

Phototherapy in dermatological maladies (Review)

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Abstract. Since the introduction of modern phototherapy in 1903 by Nobel Prize-winner Niels Ryberg Finsen, the usage of this therapy in the medical field has grown, techniques have been refined and developed, and it has gained widespread acceptance. Psoriasis vulgaris, parapsoriasis, lichen planus, atopic dermatitis, neonatal jaundice, urticaria, morphea, vitiligo, granuloma annulare and cutaneous T cell lymphoma are only a few dermatological indications that come along with satisfactory results. Most often, it is a 2nd or 3rd line therapy being an alternative in more severe or refractory diseases. Despite the side effects that may occur after phototherapy, which are often minor, the benefits can be significant. Unfortunately, the absolute contraindications limit the use of this type of treatment and implicitly the management of these patients. The current review aimed to combine the recommendations of phototherapy in dermatology, the types of phototherapy that can be suitable for certain dermatological

diseases and to emphasize its importance in certain conditions that are associated with significant remission rates.

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1. Introduction

Heliotherapy has been a therapeutic method used in the treatment of various medical conditions for >3,500 years (1). At the beginning of the 20th century, this method was considered to be revolutionary in the treatment of pulmonary tuberculosis, arthritis and small pox, the first dermatological indication being lupus vulgaris (cutaneous tuberculosis) (1). The evolution of modern phototherapy has led to an improved understanding of the ultraviolet (UV) radiation effects. This is a very important aspect to determine which conditions can benefit from this type of treatment. In dermatological maladies, phototherapy must be considered, especially in conditions that do not respond to first-line therapies. Each phototherapy session must be personalized and adapted according to a series of parameters in order to obtain an effective response without any serious side effects. This is possible by following

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the updated protocols (2). Most of the dermatological conditions listed in this review have a significant remission rate after a variable number of phototherapy sessions, which is why this therapeutic method should be taken into consideration more often. The current review aimed to combine the recommendations of phototherapy in dermatology, the types of phototherapy that can be suitable for certain dermatological diseases and to emphasize its importance in certain conditions that are associated with significant remission rates.

2. Literature review methodology

The current review aimed to synthesize the recommendations of phototherapy in dermatology, to emphasize its importance in certain conditions that are associated with significant remission rates. PubMed (<https://pubmed.ncbi.nlm.nih.gov/>), Elsevier (<https://www.elsevier.com/en-gb>) and Medscape (<https://www.medscape.com/pathology>) databases were searched, to select the published literature and articles that emerged between 2005 and 2020, using the following combinations of terms: 'phototherapy', 'recommendations', 'psoriasis', 'vitiligo', 'scleroderma', 'atopic dermatitis', 'lichen planus', 'granuloma annulare', 'cutaneous T-cell lymphoma', 'side effects'. Only clinical trials and reviews, published in English, on human subjects were included. For the theoretical section that explains the basics of phototherapy, the information was extracted from specialized treatises. This review mainly focused on the circumstances in which phototherapy is necessary, which type of phototherapy is more suitable, its benefits, risks and its effectiveness in several selected dermatological pathologies, based on 16 case studies.

3. Types of phototherapy

Phototherapy is a useful therapeutic method in the management of a number of dermatological maladies. It uses UV radiation (UVA, UVB) with different wavelengths (2). Depending on the type of radiation and their wavelength, there are several types of phototherapy: i) Narrow Band UVB (NB-UVB); ii) Broadband UVB (BB-UVB); iii) UVA (UVA 1); and iv) Psoralen UVA (PUVA) (2). Among these, PUVA therapy is associated with the highest carcinogenic risk, seven times higher than the rest (2).

4. Phototherapy protocols

The phototherapy protocol is different. Thus, in the case of NB-UVB phototherapy, the initial radiation dose is determined according to the minimal erythema dose (MED), starting with 50-70% of MED, or according to the Fitzpatrick skin phototype. At each session the dose is increased by 10-20%, 2 to 5 sessions per week can be performed (3). In the case of erythema, the dose is decreased, or the treatment is delayed (3,4).

BB-UVB phototherapy follows the same protocol, but the radiation dose is increased by 25% per session in the first 10 sessions, then it is increased by 10% per session (3,4).

