers—drugs—applied in therapy nowadays

There are few important requirements that chemical compound meets to serve as a photosensitizer for PDT. One of the first requirements is its synthetic purity and stability. A photosensitizer should be water-soluble and easily distribute in the body. It should not exhibit toxicity or mutagenicity in the human organism without light activation; therefore, it should be inert until activation by light. Ideal photosensitizers should also selectively accumulate in tumor tissue and be characterized by the clearance from healthy tissue, so therapy would only involve pathologically altered cells. In addition, they should be non-toxic to non-illuminated bystander regions. Photosensitizers should be activated by light in an appropriate wavelength that penetrates tissue deeper, and efficiently generates reactive oxygen species (especially singlet oxygen). Therefore, the repeated generation of type II reactions with a clinically successful photosensitizer is very important. The ideal photosensitizer does not induce pain during and after therapy and may be used in outpatient care. The drug, photosensitizer, should be transported in a stable state and its reconstitution should be performed by trained pharmacists without specialized laboratories. Generally, clinicians and chemists have different views concerning the ideal photosensitizer. Chemists put more stress on a high extinction coefficient and a high quantum yield of singlet oxygen, whereas clinicians emphasize low toxicity and high selectivity [3, 15, 17, 20, 21].

Most of the currently used photosensitizers in clinical PDT belong to the porphyrinoid family. These aromatic, macrocyclic compounds consist usually of four pyrrole rings linked together by methine or azomethine bridges. The first clinically applied photosensitizer and, parallel to which, a representative of the first generation of photosensitizers approved for photodynamic therapy, is Photofrin®. It is a complex mixture of porphyrin monomers, dimers, and oligomers obtained by chemical processing of hematoporphyrin with a Q1 band at 630 nm in phosphate buffered saline (PBS) and a very low singlet oxygen generation φ_{Δ} value of 0.01 in PBS. This photosensitizer is administered by intravenous route to achieve concentration in the lesion and/or clear healthy tissue ca. 48 h prior to illumination. It was found that illumination, 2–4 h post infusion to the target tissue, is possible but the preservation of healthy tissue is not achieved. It was found that this photosensitizer was evident to a certain degree in all tissues for 4–8 weeks post infusion due to a long clearance time. It possesses wide applications in PDT, e.g., in the early and late stages of lung cancer, superficial and advanced esophageal cancer, bladder cancer, cervical dysplasia and early stage cervical cancer, cancers of head and neck, brain, and skin [15, 17, 22, 23]. However, this photosensitizer has many crucial defects. Most important is its long-elimination time reaching 8 weeks, which causes long-lasting photosensitivity. Patients can experience skin burns when exposed to strong light, e.g., sunlight. Based on chlorine structure, Temoporfin 1 (**Figure 3**) belongs to the second generation photosensitizers and can be obtained in high purity and chemical identity. Moreover, it exhibits better photosensitizing properties than Photofrin® and is used under Foscan® brand name. PDT

