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Laser and Non-laser Light Sources for Photodynamic Therapy

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Abstract. Photodynamic therapy (PDT) is an anticancer combination therapy, which requires a photosensitiser, which tends to accumulate preferentially in the tumour, and light. Historically large, complex lasers have been used to carry out PDT treatment. Nowadays there is a wide range of coherent and non-coherent sources that can be used. This paper considers the important characteristics of light sources for PDT, including dye lasers pumped by argon or metal vapour lasers and frequency-doubled Nd:YAG lasers. Non-laser sources including tungsten filament, xenon arc, metal halide and fluorescent lamps are also discussed. New exiciting developments such as LEDs and femtosecond lasers are also reviewed. The relative merits of laser and non-laser sources are critically examined.

Keywords: Cancer treatment; Light sources; Photodynamic therapy (PDT); Photosensitisers

INTRODUCTION

Photodynamice therapy (PDT) is a treatment modality available for palliation or eradication of several cancers. PDT involves the use of a photoactive drug (photosensitiser) and light (typically visible or infrared) [1,2]. Upon absorption of light, the photosensitiser (PS) initiates chemical reactions that lead to the direct or indirect production of cytotoxic species such as radicals and singlet oxygen [3,4]. The reaction of the cytotoxic species with subcellular organelles and macromolecules (proteins, DNA, etc) lead to apoptosis and/or necrosis of the cells hosting the PS. The preferential accumulation of PSs in cancer cells [5,6] (which in many cases can be significant) combined with the localised delivery of light to the tumour, results in the selective destruction of the cancerous lesion [5]. Compared to other traditional anticancer therapies, PDT does not involve generalised destruction of healthy cells. In addition to direct cell killing, PDT can also act on the vasculature, reducing blood flow to the tumour causing its necrosis [7,8]. In particular cases it can be used as a less invasive alternative to surgery [9–12].

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Since PDT depends on localised light delivery, it can be applied only to tumours that can be reached by light either directly or through an optical fibre. Efficient PDT is limited, however, by the penetration of light into the tissue, which confines the treatment to superficial cancer [13]. Despite its efficacy, the application of PDT in humans is still relatively experimental and for the treatment of the same type of tumours protocols can vary considerably. Quite obviously the light source and light delivery are two of the fundamental aspects in PDT. The choice of light source for PDT can be dictated by the location of the tumour, by the light dose delivered and by the choice of photosensitiser. Lasers and lamps have both been employed to perform PDT and the superiority of one source over the other has not been demonstrated, therefore the use of lasers or lamps depends on the specific application. Although PDT has been traditionally performed using lasers, the availability of broadband sources (lamps) is challenging the use of lasers where light can be directly delivered to the tumour (skin, oral cavity, etc.) without the need to couple the source to an optical fibre.

This paper reviews the characteristics of the light sources presently employed in PDT and their preferred application. PDT research is widespread and includes studies at various stages of clinical trials, animal studies, in vitro

investigation, cellular studies, etc. We will not review light sources used for scientific research in PDT where the choice of sources for PDT is somewhat less constrained, and we will rather concentrate on sources used for PDT in human subjects. Although PDT has been the subject of many reviews, to date there has not been a comprehensive description of the light sources available to scientists and clinicians.

PHOTOSENSITISERS AND MECHANISMS OF PDT

In PDT, absorption of light by the PS initiates chemical reactions that produce transient phototoxic compounds. The mechanism of production of these transient species has been thoroughly described elsewhere [1,4,14,15]. Briefly photodynamic mechanisms proceed from the first excited single state (S_1) of the photosensitiser produced by the absorption of a photon elsewhere [14]. From S_1 the molecule either loses an electron to originate a radical cation (PS $^{\bullet -}$) or quickly relaxes into the first excited triplet state (T_1). Both PS $^{\bullet -}$ and T_1 have a relatively long lifetime and can interact with molecular oxygen to generate highly reactive compounds such as peroxides and singlet oxygen. The reaction that proceeds via PS $^{\bullet -}$ is normally called Type I and the one that proceeds from T_1 is called Type II [3]. The species produced are very reactive and can induce oxidative stress of the cell hosting the PS with consequent cell death via apoptosis and/or necrosis [16,17].

