Received: 9 November 2022 | Accepted: 12 April 2023

DOI: 10.1111/ddg.15126

CME ARTICLE

Phototherapy: Theory and practice

Bernadett Kurz | **Mark Berneburg** | **Wolfgang Bäumler** | **Sigrid Karrer**

Department for Dermatology, University Hospital Regensburg, Regensburg, Germany

Correspondence
Bernadett Kurz, Department for Dermatology, University Hospital Regensburg, Franz-Josef-Strauss-Allee 11, 93053 Regensburg, Germany.
Email: bernadett.kurz@ukr.de

Bernadett Kurz
Finanzielle Interessen: Nein
Erklärung zu nicht-finanziellen Interessen: keine

Max Berneburg
Finanzielle Interessen: Nein
Erklärung zu nicht-finanziellen Interessen: DDG, ADF, DGP

Wolfgang Bäumler
Finanzielle Interessen: Nein
Erklärung zu nicht-finanziellen Interessen: keine

Sigrid Karrer
Finanzielle Interessen: Nein
Erklärung zu nicht-finanziellen Interessen: keine

Summary
Despite the development of highly effective biologics for skin diseases such as psoriasis or atopic dermatitis, UVA and UVB therapy, alone or in combination, are still essential components of various guidelines. Phototherapy is not only a first-line treatment and highly effective for a number of skin diseases, but is also economical and has few side effects. The targeted use of UVA and UVB, if necessary, in combination with the photosensitizer psoralen in the context of PUVA therapy, enables the dermatologist to effectively treat a wide variety of skin diseases. Indications for phototherapy include epidermal diseases such as atopic dermatitis, psoriasis and vitiligo, as well as photodermatoses, mycosis fungoides, graft-versus-host disease and deep dermal diseases such as scleroderma. This article reviews the physical principles, molecular mechanisms, current treatment regimens, and individual indications for phototherapy and photochemotherapy.

INTRODUCTION

Since ancient times, light has played an important role in the treatment of diseases. The invention of the electric generator and the electric light bulb contributed to the transition from heliotherapy to phototherapy with artificial light at the end of the 19th century.[1] Modern phototherapy proper began in 1896 with Niels Ryberg Finsen, who recognized the bactericidal effects of sunlight and cured a friend suffering from lupus vulgaris within a few months using a "chemical rays" lamp. From then on, he treated more than 800 patients with lupus vulgaris at his phototherapy institute in Copenhagen using a focusable carbon arc lamp.[2] In 1903, Finsen received the Nobel Prize in Medicine "in recognition of the treatment of lupus vulgaris by means of concentrated light rays."[3] In the early 1960s, Wiskemann in Hamburg, Germany, developed a phototherapy system with Osram Ultravitalux lamps and another with UVB fluorescent tubes, which enabled the widespread use of phototherapy in dermatology.[3] Beginning in 1974, systemic photochemotherapy with oral psoralen and UVA irradiation (PUVA) revolutionized the treatment of psoriasis.[4] However, a 5-year report in 2002 showed that the use of phototherapy was declining. Between 1993 and 1998, PUVA treatments in the U.S. declined by 85%, and phototherapy in general declined by over 90%. Reasons for this decline included patient reluctance to undergo several weekly treatment sessions and fear of UV-induced malignant skin disease.[5] Between 2000 and 2015, the number of PUVA treatments in the U.S. decreased by 9% annually.[6] Several studies conducted between 2015 and 2017 show that too little time is spent learning phototherapy during residency training in the U.S. and that more than half of physicians feel unable to use

TABLE 1 Classification of optical radiation.[11]

Light type	Abbreviation	Wavelength
UV-radiation	UVR	100–400 nm
	UVC	100–280 nm
	UVB	280–320 nm
	UVA	320–400 nm
	UVA2	320–340 nm
	UVA1	340–400 nm
Visible light	VIS	400–780 nm
Infrared	IR	780 nm–1 mm

it.[7–9] In Germany, at least all non-university and university dermatology departments offer phototherapy.[10] Data for the outpatient sector in Germany are not yet available.

Photodermatology remains an indispensable part of dermatology practice and requires appropriate expertise on the part of the treating dermatologist. The purpose of this article is to provide an overview of the practical implementation of the various phototherapies and their respective indications. The important role of photodermatology, even in the age of biologics, will be emphasized. In this CME article we focus on phototherapy with UVA1, UVB, and PUVA. Other light sources and variants such as the use of visible light, excimer lamps, intense pulsed light (IPL), lasers or photodynamic therapy will not be covered.

PHYSICAL BASICS

Optical radiation is part of the total spectrum of electromagnetic radiation and covers the wavelength range from 100 nm to about 1 mm, divided into ultraviolet radiation from 100 to 400 nm, visible light from 400 to 780 nm, and infrared radiation from 780 nm to 1 mm (Table 1).

The sun is a natural source of electromagnetic radiation, which ranges from gamma rays to radio waves. Due to the filtering effect of the atmosphere, only a limited spectral range of about 290–2,500 nm reaches the Earth's surface.[12] This terrestrial solar radiation consists of about 4% UV radiation, about 43% visible light, and about 53% infrared radiation.[13] About 95% of ultraviolet radiation is UVA radiation, about 5% is UVB radiation, while UVC radiation does not reach the earth's surface.[14] Although UVC radiation from the sun does not reach the earth due to the filtering effect of the ozone layer, it is photobiologically relevant because it can occur in artificial radiation sources such as welding equipment or disinfection devices.

Artificial UV radiation (UVR) sources, such as those used in dermatology for therapy, usually consist of fluorescent tubes or high-pressure lamps whose emission is limited by optical filters to the desired spectrum in the UVB or UVA range. Spectral emission in the UVA, UVB, or UVC range can also be generated with LED technology.[15–17]

The wavelength range of the different types of ultraviolet radiation is clearly defined (Table 1), but within this range the emission of different UVB or UVA therapy devices may have different spectral distributions. It is therefore often difficult to compare these devices in terms of their dosimetry and thus their therapeutic effect.

Dosimetry refers to the energy of optical radiation and is expressed in Joules (J), for skin surface irradiation as energy density in J/cm^2. The energy density is the product of the irradiance (W/cm^2) of an artificial radiation source and the irradiation time in seconds (s).

When UV radiation reaches the skin's surface, a small portion of the radiation is reflected, while the majority penetrates the skin. Within the tissue, the radiation can be scattered and absorbed by different molecules. The extent of absorption is influenced by the wavelength of the UV radiation and the absorption characteristics of the molecules involved.

Important molecules in the skin are melanin, hemoglobin and water, but also proteins, fatty acids, DNA, endogenous porphyrins and various vitamins, for example certain B vitamins such as riboflavin (vitamin B2), niacin (vitamin B3) or pyridoxine (vitamin B6).[18] Most known endogenous photosensitizers primarily generate reactive oxygen species (ROS) such as singlet oxygen under UVA irradiation.[19] However, many of these photosensitizers also absorb UVB radiation, sometimes even to a greater extent than UVA radiation, and can generate singlet oxygen under both wavelengths.[20] Exogenous molecules such as certain antibiotics and non-steroidal anti-inflammatory drugs (NSAIDs) can also absorb UVR. Photosensitizing drugs act as exogenous chromophores and absorb photons from solar radiation.[21,22] The absorbed photons can induce conformational, structural, or chemical changes in these molecules, resulting in increased reactivity of these compounds. Depending on the molecular structure of the compounds, the absorbed photons can also promote formation of ROS or other radicals by energy or charge transfer. Some drugs react directly with DNA (e.g., psoralens), while others induce local oxidative stress (e.g., doxycycline).

UVB radiation is absorbed by many molecules in the skin. UVA radiation is not absorbed by DNA or most proteins, but it is absorbed by certain molecules such as endogenous porphyrins, oxidized fatty acids, and certain B vitamins.[20]

The scattering of optical radiation in tissue is strongly dependent on the wavelength. The shorter the wavelength, the stronger the scattering effect, which increases the interaction of the radiation with the molecules and hinders the propagation of the radiation to deeper tissue layers. As a result of the scattering and absorption of UVR, UVB penetrates the skin to a depth of about 0.1 mm and UVA to a depth of about 0.8 mm.[23]

In phototherapy, ultraviolet radiation is initially absorbed by specific target molecules in the epidermis and dermis. The different depth effects of UV rays and the molecules present in the different layers of the skin determine the clin-

ical applications of phototherapy. UVB radiation is mainly used for superficial dermatoses that manifest mainly in the epidermis. Other dermatoses that also affect the deeper dermis, such as scleroderma, are more likely to require UVA treatment.

While UVB radiation interacts almost exclusively with the epidermis, UVA radiation also reaches the upper dermis. Therefore, UVB radiation is used more for superficial dermatoses affecting the epidermis, while UVA radiation is used for deep dermatoses affecting the dermis.

The combination of a photosensitizer (e.g., 8-methoxypsoralen [8-MOP]) with UVA radiation is referred to as PUVA therapy. 8-MOP binds to nucleic acids of DNA in the presence of UVA.[24,25]

Molecular mechanisms of solar radiation

This article focuses on the clinical application of phototherapy and only briefly discusses the molecular mechanisms. For a detailed explanation of the mechanisms of action of UV radiation, please refer to the following reviews.[11,24,26]

When optical radiation such as UV radiation is absorbed by skin molecules, the energy of the radiation is rapidly converted into heat or fluorescence. It may also lead to chemical changes in the absorbing molecules (e.g., DNA, proteins, lipids). These chemically modified molecules can exhibit altered absorption spectra and absorb not only UVB but also UVA radiation.[20] During prolonged UV irradiation, the mechanisms triggered by these molecules in the skin may be different at the beginning compared to the end of exposure.[20,27]

UVB radiation can change the chemical structure of DNA, proteins, and lipids.