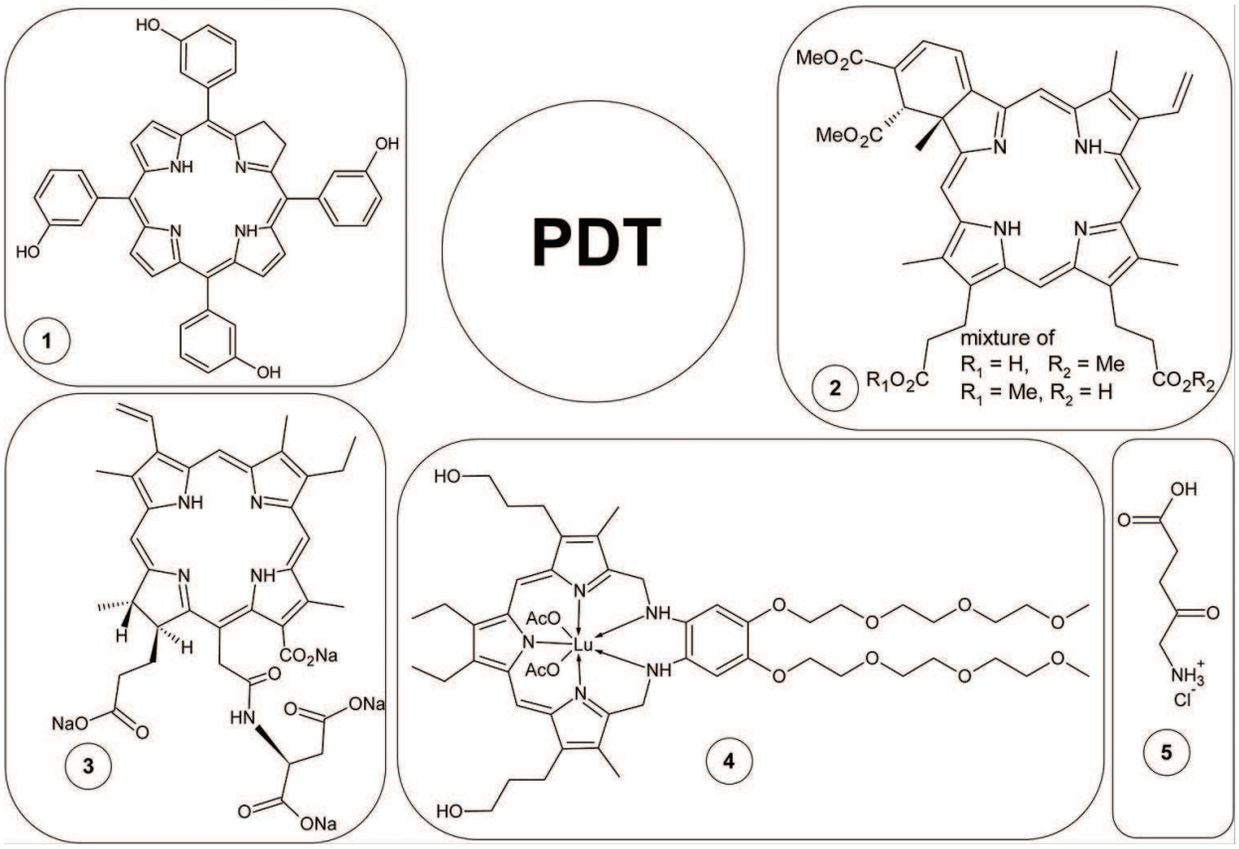

Figure 3. Chemical structures of clinically used photosensitizers: (**1**) Foscan, (**2**) Visudyne, (**3**) Talaporfin sodium, (**4**) Lutetium texaphyrin, (**5**) 5-Aminolevulinic acid.

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with Foscan® is 100 times more effective due to its absorption maximum shifted toward longer wavelengths (Q1 band appears at 652 nm), higher molar absorption coefficient, and singlet oxygen generation yield (φ_Δ value is 0.43 in aerated methanol). These features enable the use of a lower dose of administered photosensitizer ca. 0.15 mg/kg intravenously, in comparison to 2–5 mg/kg, as in the case of Photofrin®. Temoporfin has been applied against, e.g., esophageal cancer, lung cancer, gastric cancer, prostate cancer, and skin cancer. However, the elimination time of this photosensitizer is still very long (about 4–6 weeks). Another synthetic chlorine-based photosensitizer is mono aspartyl chlorine e6 (MACE), which possesses improved characteristics as compared to Photofrin®. Its sunlight photosensitivity skin reaction is in fact 2–3 weeks, but it is activated 4 h post infusion, which enables the convenient treatment in a single one day session. It possesses potential in ophthalmic lesions [11, 15, 20]. In the case of Verteporfin (Visudyne®) **2**, the accumulation and elimination times are 20 times shorter than that of Foscan®. Other advantages of **2** as a photosensitizer are the strong absorption band shifted even further into longer wavelengths (Q1 band at 686 nm) than those of Foscan® and Photofrin®. In addition, the ability to generate singlet oxygen by Visudyne® is extremely strong. This photosensitizer is used as the liposomal formulation in the PDT of age-related macular degeneration. It is also used in rheumatoid arthritis due to its immunomodulatory properties. Visudyne® has been also considered against psoriasis and cutaneous tumors [24]. Talaporfin sodium **3**, known as Laserphyrin® is a water-soluble second generation photosensitizer. It exhibits all desired features of an ideal photosensitizer, including good light absorption (Q1 band at 654 nm), efficient singlet oxygen generation (φ_Δ value is 0.43 in PBS), and fast accumulation and elimination. In Japan, Lutrin®, which is a brand name of **4**, has been used in therapy at early-stage lung cancer. Lutetium texaphyrin (Lutrin®) **4** possesses significantly lower singlet oxygen generation yield (φ_Δ value is 0.11 in methanol) than other second generation photosensitizers. However, its absorption maximum wavelength is shifted toward 732 nm. It can be administered in lower doses than Photofrin® and irradiated with lower light doses 3 h after injection. Lutrin®, which is a brand name of **4**, can be successfully used in PDT in cervical and prostate cancer. It undergoes clinical trials against melanomas, breast cancer, and Kaposi's sarcoma. Moreover, some animal *in vivo* study revealed an increase in damage to tumor blood vessels during Lutetium texaphyrin-PDT through the use of low fluence rates [11, 25].