The high reactivity of radicals and singlet oxygen also produces photobleaching of the PS. This occurs when the PS itself reacts with the transient species to undergo reversible or irreversible chemical reactions that lead to the creation of photoproducts. Such photoproducts have different absorption characteristics (different extinction coefficient and/or different absorption maxima) [18,19]. Photobleaching is normally regarded as a limiting factor in PDT as it depletes the amount of PS available during treatment. However, the role of photobleaching in PDT is not fully understood and it may also produce some benefits such as increase the penetration of PDT into the tumour as a result of the change in absorption at the excitation wavelength. Moreover the role of photoproducts on PDT in vivo has not been investigated.

The number of photosensitisers undergoing various stages of clinical trials is large and includes mostly various types of tetrapyrrolic rings such as porphyrin derivatives [20–25], phthalocyanines [15,26] and chlorins [25,27,28]. These compounds are all characterised by a large absorption band between 400 and 430 nm (Soret Band) [15,19] and smaller absorption bands (Q-bands) above 550 nm [15,19]. Q-bands above 600 nm are normally targeted for PDT purposes; they retain high quantum yields for Type I or II reactions and at the same time light above 600 nm penetrates deeper into the tissue. The absolute penetration of light depends on the optical characteristics of the tissue, and the geometry of light delivery [29–32]. The optical penetration depth (OPD) is defined as the depth at which the intensity of the propagating light is attenuated approximately 37% (1/e) of its initial value (at the air/tissue interface) [13]. For instance in brain tissue the OPD at 635 nm is 800 μm whereas in the bladder it is 4 mm [32]. Moreover, according to most tissue modelling, light in the 600–700 nm region of the spectrum penetrates 50–200% more than light in the 400–500 nm region [33,34]. When the optical properties of photosensitisers are also considered in determining tissue penetration [13] then penetration at 630 nm (for instance) is 3–4 times larger than penetration at 400–420 nm where the absorption coefficient of photosensitisers is much larger. As a result PDT is usually performed at wavelengths longer than 620 nm so that a larger volume of diseased (cancerous) tissue can be treated.

These requirements have pushed the development of light sources for PDT mostly (there are exceptions as are described below) towards outputs in the red region of the spectrum and, with the advent of newer generation of PSs, towards the near-infrared where penetration of the incident radiation is even larger.

Despite the many studies performed using different photosensitisers, only a few have reached the stage of advanced human clinical trial or even FDA approval for clinical use. These drugs include Photofrin©, Levulan©, Foscan© and Visudyne™. The characteristics of these photosensitisers are summarised in Table 1. Photofrin©, Foscan© and Visudyne™ are porphyrin or chlorins (two forms of tetrapyrrolic rings) and are administered systemically by intravenous injection and have been used mostly for malignant or premalignant lesions of internal organs such as brain [35], head and neck [9], bladder [5],

Table 1. Summary of the main characteristics of the most common commercially available photosensitisers

Commercial name	Chemical definition	Absorption maximum	Delivery
Photofrin	Mixture of di-hematoporphyrin esters and ethers	630 nm	Systemic
Foscan	Meta-tetrahydroxyphenylchlorin (m-THPC)	652 nm	Systemic
Visudyne	Benzoporphyrin derivative	690 nm	Systemic
Levulan	5-Aminolaevulinic acid (ALA) converted into protoporphyrin IX (PPIX)	635 nm	Oral/topical

lung [6], etc., and occasionally for malignancies of the oral cavity [12]. Visudyne has been used for treatment of age-related macular degeneration [36] although its application to other lesions (e.g. actinic keratosis) is under investigation. Levulan© is the commercial name for 5-aminolaevulinic acid (ALA), which is a precursor of protoporphyrin IX (PPIX) which is a clinically useful photosensitiser [24]. By supplying ALA to cells it is possible to overcome the negative feedback mechanisms in the synthesis of haem [24] and accumulate PPIX well above the physiological concentration. Unlike the other PSs, ALA can be administered topically and orally and is the preferred choice for superficial lesions in skin [23,37] and oral cavity [38] and it has been used in oesophageal and stomach malignancies and dysplasia [39]. Investigations and clinical trials are ongoing to study the benefits of ALA-esters [23]. These molecules introduce the benefit of a long lipophilic chain attached to ALA which increases penetration into tissues and through the stratum corneum (particularly important for ALA-PDT in skin) and their metabolism still leads to the formation of elevated intracellular levels of PPIX.

