Chapter 11
Application of UV Emitters in Dermatological Phototherapy

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Abstract UV phototherapy is a highly effective therapy option for the treatment of skin diseases. In this chapter light sources for and variants of dermatological phototherapy are introduced together with their indications and mechanisms of action. Moreover, the outcomes of clinical studies using novel UV emitters including UV-LEDs are discussed.

11.1 Introduction

The skin is the largest organ of the human body and represents a biological barrier between ourselves and the environment. Impairments of the skin functions are very common. They are usually associated with distress for the patient and can result in acute or chronic diseases which sometimes even require inpatient treatment. The objective of phototherapy is to use light to cure or ease skin diseases while minimizing adverse effects on non-affected skin.

Phototherapy has a long history in medicine going back to ancient Egypt. In 1903 Niels Ryberg Finsen won a Nobel Prize for the use of phototherapy to treat lupus vulgaris. This can be regarded as the birthplace of modern phototherapy which is based on artificial light sources. In 1926 William Goeckerman at Mayo Clinic invented the combined crude tar phototherapy, later named after him as Goeckerman regimen. PUVA therapy, that is Psoralen plus UVA (320–400 nm)

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radiation, was initiated in the early 1970s and in 1984 Phillips TL-01 lamps allowed narrowband UVB (280–320 nm) phototherapy with a wavelength of 311 nm ± 2 nm. Starting from here, in the last decades another type of light sources emitting at around 308 nm, namely excimer lamps and lasers, have been developed and successfully applied in phototherapy [1]. Finally, devices utilizing solid state UV light emitting diodes (UV-LEDs) begin to find their way into the clinical practice. The different light sources used in UV phototherapy are introduced in Sect. 11.2.

Nowadays both the UVB and the UVA spectrum are used therapeutically. The irradiation can be applied as a single or monotherapy, but quite often it is used in combination with drugs like in PUVA therapy [2]. Due to optical characteristics of human skin, UVB penetrates only to the epidermis and the most superficial parts of rete ridges, whereas UVA goes deeper reaching the vascular bed. This of course has some consequences on the applicability of different variants of phototherapy, which is issued in Sect. 11.3.

There are several photobiological mechanisms of action on which phototherapy is based on. In Sect. 11.4 these are specified for the majority of indications. A short introduction to mechanisms having adverse effects on the organism is given as well. Subsequently, recent studies applying phototherapeutic demonstrator devices with newly developed electrodeless excimer lamps or UV-LEDs as light sources are reviewed and an outlook on future directions in phototherapy is given.

11.2 Sources for UV Phototherapy

UV sources for dermatological phototherapy can be divided into two main groups: luminescence and incandescence emitters. Incandescence emitters are thermal radiation sources that emit a continuous spectrum according to Planck's law. Niels Ryberg Finsen, the father of modern phototherapy, applied a carbon arc incandescence lamp to mimic natural sunlight and to cure lupus vulgaris [2, 3]. The problem with incandescence sources is that they are inefficient UV sources because a lot of unwanted radiation is produced in the infrared (IR) and visible (VIS) spectral range. Thus, the only incandescence emitter used for UV phototherapeutic purposes today is the sun. Artificial therapeutic UV emitters in current dermatology are solely luminescence emitters. These are nonthermal sources that generate UV photons by de-excitation of energy states in atoms, molecules, or solids. The associated transitions result in a discontinuous line spectrum. Depending on the type of source used, the line spectrum may be broadened or superimposed by a continuum due to different physical processes like Doppler effect, Bremsstrahlung, recombination radiation, or thermal emission. Gas discharge lamps and excimer lasers are well-established UV luminescence emitters in the modern dermatological practice [4]. UV-LEDs represent solid state luminescence emitters. In the future, they may more and more become dermatological standard tools because LEDs are easy to handle, cost-effective, compact, safe, and mercury free.

11.2.1 Natural Sunlight

The sun is an incandescence emitter with a surface temperature of about 5,800 K. Its radiation has already been used by ancient healers about 3,500 years ago to treat skin diseases [2]. Radiation from the sun reaches us through its gas atmosphere and through the atmosphere of the earth. Consequently, the spectral distribution of sunlight measured at the surface of the earth deviates from the spectrum of a blackbody radiator. The UVC radiation (200–280 nm) is mostly blocked by the earth's atmosphere and the atmosphere of the sun results in Fraunhofer absorption lines, Fig. 11.1. Only about 5 % of the sunlight reaching the earth's ground level is UV radiation and more than 90 % of that is UVA radiation. The total natural UV irradiance in summer in central Germany is about 30 W/m^2. Of course this value fluctuates strongly with time, season, clouds, etc. Therefore it is difficult to apply exact and repeatable doses of natural UV light. Moreover, the spectral distribution of the UV radiation is always broad and a narrowband exposure would require additional filtering. However, in certain areas like, for example, the dead sea region [5], where the UV radiation from the sun is predictable and spectrally beneficial due to the geographical position below sea level and the climate, natural sunlight is used successfully for phototherapy.

As sufficient sunlight is not available at all times at all locations artificial UV sources that mimic the curative effect of the sun have been introduced. These sources can be optimized for the desired therapeutic effect. They also enable an exclusive irradiation of affected skin areas and a protection of surrounding, healthy skin (targeted therapy).

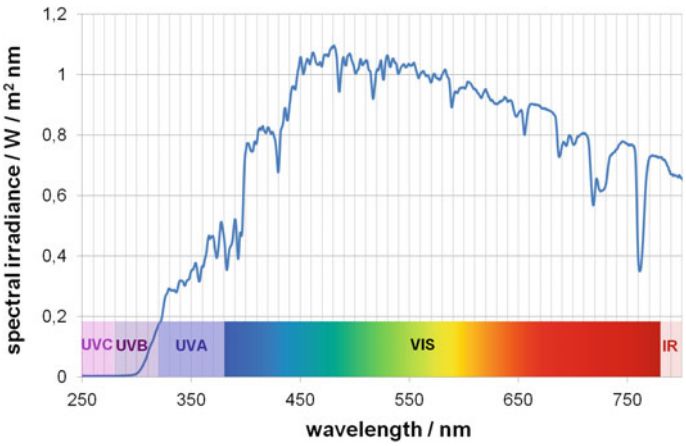

Fig. 11.1 Spectral distribution of natural sunlight in summer in central Germany at ground level

11.2.2 Gas Discharge Lamps

In gas discharge lamps an electric current is passed through a gas, a vapor or a mixture of both. That is, free charge carriers are accelerated in an electric field that penetrates a gaseous medium which is enclosed in a glass vessel. By collisions with free charge carriers the gas atoms receive energy or they are ionized. The absorbed energy is emitted again by the gas atoms in form of radiation. Thereby the wavelengths and widths of the emitted spectral lines are determined by the type of gas and the gas pressure. This is an essential difference compared to incandescent lamps, whose continuous emission spectrum is determined by the temperature of the hot material only. Because the gas pressure affects the spectral distribution of the emitted radiation significantly, gas discharge lamps are subdivided into low-, medium-, and high-pressure lamps.