Aside from the photosensitizers described above, which are commercially available and participate directly in the photodynamic reaction, there is also another approach to PDT. 5-Aminolevulinic acid (ALA, Levulan®) **5** mediated PDT has received much attention of researchers and physicians. Unlike other photosensitizers ALA is a prodrug (pro-metabolite). When administered intravenously, it enters metabolically, which physiologically leads to heme formation. However, in tumor tissue, this enzyme conducts the last step in heme synthesis, ferrochelatase, and is less active; therefore, the metabolic pathway stops at protoporphyrin IX (Pp IX). This endogenous porphyrin possesses photosensitizing activity and can be employed as a PDT agent. ALA-PDT has shown promising potential in animal testing and early clinical trials in many tumors, including epithelial nonmelanoma skin cancers [26]. Recently, the efficacy and safety of topical ALA-PDT in the treatment of extramammary Paget's disease (EMPD) and its role in surgical improvements have been discussed [27].

Although second generation photosensitizers are effective PDT agents, there is a constant need for further development and improvements. Many potential PDT active pharmaceutical

substances are under clinical trials, as well as many research reports, and embrace the very promising properties of the newly obtained compounds. The main paths of research have involved the elaboration of tumor selective agents by conjugating photosensitizers with biologically active moieties, e.g., carbohydrates [28], folate molecules [29], or antibodies targeting cancer cells [30]. This can increase the uptake of photosensitizers in cancerous cells and make PDT more effective and less harmful to healthy tissue. A huge challenge may bring the development of nanosized carriers for photosensitizers, including polymeric nanoparticles, liposomes, niosomes, micelles, nanocrystals, microcapsules, and dendrimers. It should improve the efficiency of photodynamic activity and, in this way, overcome many side effects associated with classic PDT. Huge success noted in this field is connected with two liposomal formulations of photosensitizers, such as Verteporfin (Visudyne®) and Temoporfin (Foslip®) [31, 32].

4. The expertise of the health care providers and associated specialists working collaboratively with patients during photodynamic therapy

4.1. The role of associated specialists in preclinical trials

Interdisciplinary team, including medicinal chemists, chemists, biologists, biochemists, and physicists conducts preliminary step of photodynamic therapy (**Figure 4**). Medicinal chemists and chemists are engaged in the design and chemical synthesis of compounds that may have the potential for photodynamic therapy. The production process should be efficient and easy to reproduce. As far as PDT is concerned, an important measurement is also the assessment of light absorption and emission by a photosensitizer, solubility, aggregation tendency, its chemical, and photostabilities (photobleaching). This research is usually performed by physicist and chemical physicist. In the area of biochemistry, biology, and molecular pharmacology,