Naturally, most of the light sources for PDT application have developed to optimise the output near the absorption wavelengths reported in Table 1. Moreover the tendency of agencies, such as the US Food and Drug Administration, has been to approve not just the drug but the drug and the light source to be used for its optical excitation.

PDT LIGHT SOURCES

Lasers

Historically argon lasers and metal vapour lasers (see below) were the initial choice for PDT. These lasers combined several characteristics such as high power output, the possibility of pumping dye lasers that would in turn give access to the wavelength region for excitation of porphyrins and easy coupling to optical fibres for use with endoscopes.

Argon Lasers and Argon-pumped Dye Lasers

Argon lasers-pumping dye lasers are among the most popular devices for PDT treatment. Laser dyes (such as rhodamine B, rhodamine 101 and sulphorhodamine 640) can be chosen with absorption at one of the two main emission lines of the argon (488 nm and 514 nm) and emission in the 600–650 nm region to match the absorption of porphyrins (Table 1). These lasers require a high level of technical support. For instance, because the argon laser beam has a narrow cross-section, the alignment with the dye module is critical and tends to require regular re-adjustments. Argon lasers provide high irradiance at the emission lines (up to 1 W/cm^2) (Table 2). The output of the dye laser pumped by the main argon lines is in the range 10–500 mW/cm^2 despite the intrinsic losses of the dye laser. The spectral output of the dye laser has a bandwidth of 5–10 nm. The fluence rates reported in Table 2 are sufficient to deliver effective PDT by both direct or fibre-mediated irradiation. Argon-pumped dye lasers coupled to an optical fibre have been used in primary lung cancer [40,41], oral precancer [38], oesophagus [42] and bladder cancers [5]. The core of the fibre is variable depending on the site treated and may be 200–600 μm. In many applications, a diffuser is fixed at the end of the fibre to allow uniform irradiation within a lumen or tumour. The direct expanded and attenuated beam of argon-pumped dye lasers has also been used for PDT of superficial skin cancer [10] and for PDT of vulval neoplasia [43]. The direct

Table 2. Types of lasers available for clinical PDT

	Wavelength(s)	Bandwidth	Irradiance	Pulse duration	Light delivery
Argon laser	488 and 514.5 nm	Monochorom	0.5–1 W/cm^2	CW	Direct or optical fibre
Dye laser pumped by argon laser	500–750 nm (depending on the dye)	5–10 nm	10–200 mW/cm^2	CW	Direct or optical fibre
Metal vapour laser	UV or visible (depending on metal)	Monochrom	Up to 10 W/cm^2	10–50 ns quasi-CW	Direct or optical fibre
Dye laser pumped by metal vapour laser	500–750 nm (depending on the dye)	5–10 nm	10–500 mW/cm^2	10–50 ns quasi-CW	Direct or optical fibre
Solid state	For a Nd:Yag 1064, 532, 355, 266 nm	Monochrom	Up to 10 W/cm^2	10 ps–30 ns quasi-cw	Direct or optical fibre
Dye laser pumped by solid state laser	400–750 nm (depending on dye)	5–10 nm	10–500 mW/cm^2	10 ps–30 ns quasi-cw	Direct or optical fibre
Solid state optical parametric oscillator	250–2000 nm	Monochrom	Up to 1 W/cm^2	10 ps–30 ns	Direct or optical fibre
Semiconductor diode lasers	600–950 nm	Monochrom	Up to 700 mW/cm^2	CW	Optical fibre

monochromatic emission of the argon laser has not been widely employed in PDT because of the lower penetration into the tissue of the 488 and 514 nm wavelengths. However, preliminary animal experiments are ongoing using the line at 514 nm [44]. As a final note we would like to point out that argon lasers (and argon-pumped dye lasers) are especially indicated for endoscopic PDT because the output beam has a very small cross-section (<1 mm) and can readily be coupled to optical fibres. Conversely argon lasers are not the most convenient choice in typically large skin or oral lesions where its use involves the addition of a beam expander which can become cumbersome and reduce the fluence rate.