11.2.2.1 Mercury Discharge Lamps

Low-Pressure Mercury Discharge Fluorescent Lamps

In low-pressure discharge lamps a pressure of up to 10 mbar is applied. Thereby the most important filling medium used in dermatology is mercury vapor. At the pressures quoted it gives rise to a dominant UVC spectral line at a wavelength of 254 nm. To transform the shortwave output into the UVB or UVA range the inside of the lamp's glass vessel is coated with special fluorophores, typically phosphores. The exact composition of the fluorophores determines the emission spectrum of the lamp which then is basically a fluorescent lamp. Lamps with broadband UVA and UVA-1 (340–400 nm), broadband UVB and narrowband UVB emission around 311 nm are available [6], Fig. 11.2. Low-pressure fluorescent lamps are the most commonly used sources for UV phototherapy [3]. They allow the irradiation of large areas by using long discharge tubes (>1 m) with an UV output in the range of 10 W/m, but they are also offered as compact folded fluorescent tubes [6]. These lamps are very cost-effective and have a durability of about 1,000 h [7].

Medium- and High-Pressure Mercury Discharge Lamps

When mercury vapor discharge lamps are operated at medium (10 $mbar^{-1}$ bar), high (1–20 bar), or even maximum (>20 bar) pressures, additional UV emission at 297, 302, 313, 334, and 365 nm is significant [3]. Furthermore, the spectral lines become broadened and are more and more superimposed by a continuum. High and maximum pressure discharges in mercury result in short, punctual arcs, compact lamps, and high radiances [8, 9]. Therefore they are ideally suited for irradiation devices that require a fiber coupling. For direct phototherapeutic applications metal halide lamps are more common. These lamps are medium or high-pressure mercury

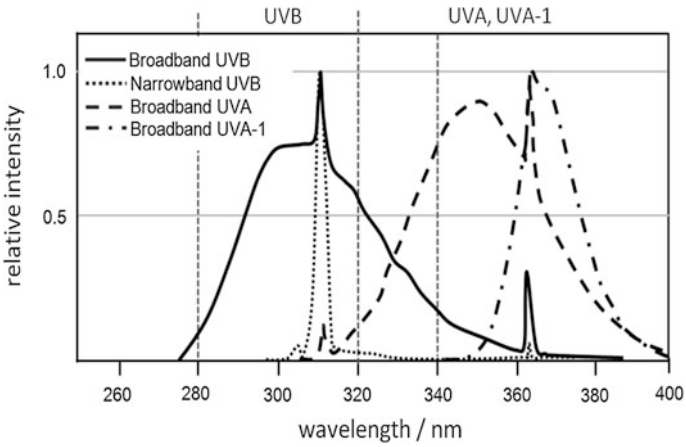

Fig. 11.2 Schematic representation of UV fluorescent lamp spectra

discharge sources with metal halide additives, e.g., iron or cobalt halides. Hereby the spectral gaps between the mercury emission lines are partly filled and a quasicontinuum is generated [6]. Almost any UVA or UVB spectral intensity distribution can be generated by choosing different metal halides and by combining the lamp with spectral filters. Metal halide lamps are more difficult to operate and more expensive than low-pressure mercury fluorescent lamps, but allow for higher UV powers and thus for shorter treatment times [3, 4]. Metal halide lamps have lengths in the range of 50–200 mm [9]. Thus a uniform whole body irradiation is difficult, but can be achieved by using multiple lamps in combination with reflectors [4].

11.2.2.2 Dielectric Barrier Discharge Lamps

Dielectric barrier discharge (DBD) UV lamps are special forms of high- or medium-pressure discharge sources that avoid the use of toxic mercury. They manage to extract narrowband (full width at half maximum less than 5 nm) UV radiation from a discharge in rare gas halide mixtures at elevated pressures by inserting at least one insulating layer (the dielectric) between metal electrodes [10]. The electrodes are supplied with an alternating high voltage. Launched discharges extinguish themselves continuously within about 10 ns because accumulated charges in the dielectric built up an electrical field that countervails and weakens the outer one. That is, the dielectric prevents the lamp from arcing and as a result it spreads the discharge over the entire electrode area in the form of multiple microdischarges. Due to the short discharge times only little gas heating appears, the plasma remains nonthermal [11] and an efficient energy transfer from energetic electrons to gas atoms can be achieved. Dermatological DBD lamps work with a mixture of xenon and chlorine gases in a glass vessel. Excited xenon–chlorine

molecule complexes (exciplexes) are generated in the microdischarges of the DBD and the subsequent decomposition of the exciplexes is associated with a narrowband UVB emission around 308 nm. Due to the generation of exciplexes these sources are also referred to as exciplex lamps or excimer lamps. Excimer lamps are non-laser sources and they may not be confused with excimer lasers. Compared to fluorescent tubes excimer lamps are more eco-friendly because they avoid the use of toxic mercury. Devices for the irradiation of surfaces up to 500 cm^2 with a narrowband UVB power of about 50 mW/cm^2 are on the market. In dermatology excimer lamps are currently mostly applied for targeted therapies. The disadvantage of dermatological DBD lamps is their limited lifetime of about 1,000 h [12, 13] and the application of high voltages, which may be a safety issue.