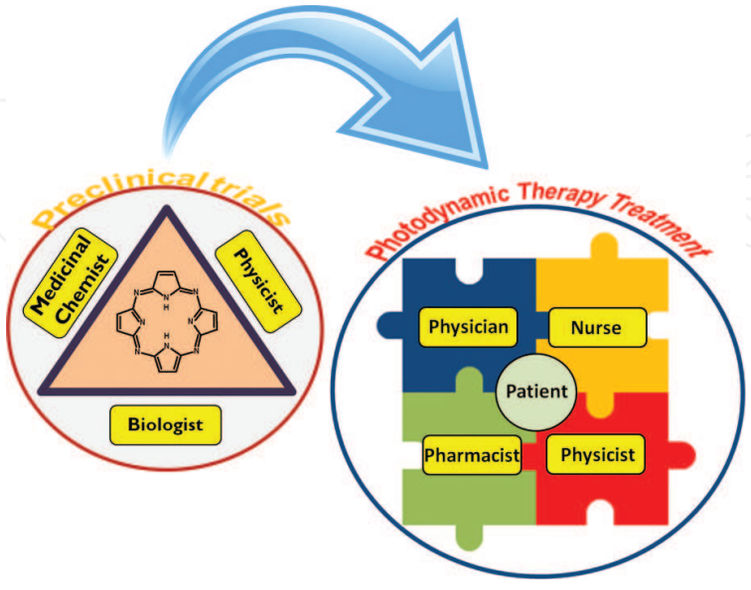

Figure 4. Health care providers and associated specialists in photodynamic therapy team.

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researchers look into the activity of the compounds. They conduct tests on cell cultures *in vitro* and using animals *in vivo* experiments [4, 21].

The role of team members listed herein is, therefore, to produce a medicine, that, when used during PDT should possess features such as: chemical purity, chemo- and photostability, a lack of activity in the dark, selective accumulation in target tissue (e.g., neoplasms), a lack of toxicity, and mutagenicity in healthy tissues. The rate of the elimination of the substances from the body and its availability to patients are apparent. One of the most important issues is also the reduction or overcoming of the adverse effects caused by photosensitizers such as photosensitivity lasting up to several weeks after treatment or elimination of pain associated with treatment [20]. Sieroń and Kwiatek [5] discussed the work carried out by an interdisciplinary team consisting of physicists and chemists, whose aim was to develop an optimal structure of a novel photosensitizer. They performed chemical synthesis in a novel potential photosensitizer and its physicochemical characterization with the detailed assessment of spectroscopic properties. Part of the team consisted of physicists focused on the determination of crystalline and electronic structures and the chemical composition of novel photosensitizers. The presence of physicists in the PDT team is recommended also for another reason. The necessary condition for the photodynamic therapy is the activation of the photosensitizer through light in the appropriate wavelength. In practice, laser and nonlaser light sources are used. Physicists are responsible for providing a source of light, establishing the wavelength, and dose of the photosensitizer suitable for irradiation during treatment. Further studies on cell and molecular aspects of PDT action with the newly elaborated photosensitizers are necessary on various cells *in vitro* and *in vivo* tumor models. All these studies can help to explore cytotoxicity, photocytotoxicity, and genotoxicity of novel photosensitizers [5, 33]. Considering the relevant aspects of medicinal chemistry and pharmaceutical chemistry important in various stages of preclinical trials, the pharmacist's expertise can also be very useful. In particular, it concerns problems arising from limited solubility and the aggregation of various photosensitizers prepared for initial preclinical biological study. Many limitation appearing in such a stage may be overcome by both chemical modification in the periphery of the photosensitizer and/or suitable pharmaceutical formulation, e.g., by entrapping the photosensitizer in liposomes or polymeric nanoparticles [32, 34].

4.2. The role of health care providers in clinical trials

Health care providers, such as physicians, nurses, and pharmacists, work closely with patients in photodynamic therapy processes.

4.2.1. Physicians

Among specialists in the interdisciplinary team of health care providers conducting photodynamic therapy, an important task falls on the doctor's shoulders. His knowledge and skills are used in each stage of PDT in the treatment of neoplastic and nonneoplastic diseases. His main task is to carry out the treatment itself and to take responsibility for the whole therapy. The doctor assesses the patient's state of health before treatment and decides on the patient's qualification for PDT, informs about the procedure and possible adverse effects [6, 7]. In Brazil,

a physician consults a nurse and physicist and considers the potential benefits and consequences of therapy for each patient. Doctors and nurses spend a lot of time in explaining details with the patient and answering his questions [4].