Metal Vapour-pumped Dye Laser

These lasers have also been (and still are) a popular choice for PDT particularly among European investigators. Unlike truly CW argon lasers, metal vapour lasers are normally pulsed, with pulsewidth ranging from 10 to 50 ns (Table 2) and pulse rates of 1 KHz. Such a high repetition rate makes the source quasi-continuous for clinical purposes. The pump beam (in the UV or visible depending on the metal mixture) provides high primary output power that can be used to pump tunable dye lasers, which in turn give access to the spectral region where porphyrins absorb. Metal vapour-pumped dye lasers are able to deliver light at irradiance up to several hundred mW/cm^2 (Table 2). These lasers can be coupled to optical fibres and used for endoscopic PDT such as in oral precancer [12], in head and neck cancer [9], the oesophagus [45], lung [11], bladder [5]. The bandwidth of the dye laser is the same as that of argon-pumped dye lases. Because of their large beam cross-section (typically 1–3 cm^2), the metal vapour laser can be applied for PDT of large lesions such as those occurring in the skin [46,47] without the need to use a beam expander. As with argon laser systems these lasers do require a good level of technical support. However, because of the large cross-section of the pump-laser beam, alignment with the dye module is not as critical as for argon lasers.

Solid State Lasers

Solid state lasers such as Nd:YAG lasers are a more recent development in laser technology and can be applied in PDT similarly to argon and metal vapour lasers. They offer more compact design than the previous lasers with obvious advantages for laboratory or clinical use. They are normally pulsed at higher rates (MHz) and shorter pulsewidths (sub-nanosecond). These lasers normally emit a fundamental line in the near infrared (e.g. for Nd:YAG at 1064 nm). The output from the fundamental line has energies of up to seven J/pulse. Pulses from Q-switched NdYAG lasers are 5–10 ns which translates into large peak energies and irradiances (Table 2) and can efficiently undergo frequency doubling to give lines in the visible (532 nm for Nd:YAG) or in the UV (266 nm for Nd:YAG) with energies of up to 50 mJ/pulse. The frequency-doubled output can then be used to pump a dye laser and obtain high power output in the region of porphyrin absorption with the same bandwidth as for the other laser-pumped dye lasers.

Optical Parametric Oscillators Lasers

Optical parametric oscillator (OPO) lasers can be used for irradiation of up to several hundred mW/cm^2. OPO are solid state-based pulsed lasers that via frequency doubling and wave-mixing give access to a large number of monochromatic wavelengths from the UV to the near-IR region of the spectrum [48]. Wavelength tunability and fluence rate for PDT are easily obtainable with these lasers (Table 2). Solid state lasers have been applied for PDT of skin lesions, oesophageal cancer [39,49], oral precancer and cancer [9,39], lung [50] and bladder [5]. A potential future advantage of solid state lasers compared to argon and metal vapour is the possibility of using the near infrared monochromatic fundamental emission of these lasers. Indeed one of the possible developments of PDT is the synthesis of photosensitisers that can be excited in the near infrared where radiation would penetrate deeper into tissues and extend PDT treatment to less superficial tumours. Solid state lasers would then be one of the main sources available.

Diode Lasers

These lasers represent a potential major breakthrough in the widespread clinical use of PDT. Lasers made with semiconductors are extremely compact (Fig. 1a) yet retain high output (Table 2). They are extremely versatile as they can be used in CW mode or be pulsed

(a)

(b)

(c)

Fig. 1. (a) Example of operating diode laser (Diomed 630); (b) example of operating tungsten filament lamp (Photocure); (c) example of metal halide lamp (Waldmann PDT 1200).

(picosecond to millisecond). Their bandwidth is typically 6 nm; the power supply is also compact and they are normally air-cooled. These lasers are very attractive for clinical use as they are easy to operate and portable for use in laboratory and clinical settings. They are normally coupled to optical fibres and are ideal for endoscopic PDT. Diode lasers have been used in the treatment of a variety of lesions in the skin, oral cavity and in the eye [51], pituitary adenomas [35], and also to treat age-related macular degeneration [36]. The fibre output can also be expanded for use in large lesions in the skin. At present diode lasers tend to offer only a single output wavelength, which limits their versatility. However, systems are being developed that will allow interchangeable laser modules with multiple wavelengths. We foresee that in the future these lasers will be more widely used for PDT.

Lamps

Lasers are not the only option for PDT. In clinical settings especially, several PDT sources now use filtered output high power lamps (Fig. 1b,c). General maintenance of lamps is normally easier and cheaper. In comparison with lasers, lamps emit a much wider spectral output. Because of the broad emission spectrum of lamps, a combination of narrowband, longpass and shortpass filters are often required. Narrowband filters select the irradiation wavelength within 10 nm, longpass filters help to cut high-power UV radiation associated with the lamp output and shortpass filters are usually necessary to cut IR emission from the filament which could cause heating of the treated area and may also damage the optics of the lamp. Although the combination of PDT and hyperthermia (due to IR radiation) has been suggested [52], in skin this is avoided as hyperthermia is associated with higher levels of pain.