11.2.2.3 Electrodeless Excimer Lamps

Electrodeless excimer lamps achieve the formation of xenon–chlorine exciplexes in a low-pressure gas discharge without the use of a dielectric. This is of interest because in this case no high voltages are required to drive the discharge and to generate narrowband UVB radiation around 308 nm by the decomposition of exciplexes. Moreover, energy is coupled inductively into the low-pressure gas discharge by using a radio frequency (RF) in the MHz range. Therefore this kind of lamp is completely electrodeless. Due to the absence of both, a dielectric and electrodes, the wear of the lamp is minimized and its durability is estimated to be in the range of about 50,000 h. Up to now, electrodeless dermatological excimer lamps have only been studied in research projects [14] and they are not commercially available for phototherapeutic use. The reasons for this are the lack of adequate compact, low-cost electronics, the comparatively low narrowband UVB power of only about 20 mW/cm^2 achieved so far, and the small size of the irradiatable area of up to now only of some square centimeters.

11.2.3 Lasers

Lasers (=**l**ight **a**mplification by **s**timulated **e**mission of **r**adiation) are luminescence emitters that are characterized by the fact that they generate radiation via a process called stimulated emission. That is, if atoms in excited states encounter photons with energy that exactly matches the energy difference between the excited state and a lower energy level, the atoms can be stimulated by these photons to change over to the lower level [8]. Hereby the atoms emit photons that are an identical copy of the stimulating ones. If the number of atoms in the excited state is higher than the number of atoms in the lower energy state, radiation of a certain wavelength can be amplified in the energetic medium by photon multiplication. In a laser device radiation passes several times through an energetically activated medium by the use of mirrors. In so doing lasers are able to generate monochromatic radiation of very

high intensities. This requires that energy is permanently pumped into the laser medium to keep it in the activated state of population inversion.

For UV phototherapeutic purposes in dermatology xenon–chlorine excimer lasers that emit monochromatic UVB at a wavelength of 308 nm are applied [15, 16]. Just like excimer lamps excimer lasers use the decay of exciplexes to generate narrowband UVB radiation. However, due to the above-mentioned amplification principle dermatological excimer lasers deliver UVB intensities that are about 10 times higher than that of excimer lamps [16]. Besides, laser radiation has a narrower bandwidth than radiation of excimer lamps. The required population inversion between the bounded XeCl* exciplex state and the free xenon plus chlorine state is built up via a pulsed high-pressure gas discharge [17]. Consequently, the laser emission is discontinuous with a typical pulse width of some 10 ns and a frequency of up to 200 Hz [15, 16]. Excimer lasers deliver small spot sizes of only some square centimeters and are therefore solely suited for targeted therapies. Furthermore, dermatological lasers are expensive and bulky devices. Nevertheless, they offer an effective and economic treatment option for selected patients with recalcitrant lesions [18].

11.2.4 UV-LEDs

LEDs are solid state luminescence emitters that consist of a junction of n- and p-doped semiconductors. They generate UV radiation by the transition of electrons between energy bands in the semiconductor material [19]. Similar to the case of gas discharge lamps, a current flow through the LED is necessary to run the UV source. To achieve this, an external low voltage has to be applied in forward direction of the diode. Photons are generated, when electrons in the conduction band recombine with positive charge carriers (“holes”) in the energetically lower valence band of the semiconductor. Although LEDs are available for more than 50 years, UV-LEDs have evolved only over the past decade [20] and just a few dermatological LED devices that work in the UVA and even in the UVB spectral range are on the market today, Table 11.6. In the UVA range around 370 nm devices that generate irradiances of up to about 250 mW/cm^2 within an area of 15 cm^2 are state of the art. Current commercial dermatological UVB-LED devices are far less powerful. In each case, the spectral bandwidth of these sources is narrow and in the range of 10 nm.

Compared to gas discharge sources, LEDs have several significant advantages. LEDs are very compact and do not require high voltages. They are mercury free, long lasting, and do not need costly electronics to operate. Currently, from an economic point of view, they are not the right tool for large area or even whole body irradiations but they are very interesting for targeted therapies. Because LEDs are semiconductor devices, it is expected that prizes will decrease and powers will increase in the future. Thus, UV-LEDs will become more and more interesting for dermatologists.

11.3 Variants of Dermatological UV Phototherapy

In clinical practice several technologies for phototherapy have been developed and are used today. The major field of application is dermatology, but not exclusively. Oncology, transplantation medicine, pediatrics, vascular medicine, dentistry, and rheumatology—just to name a few—also use phototherapy.

Dermatological phototherapy is generally contraindicated in patients with a history of skin cancer or photosensitive diseases that may aggravate during treatment, patients with defective DNA repair mechanisms (like xeroderma pigmentosum), patients taking photosensitizing drugs and during pregnancy. The indication for phototherapy is more critical for children and adolescents. All treatments need proper equipment, clinical investigations of patients, dosimetry, documentation, and follow-up.

11.3.1 Psoralen Plus UVA (PUVA) Therapy

PUVA is an acronym for psoralen plus ultraviolet A radiation. The treatment consists of drug therapy in combination with UVA irradiation. The most commonly used drug is 8-methoxypsoralen (8-MOP). A less commonly used drug is 5-methoxypsoralen (5-MOP). Trimethylpsoralen (Trioxsalen) is used in Scandinavia for bath PUVA. Psoralen has to be applied about half an hour before irradiation and then works as a photosensitizer. Psoralen may be given orally, topically (ointment) or as PUVA-bath therapy. The initial UVA dosage for oral PUVA is 75 % of the minimal phototoxic dosage (MPD). In case of bath or cream PUVA treatment is started with 20–30 % of MPD. Oral 8-MOP is given at a dosage of 0.6 mg/kg body weight (bw), oral 5-MOP at 1.2 mg/kg bw. For bath PUVA 0.5–1.0 mg/L 8-MOP is used, the concentration for topical use in ointments varies between 0.0006 and 0.005 %. PUVA therapy is performed two to four times a week [21]. It is used successfully for a number of skin disorders, Table 11.1. Compared to narrowband UVB (NB-UVB) PUVA needs fewer sessions and provides a longer lasting clearance in psoriasis [27].

Potential risks and limitations of PUVA therapy are dependent on the way of application of psoralen. With oral treatment, nausea and vomiting are not uncommon. Therefore bath or cream PUVA are preferred today to avoid gastrointestinal adverse effects. Indeed, bath PUVA may achieve systemic psoralen concentrations comparable to oral application but with shorter half-life [28]. Generally, ocular protection is recommended to avoid lens opacities and cataracts [29]. There is a variation of PUVA called PUVAsol, which is used frequently in sun-rich countries like India. Here, psoralens are combined with natural sunlight. It is very popular for vitiligo therapy [30].