The cooperation within the interdisciplinary PDT team has been professionally elaborated by researchers from the Laser Center, Thompson Cancer Survival Center of Knoxville. Their conclusions concerned the treatment of Barrett's esophagus using endoscopic ablation of Barrett's esophagectomy with PDT. The method applied is based on the medication followed by the endoscopy procedure during which the laser light is emitted to the so-called Barrett's esophagus through an endoscope. This technique requires the coordinated work of a physician, an endoscopic nurse, a laser expert, and, an endoscopic assistant. The authors of this paper, Overholt and Panjehpour [35] clearly demonstrated that the proposed construction of the "PDT team of excellence" is necessary for professional and successful treatment of the patient.

4.2.2. Nursing personnel

Nurses are professionally active and involved in the care of patients treated through phototherapy following tasks resulting from four functions of nursing: (i) health care provision, (ii) patient education, (iii) active action in health care team, and (iv) the development of nursing practice standards (**Figure 5**). As far as the above-mentioned nursing features are concerned, a nurse performs a number of tasks that contribute to improving the quality of services provided through which the most dominant feature is the provision of nursing care. The term health service means measures to strengthen, maintain, restore, or improve health, resulting from the process of diagnosis, treatment, and rehabilitation. In order to optimize health care services, specific tasks performed by nurses need to be taken on: (i) assessing the needs of patients treated with phototherapy, and the recognition of their condition and existing health problems, (ii) creation of conditions for aware patient participation in the planned form of treatment, (iii) planning and implementing nursing care during treatment and after its completion, and (iv) documenting the activities of nursing (medical history, results of preclinical examinations such as the BP intervals, heart rate, body weight, height, respiratory-rate) [36–39]. Particularly important is the provision of health care to chronically ill patients whose bio-psycho-social welfare has

Figure 5. General duties of nurses during PDT [39].

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been violated. Therefore, the principal activity carried out by nurses as health care providers is to conduct an interview with a person who is to undergo photodynamic therapy. The interview should include elements concerning the health and social situation of the family. Before the provision of health services prior to therapy, a nurse takes the height and weight measurements of patient, assesses visual acuity, heart-rate, blood pressure, and the respiratory-rate. The tasks of the nurse participating in the therapy are drug administration and observation of the patient to acute allergic reactions or other adverse effects during the course of treatment. As an essential topic in the interview, it should cover the kind of existing treatment and possibilities of occurrence of contraindications to phototherapy i.e., existing allergy, liver diseases, hypersensitivity to sunlight or pregnancy. Noteworthy, as porfimer sodium is classified as a chemotherapy agent, only a registered nurse can administer the medication [6, 40, 41]. Excellent examples concerning PDT as a treatment option for two groups of patients utilizing its curative or palliative effect for lung cancer (nonsmall cell lung cancer) patients were discussed by Collins and Garner [6]. They presented the cooperation model in a PDT team consisting of a nurse, a surgeon, an oncologist, and a pharmacist. As emphasized by Rich et al. [7], included in the nurses' tasks before treatment, a detailed interview with the patient aimed at obtaining a medical history of treatment is necessary. It is important to collect a complete medical and surgical history, including current medications used and an ophthalmologic history. Particular attention should be paid to the presence of contraindications to photodynamic therapy with Verteporfin (Visudyne), such as allergies, hypersensitivity to sunlight, liver disease, or pregnancy. Prior to the surgery, nursing personnel tests the visual acuity, blood pressure, pulse, respirations, and body weight and height of the patient for BSA (body surface area).

During surgery, the nurse, according to the doctor's recommendation, administers medication (eye drops) to the patient and starts the infusion line with use of a No. 22 angio safety catheter. The nurse also has to make sure that the patient has knowledge of the entire procedure. It is also important for the patient throughout the procedure to remain in the correct position, so that the doctor can accurately direct the laser light on the treated area. After treatment, the patient receives detailed instructions about potential side effects, the optimization of pain management, and precautions that must be taken. Mainly the patient should be told to protect skin and eyes from sunlight and other so-called sources of bright light and warned that nonadherence to these instructions may result in skin burns or eye damage. It is very important to assure that patient understands the necessity for light precautions for 5 days, even in terms of avoiding bright lights, like surgical and dental lighting. Thus, nurses are significant members of the professional team and fulfill an important role in the patient assessment including pretreatment and posttreatment teaching [7, 42].