Therefore, instead of a high intensity monochromatic source they produce high intensity over a larger spectral range. The superiority of monochromatic over broadband light delivery has not been demonstrated for PDT. The effectiveness of light sources depends on several factors, some of which can be simplified under the concept of 'total effective fluence rate' [53] which combines incident spectral irradiance, tissue transmission and the absorption properties of the photosensitiser. Dosimetry is important if meaningful comparisons are to be made between different light sources. If a laser is being used, then the wavelength is clearly identified. This becomes more complex with a broadband light source and in this case the spectral irradiance should always been given. What is required is the effective photodynamic dose. Total effective fluence rate indicates that, for instance, light in the green region of the spectrum may be more effective within a depth of 2 mm, beyond which red light appears to be superior for PDT. Lamps are portable and easy to use. They deliver light over a large area and can be

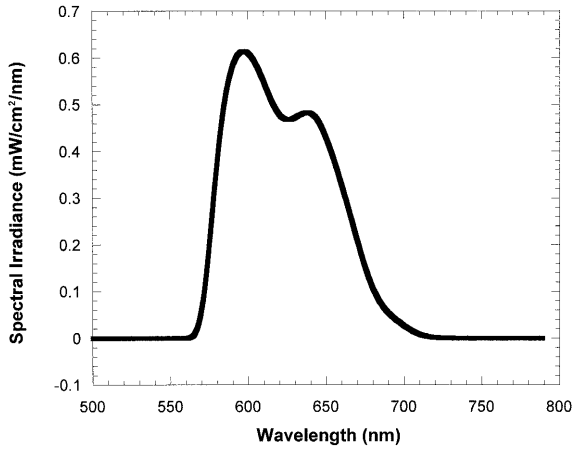

Fig. 2. Emission spectrum of the Photocure PDT Lamp (Tungsten filament lamp). The spectrum was recorded in our laboratory using a calibrated double-monochromator spectroradiometer.

coupled to large cross-section light guides and are therefore suitable for the treatment of large superficial lesions. Conversely the output of a lamp cannot be easily coupled into small optical fibres without greatly limiting their power output. For these reasons the use of lamps has been limited to skin lesion and they have not been used for endoscopic PDT.

Tungsten Filament Quartz Halogen Lamps

These are essentially incandescent sources where the temperature of the tungsten filament is raised to approximately 3000°K. At this temperature there is a considerable amount of optical radiation emitted from UV to near-IR. The use of these lamps for PDT was introduced by Pottier and Kennedy [54] who conducted animal experiments using the filtered output of a slide projector. Since then, commercial applications of the concept have been developed. These lamps can deliver up to 250 mW/cm^2 over a wide spectrum (350–850 nm) (Table 3). A single wavelength can be selected using combinations of long-pass, and narrowband filters. The output of these sources can be coupled into a liquid light guide (up to 1 cm in diameter) or expanded to several cm^2. These lamps have been mainly employed for topical ALA-PDT (i.e. PDT performed after topical application of 5-aminolaevulinic acid) in which the targeted photosensitiser is protoporphyrin IX whose absorption maximum is at 635 nm (see above). A representative spectral output, recorded using a calibrated double-grating spectroradiometer, is shown in Fig. 2.

Xenon Arc Lamps

In these lamps, radiation is provided by an electrical arc that forms between the electrodes in the presence of Xenon vapour. They are another possible light source for PDT. They are characterised by a broad spectral emission (300–1200 nm) and by high output (up to 8 W for direct exposure and up to 1 W using a liquid light guide) leading to potential fluence rates of several hundred mW/cm^2. Combination of band-pass and narrow-band filters can be used to eliminate IR radiation (consequently heat) and to select irradiation wavelengths within 60 nm (Table 3).

Although many of these light sources were assembled and used by research laboratories [23], a number of them are also available commercially. These sources have mostly been used for PDT of non-melanoma skin cancer and other skin disorders [23,55–58].