In addition, the absorption of radiation energy can lead to the formation of reactive oxygen species. This process requires the presence of a photosensitizer molecule capable of transferring charge or energy to other molecules, including oxygen, *via* an intrinsically long-lived state. In this process, various ROS such as superoxide anions, hydroxyl radicals, and singlet oxygen can be generated. Endogenous photosensitizers include porphyrins and various vitamins, provided they absorb the UVR radiation used. Reactive oxygen species, such as singlet oxygen, can be formed by absorption of UVA or UVB radiation.[20] These ROS can damage components of DNA and contribute to oxidative base damage, such as through formation of 8-oxo-guanine. Oxidized purine bases are the main products of UVA-induced cell damage.[28] Singlet oxygen is involved in T-cell apoptosis and mitochondrial DNA (mtDNA) deletions, as well as activation of heme oxygenase, collagenase genes, transcription factors, and signal transduction *via* p38.[29–31]

UVA and UVB can generate reactive oxygen species (ROS), which can cause various reactions and damage in cells.

The distinction between UVB- and UVA-induced damage mechanisms is not always clear, especially since both UVA and UVB radiation can produce ROS such as singlet oxygen. UVA radiation can also cause direct DNA damage, and UVB radiation can cause indirect DNA damage.[32]

Direct absorption of UVB energy by DNA components can lead to the formation of covalent bonds between adjacent pyrimidine bases. In particular, exposure to UVB radiation typically leads to the formation of cyclobutane-pyrimidine dimers (CPD), pyrimidine-(6-4-)pyrimidone photoproducts (6-4PP) and Dewar valence isomers. These photochemical reactions contribute significantly to the development of sunburn.[11,33] Furthermore, such a photoproduct can be the starting point for the development of mutations. Of particular importance are the C → T and CC → TT transitions, which are so characteristic of UV damage that they are referred to as signature mutations. It is hypothesized that the chromophore for the sunburn response is DNA, since the spectrum of action of erythema is very similar to the spectrum of action of the formation of direct UV-induced pyrimidine dimer lesions of DNA. This hypothesis is also supported by the observation that xeroderma pigmentosum patients with defects in the repair of these lesions show acute UVB photosensitivity with reduced minimum erythema dose (UVB MED).

C → T and CC → TT transitions are characteristic of UV damage and are referred to as signature mutations.

Mechanisms of action of phototherapy

A review of the mechanisms of action of phototherapy discusses the complex network of simultaneous events during UV irradiation. Six key effects of phototherapy are presented that may explain efficacy in etiologically distinct indications (Figure 1). Proapoptotic effects (induction of apoptosis and release of photoproducts) and immunomodulatory effects (release of immunomodulatory molecules, regulation of cell migration, induction of immunosuppression) play an important role in the treatment of psoriasis, atopic dermatitis, scleroderma, and T-cell lymphomas, among others. Propigmentary effects (production of proopiomelanocortin and α-MSH, depletion of antimelanocytic CD8 T cells) explain the efficacy in vitiligo, among others. Antifibrotic mechanisms (induction of collagen-degrading matrix metalloproteinases) can be used to treat scleroderma or sclerodermiform graft-versus-host disease. Antipruritic effects (downregulation of Th2 cytokines, degranulation of mast cells, increase of β-endorphins) lead to a reduction of itching in psoriasis, pruritus, prurigo or atopic dermatitis. Finally, UV light also leads to pro- and prebiotic effects (redistribution of the skin microbiome

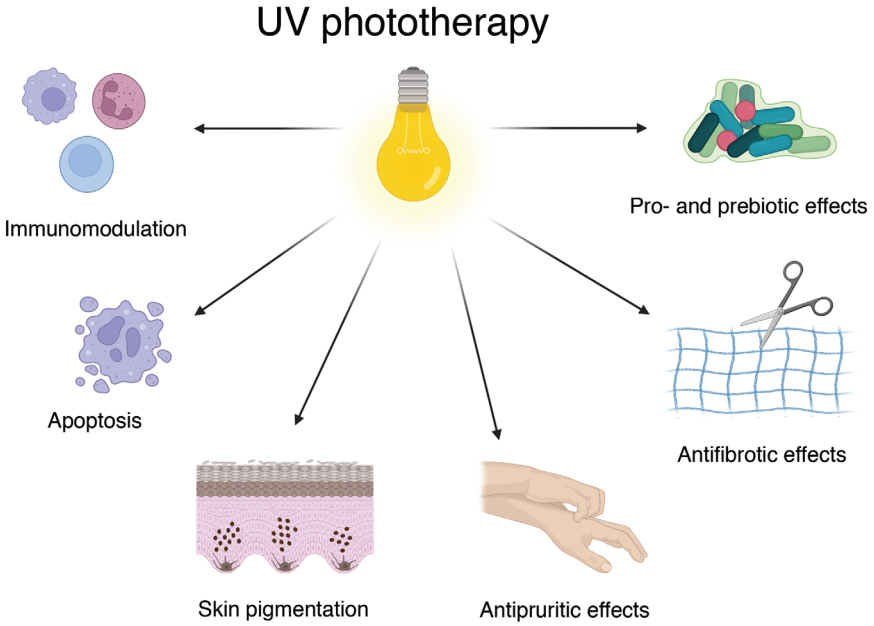

FIGURE 1 Six key components of phototherapy.

by selection of UV-resistant microbial species, decrease of *Staphylococcus aureus*, increase of immunostimulatory microbial products), which may play a role, for example, in the treatment of atopic dermatitis and psoriasis.[34]

Application of phototherapy

Before starting phototherapy, a detailed medical history regarding the use of photosensitizing medications or topicals and the presence of photodermatoses is mandatory. The presence of photodermatosis is usually a contraindication to light therapy, unless light therapy is used therapeutically as a prophylaxis to suppress photodermatosis. The use of photosensitizing drugs (mostly in the UVA wavelength range) that cannot be discontinued is not automatically a contraindication to light therapy. However, precautions such as reducing the radiation dose and gradually increasing the light exposure are necessary. Minimal erythema dose testing for UVA and UVB can help test the skin's true sensitivity to light (see "Practical implementation of UVB phototherapy"). Other relative contraindications that should be clarified before starting phototherapy include familial melanoma syndromes, lupus erythematosus, previous excessive UV exposure, previous exposure to ionizing radiation, current or previous malignant skin tumors, current pre-cancerous lesions (actinic keratoses, Bowen's disease), and previous use of immunosuppressive medications (cyclosporine A [CsA], azathioprine, mycophenolate mofetil, tacrolimus). Absolute contraindications to phototherapy are genetic defects associated with increased photosensitivity or increased risk of skin cancer (such as xeroderma pigmentosum [MIM No. 278750], Cockayne syndrome [MIM No. 133540], trichothiodystrophy [MIM No. 601675], Rothmund-Thomson syndrome [MIM No. 618625], Bloom syndrome [MIM No. 210900], Gorlin-Goltz syndrome [MIM No. 109400]). Concurrent therapy with the aforementioned systemic immunosuppressants (CsA, azathioprine, mycophenolate mofetil, tacrolimus) is also usually contraindicated.[35,36] Also, frail or circulatory unstable patients or patients with uncontrolled epilepsy who cannot stand long enough in the light therapy booth are not suitable for therapy. Although there is no evidence of teratogenicity of psoralen to date, PUVA therapy (system and bath PUVA) is contraindicated in pregnant women and breastfeeding mothers according to the Summary of Product Characteristics (SmPC) of psoralen. On the other hand, UVB phototherapy, including both broadband and narrowband, is considered safe and appropriate for use during pregnancy and breastfeeding. Due to depletion of folic acid at cumulative doses above 40 J/cm^2 or an average of 2 J/cm^2 per therapy session,[37,38] it is recommended that women of childbearing potential and pregnant patients receiving narrowband UVB therapy receive a daily supplement of 0.8 mg folic acid.

Contraindications to phototherapy: genetic defects with increased photosensitivity or increased risk of skin cancer from other causes.

Practical implementation of UVB phototherapy

In UVB phototherapy a distinction is made between broadband UVB therapy (280–320 nm) and narrowband UVB therapy (311 nm). After Parrish and Jaenicke identified the action spectrum for psoriasis phototherapy in the long-wavelength UVB range, narrowband UVB therapy became established due to its more specific antipsoriatic activity combined with lower erythematogenic potency.[39] This

TABLE 2 Recommendations for the initial dose for UVB phototherapy according to skin type.[36]

Skin type according to Fitzpatrick (phototype)[41]	Broadband UVB (J/cm²)	UVB 311 nm (J/cm²)
I	0.02	0.2
II	0.03	0.3
III	0.05	0.5
IV	0.06	0.6

TABLE 3 Recommended UVB doses to determine the mean erythema dose (MED).[36]

Broadband UVB (J/cm²)	0.02	0.04	0.06	0.08	0.1	0.12
UVB 311 nm (J/cm²)	0.2	0.4	0.6	0.8	1.0	1.2

enables the application of significantly higher doses of light with fewer side effects and correspondingly improved therapeutic efficacy. Thus, narrowband UVB therapy has been shown to be therapeutically superior to broadband UVB therapy for psoriasis, atopic dermatitis, vitiligo, and polymorphous light dermatosis (PLD).[40]

The initial irradiation dose is typically determined prior to the start of phototherapy, either based on Fitzpatrick skin type using a standardized scheme (Table 2) or by assessing the MED (Table 3). The minimum erythema dose is determined by exposing small areas of skin, for example on the buttocks or lower back, which are not normally exposed to light, to increasingly higher doses of UV radiation using the type of lamp intended for the therapy. The MED is defined as the Minimum amount of UV radiation required to cause a perceptible reddening or erythema of the skin. It is determined 24 hours after irradiation. For safety, an initial dose of 70% of the determined MED is used. UVB treatment should be administered three to five times per week according to a standardized dosing schedule (Table 4). Since UVB erythema at 311 nm is maximally expressed after 12–24 hours, there is little risk of overdosing UVB into developing erythema. The increase in light dose depends on the effect of the previous irradiation and can range from 10% to 30% (Table 4). Depending on the indication, approximately 25 treatment sessions are required to achieve remission. Once remission is attained, long-term maintenance therapy is not indicated, unless in specific cases of mycosis fungoides.[36]

UVB erythema at 311 nm is maximally expressed after 12–24 hours.