Similarly, the nurse's role is depicted in disease therapy of lung or esophageal cancers. Also, in this case, they are responsible for informing the patient about the effects of photosensitivity and explaining how and for how long patient's skin and eyes should be protected, as the illumination is connected with extreme photosensitivity, including ocular sensitivity. It is also worth mentioning that education about the procedure, side effects, and precautions should be extended to all patient family members. These subjects are of immense interest for nurses and have been included in many oncology nursing treatment schemes [6, 42, 43]. Allison et al. [44]

while discussing PDT for chest wall recurrence from breast cancer analyzed many specific precautions accompanying this kind of treatment, including photosensitivity, illumination, pain control, photosensitivity reaction, posttreatment, patient selection, curing wounds, and retreatment. Some of them are under the direct control of a physician, but many need the supervision of other medical team members. Although photosensitivity is a common problem, patients must be informed that even minimal light levels as those coming from a light bulb or fireplace or light reflected from a car window can cause photosensitivity reaction. Interestingly, giving consent to PDT therapy according to information about sunlight precautions has not prevented any patient from photosensitivity, Therefore, patients found to be unable to accept sunlight precautions should not be offered PDT. Pain may accompany the PDT therapy, therefore patient should be given narcotic or nonnarcotic pain pills prior to illumination. In some cases, patients subjected to PDT for the recurrence of breast cancer in the chest wall, pain control resulting from lesion diminishment can be seen within 2 weeks of the PDT session. Nevertheless, even at that time continued narcotic or nonnarcotic analgesia is recommended. It is very important as to how the problem is recognized when the photosensitivity reaction occurs. Although the treatment of the sign and symptoms of skin burns may be easily treated with, e.g., steroids, ice/cold compresses, the treatment of, e.g., airway and neck is more complicated and a proper intensive care approach may be required, often on an inpatient basis. Posttreatment patient management is a major therapeutic challenge. Patients need to drink plenty of fluids and be protected from light. Some patients may need steroids, while others oral narcotic and nonnarcotic analgesia, and many, in the course of treatment, antibiotics [44, 45].

Nurses take on many tasks in the PDT treatment procedure; therefore, they should know the principles of photodynamic therapy. Later after treatment, the nurse actively participates in the patient recovery process or motivating patients to continue therapy using PDT and other health procedures [40, 41]. Meticulous patient monitoring and the evaluation of the effectiveness of nursing care taken will allow the nurse to implement the next health service function, which is health education. The purpose of health education is for people with disabilities and the chronically ill to be motivated to take responsibility for their own health and to prepare for self-care. Educational activities are closely linked with health promotion, the main objective of which is to strengthen and enhance health, and, without a doubt, improve their quality of life. The concept of health promotion in relation to chronic diseases may often be as a contradiction misunderstood, in other words illogical. However, it must be kept in mind that the purpose of the promotion is to improve and control one's own health. Therefore, especially those who are ill should take care of the development of their bio-psycho-social opportunities, because no illness limits human functioning to the extent that it was impossible to creatively use the remaining potential [46]. It is important that nurses use their knowledge of health promotion to motivate patients in the field of their health protection and restoring them to health by activating compensatory mechanisms. In the nursing care process, it is important to have permanent psychotherapeutic impact, by which a positive effect on the patient and the creation of a therapeutic relationship nurse-patient is meant. An important element is to establish a relationship between the nurse and the patient and sends a "positive support message" containing, uplifting and at the same time mobilizing to action. Mutual understanding,

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creating an atmosphere of releasing a suffering person from negative feelings allows the nurse to establish efficient communication, as it was discussed during the PDT lung cancer treatment and AMD patients. Moreover, a nurse acts not only as the patient's teacher, but also an advocate [6, 47].

Considering their educational activities, nurses conduct the following tasks: (i) they collect information at the request of patients for educational and advisory activities, (ii) they set targets for educational activities, and preventional promotion actions involving the provision of behavioral information after PDT treatment. The topic of education regards behavior after illumination. Nurses should recommend avoiding sunlight, wearing headgear, clothing with long sleeves, and sunglasses. Patient should be informed that their entire skin must be covered and that daily activities, including driving should be done at night. In the case of some photosensitizers, patients should be house-bound up to 3 months. Nurses should also report any reactions to medication. Significant to patient education is learning how to cope with any stress resulting from the disease and how to control stress. Some emotional problems experienced by patients are not symptoms of their disease, but are related to a manifestation of some "adaptation efforts" arising from attempts to cope with the existing situation. It should be emphasized that all educational activities undertaken by the nurse should be tailored to the level of the recipient, and so communicated in a clear and simple manner without medical jargon. In fulfilling the role, the nurses should work with other members of the therapeutic team, who will help them and give advice. In Brazil, nurses participate not only in the whole procedure at each stage of therapy but are also in very close contact with the patient. They are responsible for education concerning the course of treatment and risk minimization of side effects. They also observe the patient during surgery for adverse events [4, 6, 48].