Metal Halide Lamps

These lamps comprise a mixture of mercury and metal halide vapour that is ignited by an electrical discharge. This produces a broad emission spectrum superimposed on a series of emission lines that depend on the gas used to fill the bulb. These light sources are another example of broadband lamps that can be used to perform PDT. The emission spectrum from one of the commercially available sources, recorded using a calibrated double-grating spectroradiometer, is shown in Fig. 3. Selection of the waveband can be achieved with filters to obtain spectral output in the 590–720 nm range (Fig. 3). The irradiance range is between 10 and 250 mW/cm^2 and the treatment area is potentially large (up to 20 cm in diameter) (Table 3). Unlike xenon arc and tungsten filament lamps, these sources are always used for direct exposure rather than coupled into a large core liquid light guide. Like the other broadband sources, metal halide lamps have been mostly employed in PDT of superficial lesions such as non-melanoma skin cancer [47,59], vulval intraepithelial neoplasia [60,61]. Although most of these lamps have been home built [47], examples of commercial metal halide lamps can also be found.

Phosphor-coated Sodium Lamp

The working principle of this lamp is similar to the metal halide lamps where an electric

Table 3. Types of lamps available for clinical PDT

	Wavelength(s)	Bandwidth	Irradiance	Light delivery
Tungsten filament	400–1100 nm	10–100 nm (depending on filters used)	Up to 250 mW/cm^2 or typically up to 1.8 mW/cm^2/nm	Direct or via liquid light guide
Xenon arc	300–1200 nm	10–100 nm (depending on filters used)	Up to 300 mW/cm^2 or typically up to 3 mW/cm^2/nm	Normally liquid light guide
Metal halide	Depending on the metal, lines between 250–730 nm (can be phosphor coated)	10–100 nm (depending on filters used)	Up to 250 mW/cm^2 or typically 1.2 mW/cm^2/nm	Direct or liquid light guide
Sodium (phosphor coated)	590–670 nm	10–80 nm (depending on filters)	Up to 100 mW/cm^2	Direct illumination
Fluorescent	400–450 nm	Approximately 30 nm	Up to 10 mW/cm^2	Direct illumination

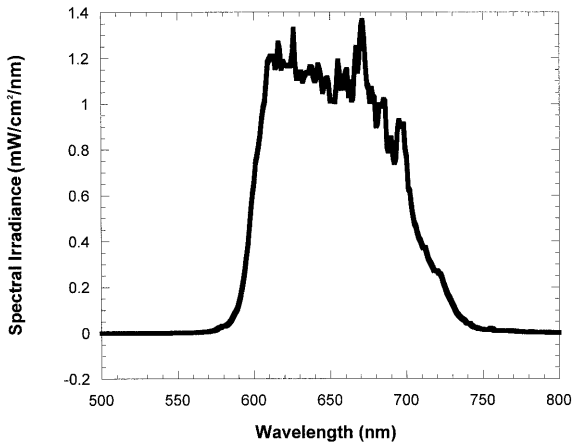

Fig. 3. Emission spectrum of the Waldmann PDT 1200 Lamp (metal halide lamp). The spectrum was recorded in our laboratory using a calibrated double-monochromator spectro-radiometer.

discharge is produced in the presence of sodium vapour. The surface of the bulb is coated with phosphors that absorb the sodium lines and emit in a different region acting similarly
to the dye lasers described previously. The spectral output includes wavelengths in the 590–670 nm region and the intensity is in the 25–100 mW/cm^2 range (Table 3). Similarly to the metal halide lamp, the area illuminated is large (up to 100 cm^2) and it can be used to perform PDT of skin lesions [62].

Fluorescent Lamps

These sources represent a different approach to PDT. As discussed above, light sources for PDT were developed to emit in the 600–700 nm region as in this region the photosensitisers currently used in therapy or clinical trials have one of their absorption maxima and light penetrates deeper into the tissue allowing treatment of thicker lesions. As described earlier photosensitisers have a more intense absorption band in the region between 400 and 450 nm (Soret Band). Fluorescent lamps have been developed to match this region of the spectrum. Higher absorption coefficients of the PS produce equal or higher efficiency of the photodynamic effect with a lower concentration of the drug in the tissue (smaller amount of drug administered either topically or systematically). Treatment, however, is limited to very superficial skin lesions since the penetration of light between 400 and 450 nm is approximately 300–400 μm. Fluorescent lamps for PDT have a maximum near 417 ± 5 nm and bandwidth of 30 nm. The power output is only 10 mW/cm^2 but their ease of use can be attractive for clinical settings. Their spectral characteristics match the absorption of protoporphyrin IX and their use has been limited to topical ALA-PDT of superficial skin lesions [63].