Practical implementation of UVA1 phototherapy

UVA radiation can be divided into two wavelength ranges: UVA1 (340–400 nm) and UVA2 (320–340 nm). The longer wavelength UVA1 light, which penetrates deeper into the dermis, represents the lowest-energy part of UV radiation.

The generation of high doses of UVA1 radiation is mainly done with high-pressure lamps. These are technically complex and require an appropriate ventilation system for dissipation of generated heat, which has limited the use of this effective therapy in practice. In the future, the implementation of LED technology may reduce heat exposure and shorten treatment time, thereby improving the feasibility of UVA1 therapy.[15]

The relatively new concept of UVA1 phototherapy is not yet as standardized as UVB irradiation. However, it can be divided into three dose ranges[36]: *(1)* low-dose UVA1 therapy with a single dose of 10–20 J/cm² per session, *(2)* medium-dose UVA1 therapy with a single dose of > 20–70 J/cm², *(3)* high-dose UVA1 therapy with a single dose of > 70–130 J/cm².

In principle, it is also possible to determine the MED for UVA1 therapy.[42] However, it is generally recommended to use low doses of UVA1 (10–20 J/cm²) at the beginning of treatment, which can be adjusted to medium doses of UVA1, depending on the skin findings. Treatment with high single doses is no longer generally recommended and is increasingly being abandoned.[42] Erythema can occur as a result of UVA1 irradiation and may persist for several days. It is important to note that this erythema should not be equated with other forms of erythema. Dose reduction should only be considered in cases where the erythema is accompanied by pain or a burning sensation.

Practical implementation of photochemotherapy (PUVA)

otherapy combines a photosensitizer, usually 8-methoxypsoralen (8-MOP, synonym methoxsalen) or 5-methoxypsoralen (5-MOP), with subsequent UVA irradiation. It can be administered in tablet form (oral PUVA or system PUVA), as a full or partial bath (bath PUVA), by applying a cream (cream PUVA), or as a so-called paint PUVA. For oral PUVA treatment with 8-MOP, the photosensitizer is taken body weight-adjusted (0.6 mg/kg body weight [bw]) 1 hour (liquid capsules) or 2 hours (tablets) before UVA irradiation. For 5-methoxypsoralen, the dose is 1.2 mg/kg bw and the interval between intake and irradiation is 3 hours. Because of the photosensitization of the cornea and retina that can occur with systemic PUVA, the patient should consistently wear sunglasses with high UVA protection. After photosensitizer administration, the eyes must be shielded from daylight for 12–24 hours with protective eyewear. In the bath PUVA treatment, the 8-MOP concentration in the bath water (0.5–1.0 mg/l) is achieved with the help of an alcoholic 8-MOP stock solution. Depending

TABLE 4 Dose scheme for UVB phototherapy (UV broadband and UVB 311 nm).[36,40,41]

Step 1 (optional)	Determination of the MED	Reading after 24 h	
Step 2	Start of therapy	Standard dosage according to skin type (Fitzpatrick) or 70% of MED	
Step 3	The following treatment 3–5 times a week	No erythema	Increase by 30%
		Minimal erythema	Maintain dose or, depending on tolerance, increase cautiously by approx. 10%–15%
		Persistent asymptomatic erythema	No increase
		Painful erythema with or without edema or blistering	Pause irradiation until symptoms resolve, resume with a reduced dose of 30%-50%, then increase by approx. 10%.
Step 4	Resumption of therapy	After the symptoms have subsided	Reduction of the last dose by 50%, further increases by 10%.

→ A simplified and practical dose regimen that has shown effectiveness is as follows:
Start with an initial dose of 0.2 J/cm^2, then increase by 0.1 J/cm^2 depending on tolerance.
A maximum dose of 2.5 J/cm^2 should not be exceeded.

on the indication, the patient can take a full bath (from the neck to the toes) or bathe and irradiate only hands and feet (PUVA hand bath). The duration of the bath is 15–20 minutes, the water temperature should be at least 37 °C at the beginning of the bath. UVA irradiation should be performed as soon as possible after the psoralen bath, ideally within 20 minutes, as skin sensitization decreases rapidly. After 30 minutes, the level of sensitization falls clearly below the therapeutic dose, and after one hour, it is barely detectable.

In particular, localized photosensitive dermatoses are a good indication for cream PUVA therapy. For cream PUVA, an 8-MOP concentration of 0.0006% is usually used (suggested formulation for hydrophilic methoxsalen cream 0.0006%, NRF [New Prescription Formulary] 11.96: Methoxsalen 0.006% Cordes® RK 10.0 g, diluted base cream DAC [German Drug Codex] to 100.0 g). The 8-MOP cream is applied thinly to the areas of the skin to be treated and left on for one hour. The cream is then wiped off and the skin immediately exposed to UVA radiation. In cases of higher concentrations or application over a large area, there is a risk of systemic photosensitization due to increased absorption of the psoralen.

A long-standing problem in the implementation of photochemotherapy is that there is no longer an approved substance in Germany since the expiration of the approval for Meladinin® (solution concentrate 0.3% and tablets 10 mg, Galderma). Therefore, 8-MOP or 5-MOP must be obtained from an international pharmacy (Internationale Apotheke) or pharmaceutical importers. It should be noted that the 8-MOP solution concentrate imported from France by the French company CLS Pharma (Meladinine® 0.75% solution for local application) is of higher concentration than the previous Galderma product (0.75% instead of 0.3%). This difference in concentration should be considered when determining the dosage for full and partial baths. For bath PUVA, a 0.5% bath concentrate may also be prescribed as an NRF formulation (Methoxsalen Bath Concentrate 5 mg/ml, NRF 11.83.).

For bath PUVA, a 0.5% bath concentrate may be prescribed as an NRF formulation (Methoxsalen Bath Concentrate 5 mg/ml, NRF 11.83.).

The initial dose of irradiation is determined either by measuring the minimum phototoxic dose (MPD) as indicated in Table 5 or by estimating it based on a standardized scheme depending on the phototype as shown in Table 6. The test area used to determine the MPD is a light-sensitive part of the body, such as the buttocks, which is little exposed to the sun. To determine the MPD, the photosensitizer should be applied in the same manner and at the dose or concentration intended for treatment. During the test irradiation, the rest of the body must be completely covered as in the MED determination. The test field readings are taken after 72–96 hours for oral application and 96–120 hours after irradiation for bath PUVA because PUVA erythema does not appear until 72–120 hours after irradiation. The faint but clearly visible erythema at the time of reading is referred to as 1 MPD. The initial dose should be set at 50% to 70% of the MPD. When assessing the MPD, it is important to observe that pink erythema is rated as "+", clear erythema without swelling or pain is rated as "++", and intense redness with mild swelling and pain is rated as "+++". "++++" refers to livid erythema

TABLE 5 Dose recommendations for the determination of the minimum phototoxic dose (MPD).[36]

Method	Dose*	Skin type	UVA dose (J/cm²)					
PUVA oral (8-MOP)	0.6 mg/kg bw	I–IV	0.5	1	2	3	4	5
PUVA oral (5-MOP)	1.2 mg/kg bw	I–IV	1	2	4	6	8	10
PUVA-Bad (1 mg/l 8-MOP)	0.5–1.0 mg/l (0.00005–0.0001 %)	I, II	0.25	0.5	1.0	1.5	2.0	2.5
		III, IV	0.5	1	2	3	4	5

Abbr.: bw, bodyweight
*There is no general international consensus on this.

TABLE 6 Recommendations for the initial dose for photochemotherapy depending on skin type.[36]

Skin type according to Fitzpatrick (phototype)[41]	Oral PUVA (8-MOP) (J/cm²)	Oral PUVA (5-MOP) (J/cm²)	Bath PUVA and Cream PUVA (J/cm²)
I	0.3	0.4	0.2
II	0.5	1.0	0.3
III	0.8	1.5	0.4
IV	1.0	2.0	0.6

with marked swelling, severe pain, and partial blister formation.

For phototherapy of palmoplantar dermatoses, determination of MPD is not useful. In cream PUVA therapy, specific individual test schemes are applied, which, however, closely follow the bath PUVA therapy and depend in their dosage on the respective concentration used in the cream.

Irradiation is typically administered two to four times per week. However, due to the delayed onset of maximum PUVA erythema, the dose should not be increased until at least 96–120 hours after the previous treatment. Since a phototoxic reaction may occur days later due to the accumulation of several individual exposures, photochemotherapy should be interrupted for at least one day after two consecutive days (e.g., irradiation on Monday, Tuesday, Thursday, Friday with breaks on Wednesday and at the weekend). It should also be noted that the MPD may decrease by up to 50% of its initial value during the first week of treatment, but may then rise again. Although the cause of this phenomenon is not well understood, it is believed that psoralen monoadducts persist in the DNA and are converted into phototoxic biadducts upon further irradiation. In general, it is recommended not to increase the dose during the first week of PUVA treatment and to increase the dose in the following weeks after two treatments and one day without treatment.

There is no standardized scheme for dose escalation, but a suggestion of how the dose might be increased (Table 7). A barely visible, non-painful erythema is considered a clinical indicator of an optimal UVA dose. Pregnant or breastfeeding patients and children should not be treated with PUVA.