Another feature of nursing is the active involvement in health care organization. Care for patients undergoing photodynamic therapy is exercised by different professionals (physician, nurse, and pharmacist) and therefore their close cooperation is required, including the exchange of experiences and information on patients. This is important because of the deliberate planning and organizing health care. Due to the frequent contact of nurses to patients, it is advisable for them to function as a link between patients and other members of the therapeutic team. Nurses cooperate with other professionals, the patient's family, and the local community. This allows them to work together with a team to come up with the optimum therapeutic care plan for the patient treated with PDT and to provide comprehensive assistance in line with the expectations of the patient. In order to fulfill this function, nurses begin work with both the team caring for the patient and with his family (through contact with a health visitor, primary care physician). The consequence of cooperation with such people is the exchange of insights and experiences on the patient's health and social situation in order to improve the quality of health services [6, 7].

Based on these experiences and research conducted on persons undergoing phototherapy, nurses should develop innovative ways of working with patients, in order to achieve better care results. It should allow them to fulfill the fourth nursing function which is the development of nursing skills. In carrying out this function, nurses should undertake the following tasks: (i) take an active part in training through participation in conferences and courses on

phototherapy, which will enable them to broaden their knowledge, (ii) keeping up to date through the self-study and analysis of the latest medical reports in the field of PDT, (iii) develop standard of nursing care for patients being treated with photodynamic therapy, implement the above-mentioned standards, and evaluate the effectiveness of nursing actions taken. Photodynamic therapy of age-related macular degeneration is a stage process, which includes intravenous administration of the photosensitizer followed by the use of lasers to activate the drug. The role of the care providers consists in administration, evaluation, and monitoring of the patient for acute drug reactions during the procedure or patient education. It is noteworthy that the implementation of formalized, proactive interdisciplinary approaches in treating other diseases, like chronic kidney disease, was found to have a positive impact on patients' well-being [49, 50].

4.2.3. Pharmacists

Many pharmacists have expressed a desire to become more involved in patient care and in providing services traditionally offered by physicians and nurse practitioners [51]. The role of the pharmacists in patient-centered medical home practices revealed knowledge and skills that can complement the care provided by other health care team members [52]. Moreover, many studies emphasize that the cooperation between general practitioners, pharmacists, and nurses is necessary to effectively dispense drugs to the patient [53]. A very interesting report concerning approaches in improving the outcome of the patient and health care system through advanced pharmaceutical experience and have recently been reviewed by Giberson et al. [54]. Moreover, Makowsky et al. [55] recently discussed working relationships in the inpatient medical setting between pharmacists, physicians, and nurse practitioners. The integration of pharmacists into the nurse practitioners and physicians teams was positively felt in terms of patient well-being (drug-therapy decision-making, continuity of care, patient safety).

Pharmacists as specialist—team players in the field of medicinal chemistry, pharmacology, and toxicology—are responsible for the preparation of drugs for both topical and systemic administration. They are also responsible for the proper drug storage, i.e., temperature control and protection against solar radiation and other light sources. Pharmacists cooperate with physicians and nurses during the procedure to ensure the adequate preparation of the drug directly before the administration to the patient [4, 6]. In this regard, it is especially important that the specialized team cooperates on the various aspects of specific medications at various stages of the procedure, such as narcotic and nonnarcotic medications including nonsteroidal anti-inflammatory drugs analgesics, acetaminophen, metamizole or topical pain relievers, antibiotics, steroids, and nausea-suppressing agents. Moreover, some patients require parenteral nutrition or hydration. Hypersensitivity to light requires specific precautions. Failure to comply with these rules may result in skin burns, peeling of the treated skin, local edema, erythema, dysuria, urethral irritation which requires the use of additional therapeutic agents [6, 20, 35, 56].