Laser vs. Lamp

As briefly discussed earlier, to date there has not been a thorough comparison between lasers and lamps in treating the same type of tumours in vivo and only sporadic studies have been reported [47,64,65]. We believe that such a comparison is fundamental for the development of PDT, and in our group, studies are ongoing on this particular topic. Lasers provide a monochromatic, very powerful source of light that can reduce the time necessary to deliver the final PDT dose. Because they are monochromatic the choice of laser wavelength becomes crucial as it must be matched with the often narrow absorption band of the photosensitiser (see Table 1) with the result that one laser can only be used in combination with one (or a limited number) PS. On the other hand, lamps provide a broad range of wavelengths at reduced fluence rates. Since most investigators limit fluence rates to relatively low values of 100–300 mW/cm^2, to avoid thermal effects, the use of lamps does not necessarily produce a dramatic increase in the time required for the treatment. Because of their broad emission, lamps can be used in combination with several PSs with different absorption maxima within the emission spectrum of the lamp. So, the same lamp could be used for PDT with Foscan, Photofrin or ALA (Tables 1 and 2). Moreover, lamps normally also excite the region where photoproducts absorb. Although the role of photoproducts in PDT is unclear, it is possible that some additional PDT effect can be obtained by photoproducts themselves. Lasers at present are the only possible light source to treat malignancies located in sites that can be reached only with optical fibres. Beam quality, dedicated optical accessories and power output are among the characteristics that make lasers the only real choice if light has to be coupled to an optical fibre with cores smaller than 500 μm in diameter. Because of the possibility of using light diffusers of different shapes and microlenses to produce uniform collimated

Table 4. Examples of new sources potentially useful for clinical PDT in the near future

	Wavelength(s)	Bandwidth	Irradiance	Pulse duration	Light delivery
Solid state lasers for two photon PDT	Near infrared	Monochorom	1 W in a volume of approximately 5–10 μm^3	0.1–10 ps	Direct, scanned over the lesion
LED	Visible and infrared	5–10 nm	Up to 150 mW/cm^2	CW	Direct

beams, lasers are also suitable for use in direct illumination of lesions located in accessible sites (such as skin or oral cavity). Lamps on the other hand cannot be used in combination with small optical fibres because of the poor beam quality, large beam size and small power density. They can, however, be used direct or coupled to a liquid light guides of between 5 and 10 mm in diameter. Moreover, compared to lasers, lamps are normally less expensive and more user friendly. Because of their characteristics lamps are well suited for treatment of accessible lesions especially for larger skin lesions (with or without the use of liquid light guides).

Other Sources

With constant advancement in photonics technology, new sources are constantly developed and will be available in the near future for large-scale use in PDT.

Light Emitting Diodes (LED)

In the past few years the development of LED has advanced them to a stage where their use in phototherapy (and PDT in particular) is possible. LED would offer several advantages for clinical and laboratory use. The choice of emission wavelength ranges from UVA (350 nm) to near infrared (1100 nm). The bandwidth is 5–10 nm and the power output can provide up to 150 mW/cm^2 over an area of approximately 20 cm^2 (Table 3). The power output can still be a limiting factor in their widespread use for PDT, however further improvement in their technology could improve this aspect. Two major characteristics in favour of the use of LED are price and versatility. LED are inexpensive (in comparison with all the other sources described so far), therefore they can be arranged in arrays to irradiate large areas. They can be powered by batteries, making them totally and easily portable. Moreover, they can be arranged in different geometric combination to compensate for difficult anatomic areas (non-melanoma skin cancer for instance tends to occur in the face and the head where large curvatures may reduce the efficacy of other light delivery systems). Prototypes for the use of LED in phototherapy and PDT are currently under development.