Psoralen can be administered orally, 0.6 mg/kg, 2 h before irradiation. The initial dose of UVA is determined according to the minimum phototoxic dose (MPD), 50-70% of the MPD

or according to the skin phototype. There can be 2 to 4 sessions per week, in which the dose is increased each week (3). Psoralen can also be given topically. Psoralen baths can be made (1 mg/l), at a water temperature of 37°C for 15 to 20 min, and then UVA exposure is administered. The initial dose of UVA is 30% of MED, 2 sessions per week can be performed, in which the dose is increased by 20% per week (3,4).

5. Effects of UV radiation

The exerted effects by non-ionizing radiation can guide us on the utility of phototherapy in dermatology. Therefore, UV radiation can cause mast cell apoptosis, collagen degradation, acanthosis and thickening of the stratum corneum (2). It can also stimulate melanogenesis and have an immunosuppressive effect by decreasing the activity of dendritic cells, thus resulting in decreased activation of T cells (2).

6. Indications for phototherapy in dermatology

Given the aforementioned effects, the dermatological disorders from Fitzpatrick's Dermatology by Fitzpatrick and Kang (2) that may benefit from phototherapy are: i) Actinic prurigo; ii) atopic dermatitis; iii) chronic eczema; iv) chronic palmoplantar pustulosis (PPP); v) chronic urticaria; vi) cutaneous T cell lymphoma; vii) granuloma annulare; viii) hydroa vacciniforme (HV); ix) indolent systemic mastocytosis; x) lichen planus; xi) localized and systemic scleroderma; xii) lymphomatoid papulosis; xiii) neonatal jaundice; xiv) parapsoriasis; xv) photodermatoses; xvi) pityriasis lichenoides; xvii) pityriasis rubra pilaris (PRP); xviii) primary localized cutaneous amyloidosis (PLCA); xix) psoriasis; xx) solar urticaria; xxi) subcorneal pustular dermatosis (SPD; also known as Sneddon-Wilkinson disease); xxii) telangiectasia macularis eruptiva perstans; xxiii) urticaria pigmentosa; and xxiv) vitiligo.

Phototherapy is the primary treatment in neonatal jaundice. Phototherapy is useful for conjugating bilirubin (5,6).

Psoriasis vulgaris is the most common indication for phototherapy (NB-UVB and PUVA being the most widely used applications) (7). Unlike topical therapy, the main advantage of phototherapy is that it can convert psoriasis to skin that is morphologically and histologically normal (7). Usually patients have a good outcome after phototherapy sessions, with long lasting effects (7). UVB therapy is usually combined with one or more topical treatments (corticosteroids, calcipotriene, tazarotene or simply bland emollients) (8). In 1925 the Goeckerman regime was published, which consisted of using coal tar followed by UVB exposure (8). Even after the introduction of novel biological agents in the treatment of psoriasis, the Goeckerman regimen remained a very effective option (9). A number of studies have shown that this regime can induce disease remission in >80% of patients (10). NB-UVB phototherapy is usually recommended, and if not available, BB-UVB may be an alternative, but with poorer results (10). Regarding PUVA phototherapy, >85% of patients reported remission of symptoms after 20 to 30 sessions (10).

Phototherapy can also be useful in sclerosing skin diseases, especially in localized scleroderma (11). PUVA and UVA 1 are the feasible options in this case, leading to the improvement of

skin sclerosis, joint mobility, ulcers and histopathology (12-16). UVA 1 phototherapy response rates range between 60 and 100% after 30 to 40 sessions (17). NB-UVB phototherapy may be an alternative especially in cases with relatively superficial dermal plaques, when PUVA or UVA 1 are not available (17). The protocol is similar to that for psoriasis (18). In a study conducted by Pavlotsky *et al* (19), on 28 patients, Bath-PUVA phototherapy was associated with complete remission in 39% of cases, partial remission in 50% of cases, and the rest did not respond to this type of treatment (19). In a study conducted on 17 patients who underwent between 25 and 35 Bath-PUVA phototherapy sessions, the results were satisfactory, with complete and marked remission of 13 patients in <3 months (20). In another study, PUVA cream phototherapy was associated with improved results, but being a study performed on a limited number of patients, we cannot reach a final conclusion (21). Regarding UVA 1 phototherapy, the study performed by Kroft *et al* (22) on 10 patients, showed significant efficiency, with complete remission on the entire study group after 20 sessions. After a follow-up of 46 weeks, complete remission was maintained for at least 26 weeks (22). Thus, these examples of studies accompanied by positive results indicate the importance of phototherapy in localized scleroderma.