In the following chapters, the main indications for phototherapy or photochemotherapy are described in more detail.

Phototherapy for atopic dermatitis (AD)

Studies have shown that high-dose UVA1 therapy[43,44] and systemic PUVA therapy are most effective for acutely exacerbated severe atopic dermatitis (AD). On the other hand, broad- or narrowband UVB therapy and medium- to low-dose UVA1 therapy are commonly used for chronic moderate AD.[45] According to the German guidelines for atopic dermatitis, medium-dose UVA1 irradiation is as effective as high-dose UVA1 irradiation for moderate atopic dermatitis.[46] UVA1 therapy has resulted in the improvement of eczema in numerous patients with acute atopic eczema after approximately 15 irradiations over a period of 3 weeks. Recurrences typically occurred within 3 months[47]. In a retrospective cohort study that evaluated patients with moderate to severe AD treated with narrowband UVB between 2000 and 2017, 55.4% of the 390 patients studied responded well to the treatment. Facial involvement, the presence of adverse effects, a lower number of treatments, and IgE levels greater than 4,000 IU/ml before treatment were associated with a worse response. The median duration of response was 12 months overall, with a higher relapse rate in patients younger than 18 years of age.[48]

For moderate atopic dermatitis, medium-dose UVA1 irradiation is as effective as high-dose UVA1 irradiation.

TABLE 7 Proposal of a dose scheme for photochemotherapy.[36]

	Method		Oral PUV	Bath PUVA
Step 1 (Optional)	Determination of MPD		Reading after 72–96 h	Reading after 96–12 h
Step 2	Start of treatment	Initial treatment dose	Standard dose according to skin type or 50–70% of MPD No increase in week 1	Standard dose according to skin type or 30% of MPD No increase in week 1
Step 3	Continue treatment 2–4 times per week	No erythema, good response	Increase by 20–30%, max. 2 x weekly (but not more than 0.5 J/cm^2)	Increase by 20–30%, max. 2 x weekly (but not more than 0.5 J/cm^2)
		Minimal erythema	No increase	No increase
		Persistent asymptomatic erythema	No increase	No increase
		Painful erythema with or without edema or blistering	No treatment until subsiding	No treatment until subsiding
Step 4	Resumption of treatment	After the symptoms have subsided	Reduction of the last dose by 50%, further increases by 10%.	Reduction of the last dose by 50%, further increases by 10%.

Abbr.: MPD, minimum phototoxic dose

Phototherapy for AD is usually administered 3–5 times per week for 6–12 weeks and can be well combined with topical glucocorticoids. Rossi et al. conducted a study in 2021 involving 45 patients with severe AD who received 12 weeks of treatment with dupilumab alone or dupilumab plus narrowband UVB. After week 12, all patients received dupilumab alone. The combination therapy resulted in superior improvement in clinical lesions and symptom relief at 4 weeks. However, after 12 and 16 weeks, the additional therapeutic effect of phototherapy diminished.[49]

According to the current European guideline for the treatment of AD, children with moderate AD (SCORAD index 25–50) can also be treated with narrowband UVB radiation.[50] The good efficacy of narrowband UVB therapy in children has been demonstrated in two clinical trials from India and England.[51] Improvement in the SCORAD index was maintained during the two-year follow-up period.[51]

Phototherapy for psoriasis

Despite the tremendous advancements in the field of psoriasis therapy and the approval of numerous highly effective biologics, the current German AWMF guidelines for the treatment of psoriasis still recommend phototherapy with UVB or PUVA therapy as first-line therapy for moderate to severe psoriasis. The clinical response to phototherapy is typically expected relatively quickly, within 1–2 weeks. With UVB phototherapy, approximately 50–75% of patients achieve at least a Psoriasis Area and Severity Index (PASI) 75 response within 4–6 weeks. With PUVA therapy 75–100% of patients achieve a PASI 75 response within this time period.[52] PUVA or bath PUVA therapy is also highly effective for pustular psoriasis.[53] Currently, however, narrowband UVB therapy at 311 nm is the first choice for psoriasis because it is superior to broadband UVB therapy in efficacy[54,55] and is easier to use than PUVA therapy, which is slightly more effective in comparison.[52] Narrowband UVB therapy is also recommended for plaque psoriasis or guttate psoriasis during pregnancy. Typically, narrowband UVB therapy is administered 3–5 times per week for a duration of 6–10 weeks or until remission is achieved. In addition to the excellent efficacy of phototherapy on the skin, phototherapy improved the quality of life of patients with psoriasis even more than therapy with the TNF-α blocker adalimumab.[56] In addition, phototherapy may suppress systemic inflammation in patients with psoriasis (lowering serum CRP and IL-6) and increase high-density lipoprotein (HDL) concentrations, which is likely to reduce cardiovascular risk.[57,58]

The combination of phototherapy with topical therapies such as calcipotriol, glucocorticoids, retinoids, or dithranol has been shown to be effective. If topicals containing emollients are used, they should be discontinued at least 2 hours prior to irradiation to prevent interference with UV transmission through the skin. The combination with systemic therapeutics such as retinoids (in combination with PUVA, so-called Re-PUVA), methotrexate, fumarates, or biologics can also increase the efficacy of the respective treatment. The improved efficacy of combination therapies also contributes to a reduction in the total cumulative UV dose. Combination with cyclosporine A should be avoided due to the additive carcinogenic risk.

Phototherapy for the prevention of photodermatoses

The principle of "hardening therapy" in patients with polymorphous light dermatosis (PLD) using narrowband UVB

radiation and PUVA is well established. However, the therapeutic effects are not sustained and therapy must be repeated annually. Narrow band UVB therapy should be preferred over PUVA therapy for the treatment of PLD due to the lower risk of photocarcinogenesis, the absence of nausea or other side effects associated with the use of 8-MOP, and the absence of the need to wear eye protection after treatment. However, if narrowband UVB therapy has proven ineffective, PUVA therapy should be considered as a potential option before exploring other systemic treatments.[59] Several comparative studies have been conducted, but the only randomized controlled trial comparing PUVA with narrowband UVB therapy, along with placebo tablets administered three times a week for 5 weeks, showed no significant difference in efficacy regarding the incidence of PLD or limitation of outdoor activities.[60] In the 10-year retrospective review by Man et al., 170 patients with moderate to severe PLD received PUVA and/or UVB phototherapy.[61] Good or moderate improvement was observed in 88% of patients treated with PUVA and 89% of patients treated with UVB.[61] In another retrospective 14-year study involving 79 patients who underwent phototherapy, the efficacy, measured as photoprotection with complete/partial remission the following summer, was 65% for PUVA, 82% for broadband UVB, and 83% for UVA alone.[62] In this particular case, PUVA treatment was reserved for the more severe forms of PLD. In about 70% of PLD patients, 3–4 weeks of PUVA treatment is sufficient to suppress the disease. In the literature, the efficacy of PUVA is reported to have a photoprotection rate of 65–100%.[59] Initial irradiation and dose escalation should be performed according to the recommendations for psoriasis. PUVA induces rapid and intense pigmentation at relatively low suberythematogenic UVA doses, usually well below the threshold doses for triggering PLD. The treatment is administered three times a week for approximately 4 weeks in early spring. PUVA therapy only provides temporary protection. However, a significant number of patients remain protected for 2 to 3 months after the pigmentation has faded. To maintain the benefits of desensitization therapy, regular sun exposure during the summer is recommended.

A relatively new approach has been the use of UVA therapy, more specifically the UVA rush hardening therapy (UVARH).[63] This UVA rush hardening regimen was initially effectively employed by Beissert et al. in the treatment of three individuals with solar urticaria.[64] This elaborate rush regimen also resulted in sustained remissions in five patients with PLD. These patients underwent treatment with UVA in a full-body booth during a PLD flare. The initial UVA dose (50% of MED) was applied to only one quadrant of the body after the other body areas were adequately covered, and then to the other three quadrants at one-hour intervals. If no side effects such as severe erythema, pruritus, or urticaria occurred, half of the body was irradiated at one-hour intervals with a UVA dose 20-30% higher than the initial dose. If again no side effects occurred, the UVA dose was gradually increased by 20% or 30%, and finally (usually after about 3 days) whole body irradiation was performed with a 1-hour interval to reach the final dose of 10 J/cm^2. UVA maintenance therapy at 10 J/cm^2 was then administered once or twice weekly for 4 weeks. The rapid induction phase lasted 4 to 8 days, the total number of treatments ranged from 18 to 39, and the cumulative UVA dose during the rapid induction phase was 117.2–215.04 J/cm^2.[63]

UVA rush hardening is a treatment option for PLD.