Femtosecond Solid State Lasers

The use of femtosecond lasers has been proposed for possible two-photon PDT. Femtosecond lasers are presently used for two-photon excitation in several advanced research areas (microscopy and spectroscopy [66]). Two-photon excitation is based on the observation that when the incident light is characterised by a high photon density two photons of equal energy can be simultaneously absorbed by a chromophore [67] to excite an electron to an energy level that is equal to the sum of the energy of the two absorbed photons. Therefore, for instance, the excitation of porphyrins in the 400–450 nm region can be obtained using light of high photon density in the 800–900 nm region. To obtain such high photon density, however, the laser has to emit a large number of photons during a very short pulse and the emitted photons have to be focused into a very small volume. These characteristics match the current femtosecond solid state lasers (Table 4), that have high energy, very short pulses and can be focused into very small (1–5 μm^3) volumes creating the necessary photon density to produce two photon absorption. It has been shown that two-photon excitation can be achieved in tissues and in vivo [66]. The advantage introduced by these lasers is related to the excitation wavelength. The incident radiation would be in the near infrared and as a result its penetration into the tissue would be much

larger [33,34,66] and would increase the depth of PDT. Despite this attractive advantage especially for the treatment of less superficial lesions, their current limitations outweigh the advantages. Femtosecond lasers are difficult to maintain and to operate and would require additional specialised personnel. More important, however, is the necessity of scanning the beam over the lesions. Because two-photon absorption occurs within a very small volume the treatment of a lesion would require raster scanning the incident radiation over the lesion with additional technical problems and longer treatment time.

CONCLUSIONS

The choice of photosensitisers for PDT is still limited compared to the choice of laser sources available for treatment and the process for approval of new photosensitisers has proven extremely lengthy. Nonetheless, the widespread availability of potentially useful light sources means that PDT is no longer limited to centres with high technical expertise; rather it is now a treatment option, which may be exploited more widely. Historically, large complex lasers were required for PDT, limiting its use to centres that could provide the necessary technical support. In clinical settings these lasers have been replaced by reliable, easy-to-use light sources which no longer require complex technologies and expensive maintenance. This means that PDT can become widely available as a realistic treatment option and it is likely that the interest in this therapeutic modality will increase. The targeted organ, photosensitiser, reliability, ease of use, cost and space are the most important variables that need to be considered in a clinical setting. In the past decade there has been renewed interest in the development of both laser and non-laser light sources for PDT and more patients will be able to benefit from this treatment.

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APPENDIX

In this appendix we will summarise some of the makers of light sources for PDT. We acknowledge the fact that light sources with the proper characteristics for PDT can be assembled by the investigators in laboratory or clinical settings, nonetheless we list commercially available sources specifically designed for clinical PDT. This review does not intend to advertise one product rather than another and does not state the superiority of one particular product. The list is as complete as possible (to our knowledge) and is limited to companies that advertise their product for specific PDT application. We apologise if some manufacturers are not listed.

Lasers

Argon and argon-pumped dye lasers
- Coherent Inc., Santa Clara, CA, USA (www.coherentinc.com)
- Spectra-Physics, Mountain View, CA, USA (www.spectraphysics.com)

Metal vapour and metal vapour-pumped dye lasers
- Oxford Lasers, Oxford, UK (www.oxfordlasers.com)

Solid state
- Laserscope, San Jose, CA, USA (www.laserscope.com)
- Coherent Inc., Santa Clara, CA, USA (www.coherentinc.com)

Diode Lasers
- Diomed, Cambridge, UK and Andover, MA, USA (www.diomed-lasers.com)
- Applied Optronics Corp., South Plainfield, NJ, USA (www.appliedoptronicscorp.com)
- Coherent Inc., Santa Clara, CA, USA (www.coherentinc.com)
- Oxford Optronix, Oxford, UK (www.oxfordshire.co.uk)
- Ceramoptec, Bonn, Germany (www.ceramoptec.com)
- Carl Zeiss, Oberkochen, Germany (www.zeiss.de)

Two-photon technology
- Coherent Inc., Santa Clara, CA, USA (www.coherentinc.com)

Lamps

Tungsten filament
- MBG Technologies (Lumacare), Newport Beach, CA, USA (www.mbgtech.com or www.lumacare.com)
- Photocure, Oslo, Norway (www.photocure.com)

Xenon arc
- Photo Therapeutics, Altrincham, UK (www.phototherapeutics.co.uk)
- ESC Medical Systems, Yokneam, Israel (www.escmed.com)

Metal halide
- Waldmann, Villingen-Schwenningen, Germany (www.waldmann.com)

Phosphor-coated sodium
- Medeikonos, Goteborg, Sweden (www.medeikonos.com)

Fluorescent
- Dusa Pharmaceuticals, Wilmington, MA, USA (www.dusapharma.com)

LED

- PRP Optoelectronics, Towcester, UK (www.prpopto.co.uk)

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