Table 11.1 Possible indications for PUVA therapy

Disorder	Remarks
Psoriasis, moderate to severe [21]	PASI[a] 75–100 after 6 weeks of treatment
Pustular psoriasis [22]	Best use in combination with oral retinoids
Cutaneous T-cell lymphomas	In particular for large plaque-type and Sezary Syndrome [23]
Disseminated granuloma annulare	In combination with fumaric acid esters [24]
Systemic sclerosis, morphoea	Improvement of skin sclerosis [25]
Graft-versus-host disease	Some improvement in lichenoid type [25]
Atopic dermatitis	Uncommonly used in severe forms [26]

[a]PASI, Psoriasis area and severity index. PASI 75 means a reduction of psoriasis area and severity by 75 %

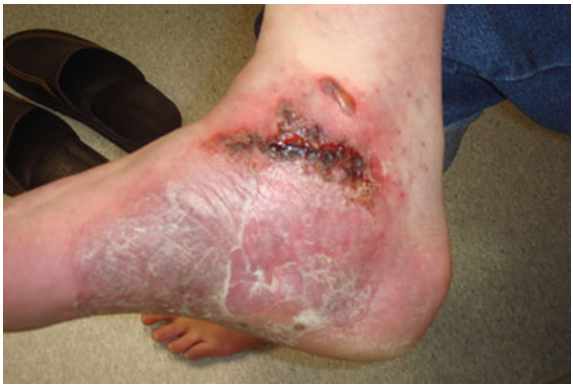

Fig. 11.3 Bullous PUVA burn during treatment of plantar psoriasis

Acute adverse effects of PUVA therapy are pruritus and burns (Fig. 11.3). These patients may develop persistent post-inflammatory hyperpigmentation [31]. The induction of lentigines is not uncommon [32]. High PUVA exposure with oral 8-MOP bears an increased risk for the development of squamous cell carcinoma of skin (SCC) as shown by the American PUVA prospective trial [33]. In contrast to this, no increased cancer risk was documented in a European PUVA follow-up study [34]. The pharmacokinetic profile of psoralens applied topically suggests a lower skin cancer risk per se [35]. A large Scandinavian trial with trioxsalen bath PUVA did not find an increased risk for nonmelanoma skin cancer at all [36]. Nevertheless, genital skin should be protected and patients with a history of drug therapies or with an increased skin cancer risk should be excluded from PUVA. Accidental burns are a possible adverse effect in vitiligo. If patients also suffer from atopic dermatitis, prurigo nodularis may result [37].

11.3.2 Broadband UVB (BB-UVB) Therapy

BB-UVB covers the range of wavelengths from 280 to 320 nm. At least in Europe bulbs emitting a spectrum of 300–320 nm have been used for therapy. BB-UVB was a standard phototherapy for mild-to-moderate psoriasis for many decades [38]. The initial dose should be about 70 % of the minimal erythema dose (MED). Dose increase is monitored by clinical assessment of erythema. When treating plaque-type psoriasis 50–75 % of patient will reach a PASI 75 (see footnote Table 11.1) at week six [21]. Spa saltwater baths taken before BB-UVB increase the short-term clinical response [39]. On the other hand, it is ineffective in pustular psoriasis [21]. Other possible indications are patch-type mycosis fungoides [23] and vitiligo [40]. Possible adverse effects include sunburn and keratitis. Protective goggles are mandatory.

Compared to narrowband UVB (NB-UVB), broadband UVB (BB-UVB) has several disadvantages. Studies suggest that BB-UVB is less effective in the treatment of psoriasis and the risk of erythema and sunburn of non-affected skin is higher [21]. Contrary, a study including 12 psoriasis patients compared the erythema dose–response on unaffected skin using either BB-UVB or NB-UVB and found no significant differences [41]. Moreover, several long-term follow-up studies of psoriasis patients treated with BB-UVA did not observe an increased risk for nonmelanoma skin cancer [42] and in a single randomized controlled trial in patients with vitiligo, BB-UVB was more effective than NB-UVB [43] in contrast to a recent meta-analysis [44] and a retrospective trial [40].

11.3.3 Narrowband UVB (NB-UVB) Therapy

NB-UVB therapy is performed with lamps that have an emission peak around 311 nm. Initial dose and dose increase are similar to the values used in BB-UVB therapy. The 311 nm peak emission of the lamps is close to the 313 nm clearance maximum for psoriasis [45]. After 20 weeks a PASI 75 can be achieved in 40–100 % of cases depending on the severity of psoriasis and the weekly frequency of phototherapy [21]. The anti-psoriatic efficacy is increased by saltwater bathing before irradiation. A randomized controlled trial reported a PASI 75 in 68.1 % of psoriasis patients with combined modality versus 16.7 % with NB-UVB alone three times a week [46]. Synergistic effects have also been described for NB-UVB and tumor necrosis alpha inhibitors [47]. A meta-analysis for vitiligo suggested that NB-UVB is the most effective treatment with the least adverse effects [44]. Possible indications for NB-UVB are summarized in Table 11.2.

The rate of acute adverse effects is low. In a multicenter study 8,784 phototherapy treatments were evaluated. NB-UVB showed acute adverse effects in only 0.6 % of the treatments compared to 1.3 % for both oral and bath PUVA [49]. The most common adverse effect is erythema. Whereas the cancer risk is increased with

Table 11.2 Possible indications for NB-UVB

Disorders	Remarks
Psoriasis, plaque-type	PASI 75 in 40–100 % after 20 weeks [21]
Atopic dermatitis	For chronic and severe types [48]
Vitiligo	Ca. 44 % improvement after 16 weeks [43]
Cutaneous T-cell lymphoma	Patch type [23]
Polymorphic light eruption	Performed before sun season for UV hardening [48]

PUVA, there are no data suggesting an increased cancer risk for UVB phototherapies. Nevertheless, for safety reasons guidelines of the French Society of Photodermatology set a maximum number of 250 treatment sessions [50].