Phototherapy for mycosis fungoides (MF)

PUVA therapy is a first-line therapy for early-stage mycosis fungoides (MF) and results in a high rate of complete remissions. Systemic PUVA is preferable to bath PUVA because bath PUVA excludes the face from treatment and thus does not provide the full-body therapy required in MF. However, much is still unknown about the mechanisms of action of PUVA therapy, including the optimal duration and frequency of treatment, dose escalation, and its role as a maintenance therapy. In stages IA, IB, and IIA, narrowband UVB phototherapy may also be used. Systemic PUVA should be preferred in patients with thick plaques or folliculotropic MF. Both PUVA and narrowband UVB are suitable for the treatment of erythrodermic MF. Although partial or complete responses can also be achieved with narrowband UVB in early MF, PUVA therapy showed a significantly higher rate of complete remission (73.8% vs. 62.2%).[65] A recent study evaluated the effect of PUVA maintenance therapy. Patients (n = 27) with stage IA to IIA MF were treated with PUVA twice weekly for 12 to 24 weeks until complete remission. During this time, 70% of patients achieved complete remission; these patients were either treated with PUVA for an additional 9 months (a total of 14 treatments: once weekly for the first month, every 2 weeks for the second and third months, and once every 4 weeks thereafter) or did not receive maintenance therapy. Maintenance therapy extended the median disease-free interval from 4 (range 1–20) to 15 (1–54) months ($p = 0.02$). The median cumulative UVA dose was only 130.3 J/cm^2. These results show that the duration of phototherapy, rather than the frequency and dose, plays a crucial role in achieving long-term therapeutic success.[66]

In addition to narrowband UVB and PUVA, treatment with UVA1 is a promising option. Nineteen patients with early-stage MF (stage IA–IIA) received fixed doses of UVA1 at 30 J/cm^2 five times a week for 5 weeks. Of the 19 patients, 12 (63%) experienced a complete response and seven (37%) had a partial response. During the follow-up period, 7 (58%) of the twelve patients with a complete response relapsed within 3 months of UVA1 therapy.[67]

In an Italian study, 12 patients with early-stage MF were treated with UVA1 according to two different protocols (three or five times weekly for a total of 22 weeks, light dose

45 J/cm^2 each). Five patients showed a complete clinical and histologic response, six a partial response and only one a minimal response.[68]

As in other indications, it may be appropriate in MF to combine phototherapy with appropriate systemic therapy, such as bexarotene or interferon alpha.

Phototherapy for Vitiligo

For vitiligo, narrowband UVB therapy with a discrete erythematogenic dose is primarily used 2–3 times per week.[68] This form of phototherapy is not only more effective than PUVA therapy, but also easier to administer and, most importantly, associated with fewer side effects. As a result, PUVA therapy is regarded as largely obsolete in vitiligo treatment guidelines.[69] Narrowband UVB is indicated for both generalized vitiligo and active, progressive vitiligo to halt disease activity. Response rates to narrowband UVB therapy range from 62.1% to 75.0%.[70] Lesions on the head and neck respond best to phototherapy, followed by areas on the trunk and extremities. Spots on the hands and feet typically show little to no response to any form of therapy.[69] Narrow band UVB therapy should be evaluated after 3 months. If there is no repigmentation, treatment should be discontinued after 6 months. The total duration of therapy should not exceed 12–24 months. Combination with topical glucocorticoids may enhance the effect of narrowband UVB. A randomized trial of 516 vitiligo patients compared mometasone furoate ointment plus sham irradiation, narrowband UVB home therapy plus placebo ointment, and narrowband UVB home therapy plus mometasone furoate ointment. After 9 months of therapy, the combination of narrowband UVB and mometasone furoate was shown to be superior to mometasone furoate alone.[71] Topical calcineurin inhibitors (tacrolimus ointment) have also been used successfully in combination with narrowband UVB for the treatment of facial vitiligo.[72–75] However, patients should be advised that the tacrolimus ointment prescribing information recommends avoiding sun exposure while undergoing treatment. Initial attempts to combine narrowband UVB with JAK inhibitors such as tofacitinib or ruxolitinib are considered promising. Patients who were treated solely with JAK inhibitors, such as tofacitinib and ruxolitinib, exhibited a significantly inferior response to therapy compared to patients who received a combination of phototherapy and JAK inhibitors. This difference was most pronounced for facial vitiligo.[76]

Lesions in the head and neck area of vitiligo respond best to phototherapy.

Phototherapy for graft versus host disease (GvHD)

In principle, both acute and chronic GvHD can be treated with UVB, UVA1 and PUVA. However, there is no consensus on the duration of treatment, and studies differ in reported remission and response rates.

Because experimental data suggest that depletion of Langerhans cells (LCs) can prevent cutaneous GvHD, Kreutz et al. investigated whether broadband UVB irradiation is tolerated immediately after allogeneic hematopoietic cell transplantation in humans and whether depletion of LCs by UVB can prevent the development of GvHD. A total of 17 patients received whole body UVB irradiation at 75% of the individually determined MED immediately after stem cell transplantation. UVB treatment reduced the number of LCs in the epidermis and also affected dermal dendritic cells. Strikingly, all nine patients with complete LC depletion developed only grade I or no GvHD by day 100.[77]

Other studies, some retrospective, have evaluated PUVA, broadband, narrowband, and UVA1 therapy in patients with acute or chronic GvHD of the skin.[78–84] Positive effects on GvHD were demonstrated for all wavelengths. One study showed that in patients with acute GvHD, UVB therapy not only heals skin lesions, but also increases circulating regulatory T cells (Treg) in the blood.[81] This indicates that phototherapy may potentially be effective in treating GvHD in organs beyond the skin. However, based on the current state of evidence, it is not possible to make a definitive recommendation or determine the superiority of one phototherapy modality over another. For instance, the UK guideline for narrowband UVB therapy does not recommend its use in treating clinically manifest GvHD due to insufficient evidence.[35] In a current German guideline on chronic GvHD, PUVA (response rate approximately 75%), UVA (response rate approximately 60%–70%), UVA1 (response rate approximately 50%–90%) and UVB therapy (response rate approximately 60%) are listed as first-line organ-specific therapies for cutaneous GvHD.[85] UVA1 therapy is reported to be particularly suitable for deep sclerosis, whereas UVB therapy is not. Phototoxicity (no combination with phototoxic drugs) and long-term risk of cutaneous malignancies should be considered. It should be noted that patients with GvHD are often taking immunosuppressants such as CsA, mycophenolate mofetil, or tacrolimus, which are contraindications to phototherapy. In a recent German guideline on acute GvHD, PUVA and UVB therapy are included in the recommendations as second-line therapy for the treatment of isolated cutaneous GvHD.[86]

Phototherapy for sclerosing connective tissue diseases

First-line phototherapy for limited subtypes of circumscribed scleroderma (CS, synonymous with morphea) is medium-high dose UVA1 therapy (30–50 J/cm^2). This is usually done 3–5 times a week for a total of 40 sessions. However, many studies have failed to show a significant difference between PUVA and UVA.[87] In the only randomized controlled trial of UVA1 phototherapy for CS to date, medium-high dose UVA1 therapy was found to be more effective than low dose.[88] Up to 50% of patients treated with UVA1 will experience a recurrence within 3 years.[89] In such cases, a repeat UV cycle should be considered. Alternatively, bath or cream PUVA therapy may be an option in the early inflammatory phase of limited CS. A treatment cycle should include a total of about 30 single irradiations 2–3 times per week. In a study published in 2013, 28 patients with CS received bath PUVA phototherapy three times a week. Complete cure was achieved in 39% of cases, clinical improvement in 50%, and no response in 10%.[90] Recent advancements in conventional UVA1 light sources, such as metal halide or fluorescent lamps, have focused attention on a new light-emitting diode (LED) technology that offers remarkable advantages in ease of use and integration into clinical practice. In terms of patient comfort, LED-based UVA1 phototherapy would offer significant advantages over conventional treatment, with less heat generation and shorter treatment times at the same irradiation intensity. So far, however, no human study has been published and no device has reached the market. In the mouse model, it has already been shown that an LED-based UVA1 irradiation device can also lead to a reduction in dermis thickness and an increase in skin mobility.[15]

First-line phototherapy for limited subtypes of circumscribed scleroderma is medium-high dose UVA1 therapy (30–50 J/cm^2).

Treatment of sclerosing diseases with UVB is less promising because UVB radiation cannot penetrate deep enough into the dermis, especially in cases of pronounced skin sclerosis. However, UVB phototherapy may be beneficial during the early inflammatory stages of cutaneous sclerosis.

In addition to circumscribed scleroderma, other sclerosing diseases such as lichen sclerosus et atrophicus, limited cutaneous systemic sclerosis, scleromyxedema, eosinophilic fasciitis, nephrogenic systemic fibrosis, or adult scleroderma respond to phototherapy, particularly UVA1.

Side effects of phototherapy

The excellent efficacy of phototherapy is offset by side effects, which can be significantly reduced through careful management and attention to contraindications.

Known chronic consequences of high cumulative UV doses are photo-aging of the skin and photocarcinogenesis. A significantly increased risk of developing squamous cell carcinoma was described after more than 150 PUVA treatments, with a greatly increased risk reported after more than 350 PUVA treatments.[91] High doses of broadband UVB radiation (over 300 treatments) have also been linked to a moderate yet significant rise in non-melanoma skin cancer (NMSC).[92] The trial data regarding narrowband UVB therapy are inconclusive.[93] Two independent studies, with a median of 29 and 18 narrowband UVB treatments respectively, found no association between narrowband UVB therapy and skin cancer.[94,95] However, Raone et al. demonstrated that out of 375 patients, eight developed an increase in NMSC after an average of 86 narrowband UVB exposures.[96] However, another study from Korea, which involved over 60,000 patients, found no overall increased risk of skin cancer, even with more than 500 narrowband UVB treatments in some cases, but it did find an increased risk of actinic keratoses.[97] Additionally, no clinically measurable increase in skin cancer associated with UVA1 therapy has been demonstrated.[98] Furthermore, it is also not clear whether therapeutically high cumulative doses of UVA or UVB increase the risk of melanoma. Data from American publications indicate an increased risk of melanoma after PUVA treatment, but this may be partly due to the fact that American protocols include monthly PUVA maintenance treatments after achieving remission,[99] whereas European protocols do not include further irradiation after remission and do not show an increased risk of melanoma.[93,100] Therefore, patients with a history of malignant skin tumors or severe actinic lesions should be carefully selected and closely monitored. A limit of 300 sessions of narrowband UVB in a lifetime is theoretically reasonable in terms of radiation, even though no increased carcinogenesis by narrowband UVB has been proven so far. In specific cases, therefore, a higher lifetime exposure to narrowband UVB may be justified after carefully considering the benefits and risks involved.