The researchers emphasize the important role of pharmacists and cooperation with the pharmacy. The application of each drug should be preceded by their compatibility studies with other medications. It is also used to assess the properties of the drug formulations considering

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patient's light hypersensitivity. Scientists dealing with modifications of oral drug forms turned their attention to the possibility of cooperation of physicians, pharmacists, and nurses. They conducted the survey among representatives of these three professions. It turned out that the personnel working in the public health centers employing specialists in various fields, for example hospitals often cooperate with each other discussing and exchanging views and experiences [6, 53].

Another expertise area of pharmacists includes drug formulation. It seems that the development of novel photosensitizers depends on both the development of novel photosensitizers, as well as novel formulations including the latest achievements of nanomedicine. Very interesting pharmaceutical studies were conducted for 5-aminolevulinic acid (5-ALA) that is a photosensitizer with broad applications in photodynamic therapy and photodynamic diagnosis. This compound is a prodrug/prometabolite which is converted into protoporphyrin IX (PpIX) and possesses photosensitizing properties [44]. Its topical formulations are used in the treatment of neoplastic and nonneoplastic diseases. Unfortunately, ALA-PDT treatment has certain drawbacks. One of them is low skin permeability, limiting this treatment only to surface skin lesions, e.g., malignant skin tumors [5, 20]. Researchers, who rely on their knowledge and clinical experience, are attempting to modify the drug formulations containing this compound [57]. Therefore, a 20% topical solution of 5-aminolevulinic under the brand name of Levulan® Kerastick® is being used. A lack in the stability of the substance in solution requires combining the drug with a solvent just before application. Another product called Metvix® is a 16% cream containing the methyl ester of 5-aminolevulinic acid (methyl aminolevulinate) as hydrochloride, which in comparison to the parent compound should penetrate the skin more effectively. In searching for another stable formulation, a precise dose to the affected area was provided by Donnelly et al. [57] and E.P. Patent No. 1467706 B1 [58]. They described an adhesion patch based on Eudragit® NE that contains ALA dispersed in the adhesive matrix and requires moisture for activation. It is also of interest that mucoadhesive Carbopol® 941- and Poloxamer® PF127-based polymeric mucoadhesive thermoresponsive gel containing ALA was described by Tsui-Min [59]. Promising data was obtained for 20% oil-in-water emulsion formulations of 5-aminolevulinic acid. These drugs were administered topically to patients with various types of skin diseases [60]. Interesting experiments that compared the efficacy of 5-aminolevulinic acid (5-ALA) and its methyl ester (mALA) were performed for Lutrol F-127-based thermolabile gel 10% formulation in treatment of basal cell carcinomas of the skin [61].

A very interesting study on pharmaceutical development, composition, and quantitative analysis of the phthalocyanine photosensitizer for cancer photodynamic therapy has recently been presented by Jiang et al. [62]. The authors discussed phthalocyanine derivatives in terms of pharmaceutical development and molecular modification in order to enhance drug effectiveness and to improve its intracellular localization. Therefore, various approaches concerning the conjugation of photosensitizers to various antibodies, proteins, and peptides have also been described. In addition, various strategies concerning an improvement of pharmaceutical properties utilizing direct formulations of phthalocyanines were discussed.

5. Perspectives

The aim of this short review was to present the topic of photodynamic therapy and activities taken by health care providers and associated specialists working together with patients during the photodynamic therapy. The expert literature indicates that the effective implementation of photodynamic therapy requires intensive cooperation within the interdisciplinary team and possesses a broad knowledge in various fields. Coordinated actions of representatives possessing expertise in various fields of medical and natural sciences, especially doctors, nurses, pharmacists, chemists, physicists, biologists, and biochemists, are necessary both during joint research, development and during the course of the PDT procedure.

During therapy, the patient plays the most important role and is responsible for acting in accordance with the schedule set by the physician, nurse, and pharmacist. Activities aimed to increase the effectiveness of treatment conducted by the physician or surgeon, minimizing side effects, and ensuring of the comprehensive care to patients also require the participation of physicians, nurses, and pharmacists. In conclusion, only the effective interaction between professionals and clear sharing of responsibilities at different stages of therapy should guarantee successful treatment.

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