In several countries like Spain, USA and the Netherlands, home-based phototherapy is performed. Home-based NB-UVB therapy in the Netherlands was evaluated safe and as effective as in outpatient settings for psoriasis [51, 52]. NB-UVB was evaluated cost-effective and more efficient than biological drugs [53]. It is important to note that ocular protection is necessary to prevent cataract.

11.3.4 UVA-1 Therapy

UVA-1 phototherapy emerged as a specific phototherapeutic modality using the 340–400 nm wavelength range. Due to the deep penetration into the skin, UVA-1 affects T lymphocytes and activates endothelial cells, thereby promoting neovascularization [54]. Furthermore, UVA-1 can induce rapid apoptosis by induction of the Fas-FAAD (Fas-associating protein with death domain)-caspase 8 death complex [55].

UVA-1 is used in a variety of chronic inflammatory skin diseases. It is considered the first-line treatment in sclerotic skin diseases like morphoea, granuloma annulare, and sarcoidosis [56]. In contrast to PUVA and UVB phototherapy large trials are completely missing, but patients with darker skin types seem to benefit more than skin types I and II [57]. A selection of possible indications is summarized in Table 11.3. Acute adverse effects are rare and minimal [21]. Long-term risks such as skin cancer are unknown [57]. Currently, the major limitation for UVA-1 treatment is the expensive and large equipment [62].

11.3.5 Targeted UV Phototherapy

Targeted phototherapy describes the irradiation of small areas of lesional skin, often in psoriasis or vitiligo [63]. The concept is to protect uninvolved skin while using the highest tolerable doses for the target lesions to obtain a reliably and rapid response. There are several types of targeted phototherapy available:

Table 11.3 Possible indications for UVA-1 phototherapy

Disorders	Remarks
Morphoea	Improves skin sclerosis [58]
Atopic dermatitis	Severe cases [26]
Subacute cutaneous lupus erythematosus	For skin lesions only [59]
Systemic lupus erythematosus	Adjuvant for milder cases [60]
Subacute prurigo	Mixed response [58]
Cutaneous T-cell lymphoma	Plaque and patch types [23]
Graft-versus-host disease	[58]
Sarcoidosis	[61]

- Targeted UVB phototherapy
- Monochromatic light targeted therapy (308 nm excimer laser or excimer light)
- Targeted PUVA therapy
- Targeted photodynamic therapy

Targeted UVB phototherapy is also known as localized or focused or microphototherapy. The targeted NB-UVB device Biopsorin™ demonstrated a 75 % improvement of psoriasis lesions in 64 % of patients after 12 sessions [64]. Comparing different modalities in vitiligo, targeted NB-UVB and topical bethamethasone ointment were the most effective [65].

The 308 nm excimer laser is used in several skin conditions. A meta-analysis of excimer laser therapy in psoriasis comes to the conclusion that the laser is not more effective than NB-UVB, although it spares unaffected skin [66]. On the other hand, at difficult to treat areas like scalp or palms and soles 308 nm excimer laser seems to work safe and fast [67]. In an intraindividual comparison 307 nm excimer light was as effective as topical dithranol but less irritating [68, 69]. In vitiligo excimer laser and noncoherent excimer lamp seem to be of comparable efficacy [70, 71]. In a head-to-head comparison 308 nm excimer laser was less effective as targeted NB-UVB [72]. A list of possible indications is provided in Table 11.4.

11.3.6 Extracorporeal Photochemotherapy (ECP)

Extracorporeal photochemotherapy (ECP) is an apheresis-based immunomodulatory treatment targeting primarily circulating blood cells. Autologous peripheral mononuclear cells harvested by leukapheresis are exposed to the photosensitizer 8-MOP in a soluble form (Uvadex®). These cells are irradiated by UVA light of an approximate exposure of 1.5 J/cm^2. The photoactive blood cells are eventually reinfused into the patient. The technical equipment developed by Therakos, Inc. (Westchester, PA, USA) is now available in its third generation called Cellex. The standard treatment schedule consists of ECP on two consecutive days every 2–4 weeks [78].

Table 11.4 Possible indications for targeted phototherapy

Disorders	Targeted therapy
Psoriasis	Targeted NB-UVB [64]
	308 nm excimer laser [66]
	Excimer light [68, 69]
Vitiligo	Targeted NB-UVB [65]
	308 nm excimer laser [71]
	Excimer light [71]
Alopecia areata	Targeted UVA [73]
Mycosis fungoides	308 nm excimer laser [74]
Chemical leukoderma	308 nm excimer laser [75]
Pityriasis alba	308 nm excimer laser [76]
Lichen planopilaris	308 nm excimer laser [77]

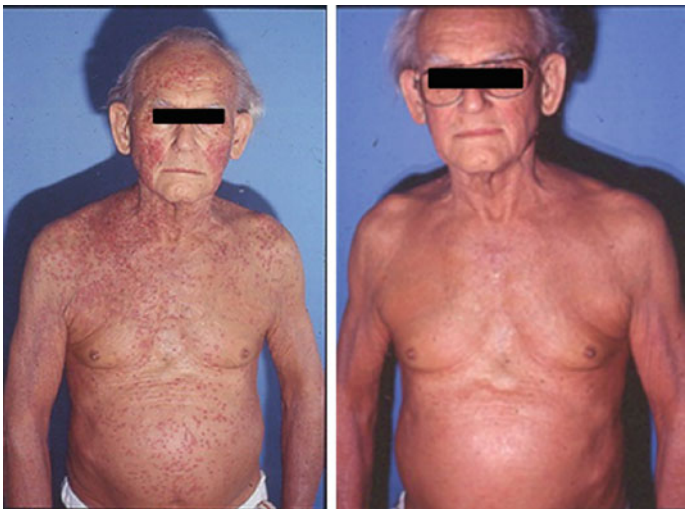

Fig. 11.4 A patient with pre-erythrodermic cutaneous T-cell lymphoma. *Left* before treatment. *Right* with complete remission after a 6 months course with ECP as monotherapy

ECP was approved by the Food and Drug Administration (FDA) in the late eighties for cutaneous T-cell lymphoma. It can be used as monotherapy or in combination with interferon or oral systemic retinoids (Fig. 11.4) [23]. Patients who are responders show a long-term survival [79]. A number of other indications that have been investigated are summarized in Table 11.5.