Therefore, it is generally recommended that all UV treatments be documented in a UV passport with details of the light dose applied. However, the use of phototherapy in children should be subjected to stringent indications. While PUVA therapy in children should be reserved for exceptional cases, broadband and narrowband UVB, as well as UVA1 treatments in the low to medium dose range, are generally admissible.[36]

No clinically measurable increase in skin cancer has been observed for narrowband UVB and UVA1 therapy.

Acute risks of phototherapy include phototherapy-induced erythema in overdose and phototoxic reactions following intentional, unavoidable, or accidental ingestion of photosensitizing substances. Potential systemic photosensitizers include tetracyclines, vemurafenib, hydrochlorothiazide, fluoroquinolones, voriconazole, chlorpromazine, azathioprine, and amiodarone. Phototoxic drugs such as voriconazole or azathioprine may also

increase the risk of skin cancer after phototherapy.[101] Therefore, a careful medication history is necessary before and during light therapy.

The immunosuppressive effect of UV radiation may contribute to reactivation of herpes infections, especially in atopic patients and when undergoing high-dose UVA1 therapy.

Particularly with PUVA therapy, it is important to note the delayed onset of erythema, which can be prevented by appropriately scheduling the intervals between irradiation sessions. Typical side effects of PUVA therapy include PUVA pruritus, the development of PUVA freckles (PUVA-induced lentigines), and, in rare cases, the formation of blisters of blisters on highly stressed acral areas. PUVA pain should be mentioned as a contraindication to continued therapy. Gastrointestinal side effects such as nausea and vomiting may occur after administration of 8-MOP but are not commonly associated with 5-MOP. Since gastrointestinal side effects are almost obligatory with 8-MOP, non-absorption (in 10% of patients) should be considered in the absence of side effects and evaluated by phototest if necessary.

Acute keratitis or conjunctivitis may occur as a result of inadequate eye protection during irradiation. This side effect can be avoided by consistently wearing appropriate eye protection (complete absorption of UVB and UVA up to 400 nm).

ACKNOWLEDGEMENTS

Open access funding enabled and organized by Projekt DEAL.

CONFLICT OF INTEREST

None.

REFERENCES

1. Grzybowski A, Sak J, Pawlikowski J. A brief report on the history of phototherapy. *Clin Dermatol*. 2016;34(5):532-537.
2. Finsen N, Forchhammer H. Resultate der Lichtbehandlung bei unseren ersten 800 Fällen von Lupus vulgaris.[Results of light therapy in our first 800 cases of lupus vulgaris]. *Mitt Fins Med Lichtinst*. 1904;5(6):1-48.
3. Hönigsmann H. History of phototherapy in dermatology. *Photochem Photobiol Sci*. 2012;12:16-21.
4. Parrish JA, Fitzpatrick TB, Tanenbaum L, Pathak MA. Photochemotherapy of psoriasis with oral methoxsalen and longwave ultraviolet light. *N Engl J Med*. 1974;291(23):1207-1211.
5. Housman TS, Rohrback JM, Fleischer AB, Feldman SR. Phototherapy utilization for psoriasis is declining in the United States. *J Am Acad Dermatol*. 2002;46(4):557-559.
6. Tan SY, Buzney E, Mostaghimi A. Trends in phototherapy utilization among Medicare beneficiaries in the United States, 2000 to 2015. *J Am Acad Dermatol*. 2018;79(4):672-679.
7. Goyal K, Nguyen MO, Reynolds RV, et al. Perceptions of US dermatology residency program directors regarding the adequacy of phototherapy training during residency. *Photodermatol Photoimmunol Photomed*. 2017;33(6):321-325.
8. Anderson KL, Huang KE, Huang WW, Feldman SR. Training for prescribing in-office and home phototherapy. *Photodermatol Photoimmunol Photomed*. 2015;31(6):325-332.
9. Danesh MJ, Butler DC, Beroukhim K, et al. A cross-sectional survey study to evaluate phototherapy training in dermatology residency. *Photodermatol Photoimmunol Photomed*. 2015;31(5):269-270.
10. Augustin M, Girbig G, Hertl M, et al. Status quo und Perspektiven der Hautkliniken in Deutschland: Versorgungsspektren und Personalsituation. *J Dtsch Dermatol Ges*. 2021;19(S5):14-24.
11. Kurz B, Ivanova I, Bäumler W, Berneburg M. Turn the light on photosensitivity. *J Photochem Photobiol*. 2021;8:100071.
12. Gueymard CA. Parameterized transmittance model for direct beam and circumsolar spectral irradiance. *Solar Energy*. 2001;71(5):325-346.
13. Zou Z, Ye J, Sayama K, Arakawa H. Direct splitting of water under visible light irradiation with an oxide semiconductor photocatalyst. *Nature*. 2001;414(6864):625-627.
14. Wondrak GT, Jacobson MK, Jacobson EL. Endogenous UVA-photosensitizers: mediators of skin photodamage and novel targets for skin photoprotection. *Photochem Photobiol Sci*. 2006;5(2):215-237.
15. Arndt S, Lissner C, Unger P, et al. Biological effects of a new ultraviolet A1 prototype based on light-emitting diodes on the treatment of localized scleroderma. *Exp Dermatol*. 2020;29(12):1199-1208.
16. Bormann M, Alt M, Schipper L, et al. Disinfection of SARS-CoV-2 contaminated surfaces of personal items with UVC-LED disinfection boxes. *Viruses*. 2021;13(4):598.
17. Kalajian TA, Aldoukhi A, Veronikis AJ, et al. Ultraviolet B light emitting diodes (LEDs) are more efficient and effective in producing vitamin D3 in human skin compared to natural sunlight. *Sci Rep*. 2017;7(1):11489.
18. Bäumler W. Singlet oxygen in the skin. In: *Singlet Oxygen*. 2016:205-226.
19. Bäumler W, Regensburger J, Knak A, et al. UVA and endogenous photosensitizers – the detection of singlet oxygen by its luminescence. *Photochem Photobiol Sci*. 2012;11(1):107-117.
20. Knak A, Regensburger J, Maisch T, Bäumler W. Exposure of vitamins to UVB and UVA radiation generates singlet oxygen. *Photochem Photobiol Sci*. 2014;13(5):820-829.
21. Hofmann GA, Weber B. Drug-induced photosensitivity: culprit drugs, potential mechanisms and clinical consequences. *J Dtsch Dermatol Ges*. 2021;19(1):19-29.
22. Lankerani L, Baron ED. Photosensitivity to exogenous agents. *J Cutan Med Surg*. 2004;8(6):424-431.
23. Finlayson L, Barnard IRM, McMillan L, et al. Depth penetration of light into skin as a function of wavelength from 200 to 1000 nm. *Photochem Photobiol*. 2022;98(4):974-981.
24. Singer S, Berneburg M. Phototherapie. *J Dtsch Dermatol Ges*. 2018;16(9):1120-1131.
25. Cadet J, Voituriez L, Nardin R, et al. A new class of psoralen photoadducts to DNA components: Isolation and characterization of 8-MOP adducts to the osidic moiety of 2′-deoxyadenosine. *J Photochem Photobiol B*. 1988;2(3):321-339.
26. Singer S, Schwarz T, Berneburg M. Grundlagen zur Phototherapie. In: *Phototherapie*, Springer, 2016:1-7.
27. Regensburger J, Knak A, Maisch T, et al. Fatty acids and vitamins generate singlet oxygen under UVB irradiation. *Exp Dermatol*. 2012;21(2):135-139.
28. Von Thaler AK, Kamenisch Y, Berneburg M. The role of ultraviolet radiation in melanomagenesis. *Exp Dermatol*. 2010;19(2):81-88.
29. Morita A, Werfel T, Stege H, et al. Evidence that singlet oxygen-induced human T helper cell apoptosis is the basic mechanism of ultraviolet-A radiation phototherapy. *J Exp Med*. 1997;186(10):1763-1768.
30. Berneburg M, Grether-Beck S, Kürten V, et al. Singlet oxygen mediates the UVA-induced generation of the photoaging-associated mitochondrial common deletion. *J Biol Chem*. 1999;274(22):15345-15349.
31. Tyrrell RM. Role for singlet oxygen in biological effects of ultraviolet A radiation. *Methods Enzymol*. 2000;319:290-296

32. Tewari A, Sarkany RP, Young AR. UVA1 induces cyclobutane pyrimidine dimers but not 6-4 photoproducts in human skin in vivo. *J Invest Dermatol*. 2012;132(2):394-400.
33. Douki T, Sage E. Dewar valence isomers, the third type of environmentally relevant DNA photoproducts induced by solar radiation. *Photochem Photobiol Sci*. 2016;15(1):24-30.
34. Vieyra-Garcia PA, Wolf P. A deep dive into UV-based phototherapy: Mechanisms of action and emerging molecular targets in inflammation and cancer. *Pharmacol Ther*. 2021;222:107784.
35. Goulden V, Ling TC, Babakinejad P, et al. British Association of Dermatologists and British Photodermatology Group guidelines for narrowband ultraviolet B phototherapy 2022. *Br J Dermatol*. 2022;187(3):295-308.
36. Herzinger T, Berneburg M, Ghoreschi K, et al. S1-Guidelines on UV phototherapy and photochemotherapy. *J Dtsch Dermatol Ges*. 2016;14(8): 853-76.
37. Elmets CA, Lim HW, Stoff B, et al. Joint American Academy of Dermatology-National Psoriasis Foundation guidelines of care for the management and treatment of psoriasis with phototherapy. *J Am Acad Dermatol*. 2019;81(3):775-804.
38. Zhang M, Goyert G, Lim HW. Folate and phototherapy: What should we inform our patients? *J Am Acad Dermatol*. 2017;77(5): 958-964.
39. Parrish JA, Jaenicke KF. Action spectrum for phototherapy of psoriasis. *J Invest Dermatol*. 1981;76(5):359-362.
40. Stege H, Ghoreschi K, Hünefeld C. UV-Phototherapie. *Der Hautarzt*. 2021;72(1):14-26.
41. Fitzpatrick TB. The validity and practicality of sun-reactive skin types I through VI. *Arch Dermatol*. 1988;124(6):869-871.
42. Gambichler T, Majert J, Pljakic A, et al. Determination of the minimal erythema dose for ultraviolet A1 radiation. *Br J Dermatol*. 2017;177(1):238-244.
43. Krutmann J, Diepgen TL, Luger TA, et al. High-dose UVA1 therapy for atopic dermatitis: results of a multicenter trial. *J Am Acad Dermatol*. 1998;38(4):589-593.
44. Krutmann J, Czech W, Diepgen T, et al. High-dose UVA1 therapy in the treatment of patients with atopic dermatitis. *J Am Acad Dermatol*. 1992;26(2):225-230.
45. Krutmann J, Hönigsmann H. *Handbuch der dermatologischen Phototherapie und Photodiagnostik*. Springer-Verlag, 2013.
46. Werfel T, Heratizadeh A, Aberer W, et al. S2k-Leitlinie Neurodermitis (atopisches Ekzem, atopische Dermatitis) – Kurzversion. *Allergo J*. 2016;25(3):36-51.
47. Abeck D, Schmidt T, Fesq H, et al. Long-term efficacy of medium-dose UVA1 phototherapy in atopic dermatitis. *J Am Acad Dermatol*. 2000;42(2):254-257.
48. Ben Mordehai Y, Barzilai A, Dalal A, Pavlotsky F. Long-term narrowband UV-B efficacy in moderate to severe atopic dermatitis. *Dermatitis*. 2022;33(4):282-286.
49. Rossi M, Rovati C, Arisi M, et al. A short cycle of narrow-band UVB phototherapy in the early phase of dupilumab therapy can provide a quicker improvement of severe atopic dermatitis. *Dermatology*. 2021;237(3):407-415.
50. Wollenberg A, Barbarot S, Bieber T, et al. Consensus-based European guidelines for treatment of atopic eczema (atopic dermatitis) in adults and children: part I. *J Eur Acad Dermatol Venereol*. 2018;32(5):657-682.
51. Dayal S, Pathak K, Sahu P, Jain VK. Narrowband UV-B phototherapy in childhood atopic dermatitis: efficacy and safety. *An Bras Dermatol*. 2017;92:801-806.
52. Nast A, Altenburg A, Augustin M, et al. Deutsche S3-Leitlinie zur Therapie der Psoriasis vulgaris, adaptiert von EuroGuiDerm – Teil 1: Therapieziele und Therapieempfehlungen. *J Dtsch Dermatol Ges*. 2021;19(6):934-951.
53. Hofer A, Fink-Puches R, Kerl H, et al. Paired comparison of bathwater versus oral delivery of 8-methoxypsoralen in psoralen plus ultraviolet: A therapy for chronic palmoplantar psoriasis. *Photodermatol Photoimmunol Photomed*. 2006;22(1):1-5.
54. Berneburg M, Brod C, Benedix F, Röcken M. New and established indications for phototherapy with narrowband UVB. *J Dtsch Dermatol Ges*. 2005;3(11):874-882.
55. Berneburg M, Röcken M, Benedix R. Phototherapy with narrowband UVB. *Acta Derm Venereol*. 2005;85:1-11.
56. Noe MH, Wan MT, Shin DB, et al. Patient-reported outcomes of adalimumab, phototherapy, and placebo in the Vascular Inflammation in Psoriasis Trial: A randomized controlled study. *J Am Acad Dermatol*. 2019;81(4):923-930.
57. Marsche G, Holzer M, Wolf P. Antipsoriatic treatment extends beyond the skin: recovering of high-density lipoprotein function. *Exp Dermatol*. 2014;23(10):701-704.
58. Vieyra-Garcia PA, Wolf P. Extracorporeal photopheresis: a case of immunotherapy ahead of its time. *Transfus Med Hemother*. 2020;47(3):226-235.
59. Ling T, Clayton T, Crawley J, et al. British Association of Dermatologists and British Photodermatology Group guidelines for the safe and effective use of psoralen–ultraviolet A therapy 2015. *Br J Dermatol*. 2016;174(1):24-55.
60. Bilsland D, George S, Gibbs N, et al. A comparison of narrow band phototherapy (TL-01) and photochemotherapy (PUVA) in the management of polymorphic light eruption. *Br J Dermatol*. 1993;129(6):708-712.
61. Man I, Dawe R, Ferguson J. Artificial hardening for polymorphic light eruption: practical points from ten years' experience. *Photodermatol Photoimmunol Photomed*. 1999;15(3-4):96-99.
62. Mastalier U, Kerl H, Wolf P. Clinical, laboratory, phototest and phototherapy findings in polymorphic light eruptions: a retrospective study of 133 patients. *Eur J Dermatol*. 1999;8(8):554-559.
63. Gong Y-Y, Rong W, Li L, et al. Successful treatment of polymorphic light eruption with UVA rush hardening: A report of 5 cases. *Photodermatol Photoimmunol Photomed*. 2020;36(4): 322-323.
64. Beissert S, Ständer H, Schwarz T. UVA rush hardening for the treatment of solar urticaria. *J Am Acad Dermatol*. 2000;42(6): 1030-1032.
65. Pattamadilok B, Poomputsar T. A retrospective, descriptive study of patients with Mycosis fungoides treated by phototherapy (oral PUVA, NB-UVB) with a twice-weekly regimen at the Institute of Dermatology, Bangkok, Thailand, with an experiential timeline of 13 years. *Photodermatol Photoimmunol Photomed*. 2021;37(1): 49-55.
66. Vieyra-Garcia P, Fink-Puches R, Porkert S, et al. Evaluation of low-dose, low-frequency oral psoralen – UV-A treatment with or without maintenance on early-stage mycosis fungoides: a randomized clinical trial. *JAMA Dermatology*. 2019;155(5):538-547.
67. Adışen E, Tektaş V, Erduran F, et al. Ultraviolet A1 phototherapy in the treatment of early mycosis fungoides. *Dermatology*. 2017;233(2-3):192-198.
68. Trovato E, Pellegrino M, Filippi F, et al. Clinical and histological evaluation in patients with mycosis fungoides treated with UVA1. *G Ital Dermatol Venereol*. 2020;155(3):306-311.
69. Böhm M, Schunter JA, Fritz K, et al. S1 Guideline: Diagnosis and therapy of vitiligo. *J Dtsch Dermatol Ges*. 2022;20(3):365-378.
70. Bae JM, Jung HM, Hong BY, et al. Phototherapy for vitiligo: a systematic review and meta-analysis. *JAMA Dermatol*. 2017;153(7): 666-674.
71. Batchelor JM, Thomas KS, Akram P, et al. Home-based narrowband UVB, topical corticosteroid or combination for children and adults with vitiligo: HI-Light Vitiligo three-arm RCT. *Health Technol Assess*. 2020;24(64):1-128.
72. Castanedo-Cazares JP, Lepe V, Moncada B. Repigmentation of chronic vitiligo lesions by following tacrolimus plus ultraviolet-B-narrow-band. *Photodermatol Photoimmunol Photomed*. 2003;19(1):35-36.
73. Fai D, Cassano N, Vena GA. Narrow-band UVB phototherapy combined with tacrolimus ointment in vitiligo: a review of 110 patients. *J Eur Acad Dermatol Venereol*. 2007;21(7):916-920.