Table 11.5 Possible indications for ECP

Disorders	Remarks
Cutaneous T-cell lymphoma	More effective when combined with interferon alfa or retinoids [80]
Graft-versus-host disease	More data are available for chronic than acute graft-versus-host disease [81]
Systemic sclerosis	Effects on skin sclerosis [82]
Crohn's disease	50 % response rate [83] and reduction of steroids [84]
Atopic dermatitis	In severe type 73 % response rate [85]
Pemphigus and pemphigoid	Steroid-refractory cases [86]
Solid organ transplant rejection	Significant reduction of rejection in heart and lung transplantation [87]

11.4 Mechanisms of Action for Major Dermatological Indications

UV irradiation in general induces a cellular and cytokine response of tissue. UVB can induce single cell death (apoptosis) of keratinocytes, generally known as sunburn cells. Furthermore epidermal uric acid becomes isomerized. Proinflammatory cytokines like interleukin-1, which is responsible for fever reaction after severe sunburn, are released. In addition, UVB has an impact on the sensory skin function by interacting with transient receptor potential ion channels of epidermal keratinocytes—a mechanism that is involved in sunburn pain [88].

UVA can aggravate skin aging (extrinsic aging) and potentiate negative effects on smoking, another extrinsic pro-aging factor. UVA affects in particular the skin-associated lymphocytic tissue (SALT) and causes molecular injuries of dermal elastic fibers leading to elastosis. When used in combination with psoralens as in PUVA therapy, oxygen-dependent and oxygen-independent photoreactions occur. The latter type of reaction leads to DNA crosslinks and cyclobutane rings. The oxygen-dependent pathway produces reactive oxygen species that result in membrane damage, protein and lipid oxidation, and mitochondrial disturbances. Keratinocytes seem to be less sensitive compared to inflammatory cells [89–92].

The major dermatological indications for phototherapy are chronic inflammatory disorders like psoriasis, autoimmune diseases of skin such as lichen ruber or vitiligo and selected cutaneous malignancies in particular cutaneous T-cell lymphoma. In the following section the corresponding photobiological mechanisms of action are discussed.

11.4.1 Psoriasis

Psoriasis is a chronic or chronic relapsing disease of unknown origin. T lymphocytes and dendritic cells seem to play a major role in psoriasis pathogenesis. Psoriasis affects about 2–3 % of the world population. It can occur in every age but is most frequently in adults of younger and middle age. Psoriasis has a broad variety of cutaneous lesions and severity. Phototherapy is normally applied together with topical therapy and/or systemic therapies. The goal of the treatment is complete remission, i.e., PASI 100. The mode of action seems to be the inhibition of leukocyte and T-lymphocyte proinflammatory activity and apoptosis of inflammatory cells. For pustular psoriasis phototherapy is combined with oral retinoids, i.e., Re-PUVA. Phototherapy has no significant effects on extracutaneous manifestations of psoriasis, e.g., arthritis, dactylitis, enthesitis, and iridocyclitis [93].

11.4.2 Atopic Dermatitis

Atopic dermatitis is a common inflammatory disease that belongs to a group of atopic disorders together with pollinosis and allergic asthma. Its incidence is increasing and up to 20 % of western population is affected. About two-third of patients have their first manifestation of atopic dermatitis in preschool age. The disease is associated with dry and sensitive skin. It can run a limited or a generalized severe course, Fig. 11.5.

For atopic dermatitis UVB, UVA, UVB/UVA mixed spectrum, high intensity UVA-1, and ECP all have been used as an adjuvant treatment during maintenance. All UV-based therapies improve the major symptom—pruritus. There is a decrease of epidermal Langerhans cells, apoptosis of inflammatory cells, reduction of proinflammatory cytokines, and reduction of bacterial colonization. Another possible effect is the improvement of vitamin D levels. Phototherapy alone is not effective in atopic dermatitis. The basis of treatment is skin care with moisturizer to repair the epidermal barrier function and topical anti-inflammatory drug therapy.

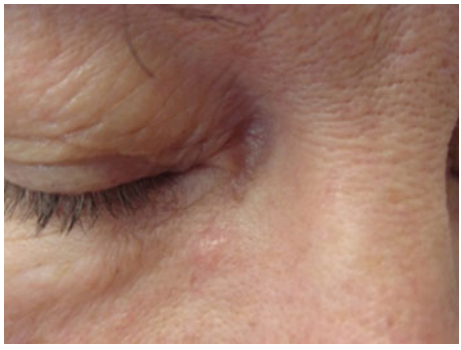

Fig. 11.5 Subacute atopic eczema of the eyelids. Lid edema is obvious

The average broad-spectrum UV/UVB/UVA/PUVA treatment consists of a course of 2–3 weeks with at least three treatments per week [94, 95].

11.4.3 Vitiligo

Vitiligo is a disorder of pigmentation, known as white spot disease. Although the disease is not life-threatening, it has a great social and psychological negative impact. About 2 % of the world population is affected by this disease. There are a number of hypotheses including autoimmune pathogenesis, but the disease is not completely understood. There is a loss of pigmentation and a loss of melanocytes in lesional skin. This leads to an imbalance of reactive oxygen production and oxygen radical scavengers during UV irradiation. Phototherapy of vitiligo is widely accepted, but needs many months up to 2 years for a stable response. The response is often only partial. The mode of action is at least twofold. (a) Resting melanocytes become stimulated again to produce melanin by UV irradiation. (b) The cellular inflammatory infiltrate in young lesions is suppressed. A 75 % re-pigmentation is considered a good outcome. Acral vitiligo of hands and feet is almost unresponsive to phototherapy. Generalized vitiligo is no indication for phototherapy at all. Due to the higher risk of sunburn in vitiligo skin, dose increase should be slow and carefully monitored.

11.4.4 Cutaneous T-Cell Lymphomas

Cutaneous T-cell lymphomas are rare disorders. The most common types are mycosis fungoides and Sezary syndrome. The patch and plaque type of mycosis fungoides can be treated by phototherapy. Patches are responsive to UVB, plaques need PUVA. The efficacy of PUVA can be further increased by combining it with oral retinoids. This is also known as Re-PUVA. The treatment is focussing on intraepidermal malignant T lymphocytes and aims to induce apoptosis.