74. Nordal EJ, Guleng GE, Rönnevig JR. Treatment of vitiligo with narrowband-UVB (TL01) combined with tacrolimus ointment (0.1 %) vs. placebo ointment, a randomized right/left double-blind comparative study. *J Eur Acad Dermatol Venereol*. 2011;25(12):1440-1443.
75. Passeron T, Ostovari N, Zakaria W, et al. Topical tacrolimus and the 308-nm excimer laser: a synergistic combination for the treatment of vitiligo. *Arch Dermatol*. 2004;140(9):1065-1069.
76. Phan K, Phan S, Shumack S, Gupta M. Repigmentation in vitiligo using Janus kinase (JAK) inhibitors with phototherapy: systematic review and Meta-analysis. *J Dermatolog Treat*. 2022;33(1): 173-177.
77. Kreutz M, Karrer S, Hoffmann P, et al. Whole-body UVB irradiation during allogeneic hematopoietic cell transplantation is safe and decreases acute graft-versus-host disease. *J Invest Dermatol*. 2012;132(1):179-187.
78. Sorenson E, McAndrew R, Patel V, et al. Narrowband UV-B phototherapy for steroid-refractory sclerotic chronic cutaneous graft-vs-host disease. *JAMA Dermatol*. 2015;151(6):635-637.
79. George L, Peter D, Chopra M, et al. Efficacy of narrow band UVB in the treatment of cutaneous GvHD: an Indian experience. *Bone Marrow Transplant*. 2016;51(7):988-990.
80. Grundmann-Kollmann M, Martin H, Ludwig R, et al. Narrowband UV-B phototherapy in the treatment of cutaneous graft versus host disease. *Transplantation*. 2002;74(11):1631-1634.
81. Iyama S, Murase K, Sato T, et al. Narrowband ultraviolet B phototherapy ameliorates acute graft-versus-host disease by a mechanism involving in vivo expansion of CD4+ CD25+ Foxp3+ regulatory T cells. *Int J Hematol*. 2014;99(4):471-476.
82. Enk C, Elad S, Vexler A, et al. Chronic graft-versus-host disease treated with UVB phototherapy. *Bone Marrow Transplant*. 1998;22(12):1179-1183.
83. Schlaak M, Schwind S, Wetzig T, et al. UVA (UVA-1) therapy for the treatment of acute GVHD of the skin. *Bone Marrow Transplant*. 2010;45(12):1741-1748.
84. Connolly KL, Griffith JL, McEvoy M, Lim HW. Ultraviolet A1 phototherapy beyond morphea: experience in 83 patients. *Photodermatol Photoimmunol Photomed*. 2015;31(6):289-295.
85. Wolff D, Zeiser R, Scheid C, et al. Graft-versus-Host Erkrankung, chronisch. 2022. Available from: https://www.onkopedia.com/de/onkopedia/guidelines/graft-versus-host-erkrankung-chronisch/@@guideline/html/index.html [Last accessed February 24, 2023].
86. Zeiser R, Wolff D, Scheid C, et al. Graft-versus-Host Erkrankung, akut. 2022. Available from: https://www.onkopedia.com/de/onkopedia/guidelines/graft-versus-host-erkrankung-akut/@@guideline/html/index.html [Last accessed February 24, 2023].
87. Malewska-Woźniak A, Osmola-Mańkowska A, Adamski Z. Effectiveness of PUVA vs. UVA1 phototherapy in the treatment of morphea patients. *Postepy Dermatol Alergol*. 2022;39(4):757-761.
88. Kreuter A, Hyun J, Stücker M, et al. A randomized controlled study of low-dose UVA1, medium-dose UVA1, and narrowband UVB phototherapy in the treatment of localized scleroderma. *J Am Acad Dermatol*. 2006;54(3):440-447.
89. Vasquez R, Jabbar A, Khan F, et al. Recurrence of morphea after successful ultraviolet A1 phototherapy: a cohort study. *J Am Acad Dermatol*. 2014;70(3):481-488.
90. Pavlotsky F, Sakka N, Lozinski A, Barzilai A. Bath psoralen – UVA photochemotherapy for localized scleroderma: experience from a single institute. *Photodermatol Photoimmunol Photomed*. 2013;29(5):247-252.
91. Stern RS. Study PF-U. The risk of squamous cell and basal cell cancer associated with psoralen and ultraviolet A therapy: a 30-year prospective study. *J Am Acad Dermatol*. 2012;66(4):553-562.
92. Lim JL, Stern RS. High levels of ultraviolet B exposure increase the risk of non-melanoma skin cancer in psoralen and ultraviolet A-treated patients. *J Invest Dermatol*. 2005;124(3):505-513.
93. Archier E, Devaux S, Castela E, et al. Carcinogenic risks of psoralen UV-A therapy and narrowband UV-B therapy in chronic plaque psoriasis: a systematic literature review. *J Eur Acad Dermatol Venereol*. 2012;26:22-31.
94. Hearn RM, Kerr AC, Rahim KF, et al. Incidence of skin cancers in 3867 patients treated with narrow-band ultraviolet B phototherapy. *Br J Dermatol*. 2008;159(4):931-935.
95. Weischer M, Blum A, Eberhard F, et al. No evidence for increased skin cancer risk in psoriasis patients treated with broadband or narrowband UVB phototherapy: a first retrospective study. *Acta Derm Venereol*. 2004;84(5):370-374.
96. Raone B, Patrizi A, Gurioli C, et al. Cutaneous carcinogenic risk evaluation in 375 patients treated with narrowband-UVB phototherapy: A 15-year experience from our Institute. *Photodermatol Photoimmunol Photomed*. 2018;34(5):302-306.
97. Bae JM, Ju HJ, Lee RW, et al. Evaluation for skin cancer and precancer in patients with vitiligo treated with long-term narrowband UV-B phototherapy. *JAMA Dermatol*. 2020;156(5):529-537.
98. Bedair K, Elhadad A, Hamad S, et al. No association between whole-body ultraviolet A1 phototherapy and skin cancers in humans: A cancer registry linkage study. *Br J Dermatol*. 2020;183(3): 586-587.
99. Stern RS, Nichols KT, Väkevä LH. Malignant melanoma in patients treated for psoriasis with methoxsalen (psoralen) and ultraviolet A radiation (PUVA). *N Engl J Med*. 1997;336(15):1041-1045.
100. Lindelöf B, Sigurgeirsson B, Tegner E, et al. PUVA and cancer risk: the Swedish follow-up study. *Br J Dermatol*. 1999;141(1):108-112.
101. Hofbauer G. Phototherapie und Karzinogenese. *Der Hautarzt*. 2013;64(5):349-353.

How to cite this article: Kurz B, Berneburg M, Bäumler W, Karrer S. Phototherapy: Theory and practice. *JDDG: Journal der Deutschen Dermatologischen Gesellschaft*. 2023;1-14. https://doi.org/10.1111/ddg.15126

[CME Questions / Lernerfolgskontrolle]

1. Welche der folgenden Aussagen ist korrekt? UVA-Strahlung …
   a. wird fast vollständig in der Erdatmosphäre absorbiert.
   b. dringt in die Dermis ein.
   c. ruft vorwiegend direkte Schäden in der DNA hervor.
   d. ist der energiestärkste Teil des UV-Spektrums.
   e. hat eine kleinere Wellenlänge als UVB.

2. Welche der folgenden Aussagen ist korrekt? UVB-Strahlung…
   a. entfaltet seine gesamte Wirkung fast ausschließlich in der Dermis.
   b. ruft vorwiegend indirekte Schäden in der DNA hervor.
   c. sollte auf keinen Fall in der Behandlung von Kindern Anwendung finden.
   d. wird nicht zur Therapie der Psoriasis eingesetzt.
   e. Die Schmalband-UVB-Therapie hat aufgrund geringerer erythematogener Potenz die Breitband-UVB-Therapie weitgehend abgelöst.

3. Welche der folgenden Erkrankungen ist keine optimale Indikation für die Schmalband-UVB-Therapie?
   a. Morphea
   b. Psoriasis vulgaris
   c. Atopische Dermatitis
   d. Vitiligo
   e. Polymorphe Lichtdermatose

4. Bei welcher Substanz ist nicht mit einer Photosensibilisierung zu rechnen?
   a. Tetrazykline
   b. Methoxypsoralen
   c. Voriconazol
   d. Azathioprin
   e. Penicillin

5. Was ist keine Schlüsselkomponente der Phototherapie?
   a. Immunmodulation
   b. Antipruritische Effekte
   c. Fibrotische Effekte
   d. Apoptose
   e. Pro-präbiotische Effekte

6. Was ist keine relative oder absolute Kontraindikation für die Einleitung einer Phototherapie?
   a. Lupus erythematodes
   b. Xeroderma pigmentosum
   c. Die Einnahme von Ciclosporin
   d. Familiäre Melanom-Syndrome
   e. Photohauttyp I nach Fitzpatrick

7. Welche Aussage über die Photochemotherapie ist richtig?
   a. Es empfiehlt sich, die UV-Dosis in der ersten Woche nicht zu steigern.
   b. Bei einem minimalen Erythem soll die Bestrahlungsdosis gesteigert werden.
   c. Die PUVA-Photochemotherapie ist eine Behandlung der ersten Wahl bei Mycosis fungoides (MF) im Spätstadium.
   d. Meladinine® ist in Deutschland zugelassen.
   e. Die minimale phototoxische Dosis (MDP) wird in einem lichtexponierten Areal ermittelt.

8. Welche Aussage zur Vitiligobehandlung ist richtig?
   a. Schmalband-UVB-Therapie ist wirksamer als die PUVA-Therapie.
   b. Läsionen im Kopf-Hals-Bereich sprechen schlecht auf eine Phototherapie an.
   c. Bei fehlender Repigmentierung sollte die Bestrahlung nach spätestens 2 Monaten abgebrochen werden.
   d. Schmalband-UVB wird mit einer stark erythematogenen Dosis 2–3 x pro Woche eingesetzt.
   e. Schmalband-UVB ist nicht indiziert bei generalisierter Vitiligo.

9. Welche Aussage über die UVB-Phototherapie ist richtig?
   a. UVB-Behandlungen sollten maximal ein- bis zweimal wöchentlich durchgeführt werden.
   b. Das UVB 311 nm Erythem ist nach 48 Stunden maximal ausgeprägt.
   c. Schwangere Frauen sollen keine Folsäure während einer Phototherapie mit UVB substituieren.
   d. Bei der Therapie mit Schmalband-UVB können deutlich höhere Lichtdosen als bei der Breitband-UVB-Therapie appliziert werden.
   e. Als anfängliche Lichtdosis wird 100 % der ermittelten MED verwendet.

10. Welche Aussage zur Phototherapie bei sklerosierenden Bindegewebserkrankungen ist richtig?
    a. Phototherapie der ersten Wahl bei limitierten Subtypen der zirkumskripten (ZS) ist die mittelhoch dosierte UVA1-Therapie (30–50 J/cm^2)
    b. Bade-PUVA-Phototherapie ist in der späten Phase der

limitierten ZS sehr wirkungsvoll.

c. Leuchtdiodentechnologie (LED) wird keine Behandlungsoption für die ZS werden.
d. Der Lichen sclerosus et atrophicus spricht nicht auf eine UVA1-Phototherapie an.
e. Eine UVA1-Therapie bei ZS sollte maximal 20-mal erfolgen.

Liebe Leserinnen und Leser,
der Einsendeschluss an die DDA für diese Ausgabe ist der 31. Oktober 2023.

Die richtige Lösung zum Thema "Syphilis" in Heft 5/2023 Lösung: 1d, 2a, 3b, 4c, 5d, 6b, 7b, 8a, 9a, 10b

Bitte verwenden Sie für Ihre Einsendung das aktuelle Formblatt auf der folgenden Seite oder aber geben Sie Ihre Lösung online unter http://jddg.akademie-dda. de ein.