When cutaneous T-cell lymphomas are treated by ECP, the goal is to produce a higher number of dendritic cells from circulating macrophages acting against malignant T lymphocytes. The assumed mode of action is immunostimulatory to target neoplastic T lymphocytes in cutaneous T-cell lymphomas. Apoptotic lymphocytes stimulate the differentiation of monocytes into dendritic cells releasing tumor necrosis factor-alpha and interleukin-6. These cells also produce cytokines with an immunosuppressive effect like interleukin-10 and interleukin-1Ra [96].

The treatment aims to get a complete remission or at least a partial remission to control the disease [23].

11.4.5 Lichen Planus and Alopecia Areata

In lichen planus and alopecia areata, an autoimmune T-cell response against either basal keratinocytes or hair follicle epithelium is responsible for the clinical symptoms. Both disorders are not uncommon. They may affect patients of any age. Phototherapy is used to interrupt the T-cell reaction and serves as an induction therapy rather than a maintenance therapy. PUVA seems to work better than UVB due to the location of the inflammatory infiltrate within the dermis [58].

11.4.6 Systemic Sclerosis and Morphoea

Systemic sclerosis and morphoea are autoimmune connective tissue diseases. Morphoea usually runs a milder and often self-limiting course, whereas systemic sclerosis is a multiorgan disease with significant mortality. A major player in skin fibrosis is tumor necrosis factor-beta. Phototherapy including ECP leads to a reduction of this cytokine and a partial remission of skin fibrosis. It has no significant effects on internal organs. Therefore phototherapy is used as an adjuvant therapy [58, 82].

11.4.7 Graft-Versus-Host Disease

Graft-versus-host disease (GVHD) is the consequence of infusion of mature donor T lymphocytes in allogeneic hematopoietic cellular transplantation. Clinically, GVHD can be separated into an acute and chronic type. The incidence of acute GVHD varies from 20 to 70 % depending on genetic differences between donor and patients. The donor T lymphocytes attack skin, gastrointestinal system, and liver. Patients not responsive to corticosteroids may be candidates for ECP since mortality rates are up to 70 %. Chronic GVHD affects about 50–70 % of patients after allogeneic transplantation. Here the skin is the most affected organ but virtually every organ may be affected. Acute GVHD shows three separate phases. It starts with liberation of cytokines during the cytotoxic conditioning treatment. During transplantation allogeneic T lymphocytes are transferred and in the last phase they expand into cytotoxic T lymphocytes attacking disparate antigens in multiple tissues. The chronic GVHD is less understood. But here the donor T lymphocytes attack also common antigens of donor and recipient [81].

The mode of action of ECP is apoptosis of inflammatory cells, induction of dendritic cells of the recipient and development of peripheral tolerance to self [96]. Most data are available from ECP treatment of chronic GVHD [97].

11.4.8 Polymorphic Light Eruption

Polymorphic light eruption (PLE) is a photosensitive pruritic skin disease. It has a prevalence of up to 20 % in Central and Northern Europe and the USA. An impairment of neutrophil responsiveness to leucotriene B4 and formyl-methionyl-leucyl-phenylalanin has been detected in PLE patients. Diagnosis is made on clinical presentation of pruritic papules and plaques in sun-exposed areas during early summertime confirmed by photoprovocation with UVA and UVB light. In PLE phototherapy is a preventive measure not suitable after clinical manifestation. It is used before the sunny season to adapt the skin to higher dosages of light. The therapeutic principle is known as skin hardening. Skin hardening aims to stimulate the cutaneous protective measures before the skin becomes exposed to higher intensity sunlight. Such effects include increase of epidermal thickness and increased pigmentation by melanin. Furthermore, skin hardening restores the neutrophil responsiveness to leucotriens [98]. Skin hardening is effective with UVA and/or UVB devices depending on the responsible wavelength. A home-based UVB device (SunshowerMedical™) was as effective and safe as an office-based broadband UVB irradiation in a smaller trial from the Netherlands [99].

11.5 Clinical Studies with Novel UV Emitters

The efficacy of dermatological phototherapy has been demonstrated in numerous clinical studies and NB-UVB is recommended for the treatment of psoriasis in national guidelines all over the world [21, 50, 100]. One of the major technological trends that can be identified within this field is represented by the application of mercury-free UV sources for targeted NB-UVB phototherapy. Examples for this approach are excimer lamps and UV-LEDs. In this chapter two recent clinical studies on psoriasis using an electrodeless excimer lamp and UVB-LEDs will be discussed in detail to illustrate the clinical methodology and to show that an UVB-LED based phototherapy is a promising and feasible concept, especially for home therapy purposes.

11.5.1 Study with an Electrodeless Excimer Lamp

The efficacy of UVB excimer lamps for psoriasis phototherapy has been described in a variety of publications [101–103]. By the authors of this chapter, a clinical study on psoriasis has been carried out using the unique electrodeless excimer lamp demonstrator setup described in Sect. 11.2 [14, 68, 69]. The proband collective consisted of 21 hospitalized patients. 15 patients were male and six female subjects. The age of the patients was in the range of 26–84 years. During the study two

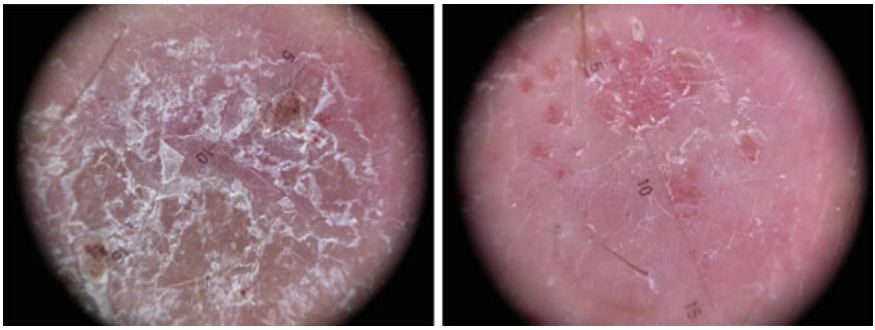

Fig. 11.6 Photo documentation of a psoriatic lesion. *Left* initial state. *Right* end state of the irradiated lesion (scale in mm)

dropouts appeared that were not related to the UVB treatment. For this research, patients with small localized lesions of a size that roughly matches the maximum irradiatable area of 3 cm^2 were selected. All patients were suffering from psoriasis for many years with a recent acute episode that necessitated a stationary treatment. 15 patients had psoriasis vulgaris, three patients plaque psoriasis and three patients psoriasis vulgaris of plaque-type. For each patient one selected lesion was irradiated with UVB and all other lesions, including a comparison lesion, were treated twice daily with dithranol, a strong anti-psoriatic drug applied topically. Before each UVB application clinical inspections as well as an objective spectroscopic measurement of the lesions were performed. For almost all patients the UVB application has been carried out three times at intervals of approximately a week. The applied dose was adjusted by means of the irradiation time and dependent on the skin type of the proband and the type of disease. However, the starting doses were the minimal erythema dose of the patients in each case. The irradiation periods for single sessions have been in the range of 10–30 s with an average value of 20 s and an irradiance of about 20 mW/cm^2.

For the clinical diagnosis of the patients the local Psoriasis Severity Index (PSI) was used. The PSI is a modified PASI index for selected plaques [104]. It describes erythema, scaling and infiltration as features of local psoriasis intensity. Based on the PSI score, a successful NB-UVB treatment could be demonstrated, Fig. 11.6. The total averaged PSI improvement was 3.0 points. This corresponds to a 40 % enhancement. Moreover, the results demonstrated that NB-UVB irradiation is equipotent to topical dithranol when the PSI score is considered. But, in total, the UVB treatment consumes less time and it is not associated with skin staining as in the case of dithranol. The most common adverse effects of excimer light treatment were mild-to-moderate erythema and temporary blistering.

11.5.2 Study with UV-LEDs

Devices for targeted phototherapy using UV-LEDs are still rare. Currently, no more than three units that have been developed for commercialization could be identified on the market, Table 11.6. It is expected that the number of dermatological LED-based irradiation devices will increase with the emergence of more efficient UV-LEDs. Due to the small number of commercially available irradiation devices only very few clinical studies that applied UV-LEDs for dermatological phototherapy exist. One of them is a study of Kemény et al. [105, 106] which used an array of 72 UVB-LEDs for psoriasis treatment with particular reference to a home-based therapy. The applied LED device was exclusively manufactured for this research by Allux Medical Inc. and is not yet commercially available. It emits 1 mW/cm^2 at a central wavelength of 310 nm with 15 nm bandwidth and a maximum irradiatable area of about 100 cm^2. Although the delivered irradiance is comparatively low, the study demonstrates that this device is capable of treating psoriasis lesions successfully. Twenty subjects with chronic plaque-type psoriasis were participating in the study. Three of the subjects were female and 17 male. The age was ranging from 29 to 71 years (average 51.7 years). The dimensions of the used LED irradiation device were very compact and amounted to only 128 mm × 90 mm × 38 mm so that the unit could be attached to the patient for treatment, Fig. 11.7. To protect surrounding healthy skin during delivery of the UVB irradiation an UV-blocking polymer foil was used.

Table 11.6 Devices for UV phototherapy using UV-LEDs

Device	Manufacturer	Spectral range
LEDA HP 370	Alma Laser GmbH	UVA
Psoria-Light	Psoria-Shield Inc.	UVA and UVB
Resolve UVB Phototherapy system	Allux Medical Inc.	UVB

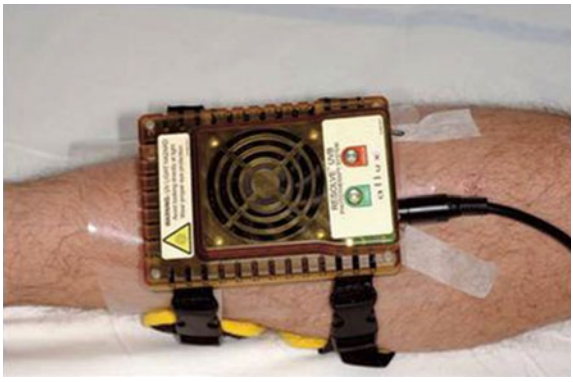

Fig. 11.7 UVB-LED irradiation device attached to a patient. Reprinted with permission from [106], Copyright 2010, John Wiley & Sons

For purpose of assessment of the treatment success symmetrical psoriasis lesions located on extremities or trunk were chosen. One of the lesions was treated with the LED device, whereas the other one served as an untreated control. Just like described in Sect. 11.5.1, the PSI was used to evaluate clinical improvements numerically. UV treatments were performed four times weekly for up to 8 weeks or until complete clearance has been achieved. Two different irradiation regimens were used in the study, one with a fast dose increase from session to session according to the doses typically used for outpatient treatment and one with a slow increase in dose, similar to regimens used for home-based treatments. In each case, ten subjects have been treated. The starting dose in the first regime was one MED. The dose was increased every visit by 20–50 % up to a final maximum dose of five MED. This maximal dose corresponded to 1.75 J/cm^2. In the second regimen (low dose home therapy range) the starting dose has been only 0.7 MED and the dose was increased by only 0.1 MED per session up to a maximum value of 3.8 MED.

Patients in both groups responded very well to the UVB therapy. Overall improvement of PSI at the end of the therapy was 93 and 84 % for the high and the low dose regimen, respectively. Thus, one important outcome of the study is that comparable results were achieved in the high and the low dose group. But, in contrast to the high dose group, in the low dose regime no side effects were reported. That is, it has been demonstrated that UVB-LEDs are well suited for a psoriasis home therapy. The safety profile of such a therapy is considered excellent and the therapy may also be useful for other UV responsive diseases [106].

11.6 Summary and Outlook

UV phototherapy is well established in the treatment of a wide range of photoresponsive skin diseases. Historically several variants, benefiting also from technological innovations in the field of UV light sources, have evolved and now are routinely applied in the clinical practice. The introduction of UV-LEDs undoubtedly is the most recent step in the development of new light sources for phototherapeutic purpose. The combination of these safe and economic light sources with additional device integrated safety features holds the potential to bring phototherapy out of the clinic and into the patient's home environment in a larger extend. Home phototherapy devices have first become available in the 1980s and since then home phototherapy has been growing steadily, especially for the treatment of psoriasis [107]. In the future also smart textiles equipped with flexible organic light emitting diodes may be used for home phototherapy [108]. Nevertheless, an adequate therapy management under guidance by professional dermatologists will stay mandatory in order to ensure the proper application of phototherapy.

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