Generalized vitiligo can be treated with PUVA or NB-UVB phototherapy. NB-UVB seems to be the preferable option giving the favorable outcome, as found in several studies (23,24).

Even though the main method of treating lichen planus is topical and systemic corticosteroids, NB-UVB phototherapy has proven to be a good alternative, especially in the disseminated forms (25,26). Also, one study showed that NB-UVB phototherapy may be a promising treatment modality for erosive oral lichen planus (27).

In the early stages of cutaneous T cell lymphoma, besides topical steroids and nitrogen mustard (28), phototherapy can also be considered, PUVA and NB-UVB being first-line treatments. PUVA phototherapy seems to be associated with much more favorable results (29). A study conducted by Ahmad *et al* (30) showed the effectiveness of both NB-UVB phototherapy and PUVA phototherapy, registering complete remissions especially in the early stages (IA, IB) of cutaneous T cell lymphoma in 50 and 64% of patients, respectively (30).

Furthermore, even in the case of chronic eczema, phototherapy can be an alternative, given the possible anti-inflammatory effect exerted by UV radiation (31).

Atopic dermatitis, also known as atopic eczema, is a common skin condition characterized by chronic inflammation of the skin (32). It can occur at any age (32). Phototherapy is the 2nd line therapy in this condition (33). It may or may not be associated with systemic drugs, especially corticosteroids (33). Studies have shown satisfactory results after performing UVA-1 and NB-UVB phototherapy (33,34). NB-UVB causes the destruction of T cells in the epidermis and inhibits the release of cytokines and the activity of T helper (Th)1 lymphocytes (which in chronic atopic dermatitis are hyperstimulated) leading to a Th2 response (34). UVB radiation penetrates only the epidermis, so the phototherapy effect is superficial, which is suitable for chronic atopic dermatitis (34). Since UVA radiation penetrates deep into the dermis, this form of therapy is suitable for acute atopic dermatitis (35).

In a previous study conducted by Dayal *et al* (36) on a group of 30 children, a considerable remission rate was registered after 6, 12, 18 and 24 NB-UVB phototherapy sessions, and the results were maintained for at least 2 years (36). Another study conducted by Tintle *et al* (37), on 12 adult patients with moderate to severe atopic dermatitis showed a remission rate of at least 50% after a variable number of NB-UVB phototherapy sessions, no more than 23. According to another study performed on a group of 32 patients with acute exacerbated atopic dermatitis, UVA 1 phototherapy gave very good results, but after 3 months, the skin condition had reached the pretreatment level (38). Therefore, it can be concluded that NB-UVB phototherapy is feasible for chronic atopic dermatitis, which is accompanied by long-term results, and UVA 1 phototherapy has implications in acute atopic dermatitis, unfortunately with short term results.

Granuloma annulare is a fairly rare, benign and asymptomatic inflammatory skin condition of unknown etiology, frequently associated with diabetes mellitus (2). There are multiple forms of treatment, including topical and systemic steroids, dapsone, cyclosporine, systemic retinoids, phototherapy and rifampicin, ofloxacin and minocycline therapy (39). The case presented by Muylaert *et al* (40) highlights the efficiency of NB-UVB phototherapy in disseminated annular granuloma, refractory to other therapies. Along with this case, other studies were carried out and reached the same conclusion (41-43).

PPP is a rare chronic recurrent disease of unknown etiology characterized by the appearance of sterile blisters on the palms of the hands and/or soles of the feet (2). In addition to corticosteroids, PUVA and NB-UVB may be considered for the treatment of this condition, NB-UVB being preferred given the lower risk of secondary skin cancer development (44).

Another rare disease of unknown etiology is pityriasis lichenoides. This is characterized by the appearance of small, scaly papules (45,46). The treatment of this dermatosis consists of corticosteroids, oral antibiotics and phototherapy, which is primarily used in the recurrent and resistant cases of the disease (47,48). A study conducted by Fernández-Guarino *et al* (49), performed on eight patients undergoing an average of 23 NB-UVB sessions resulted in a complete remission rate of 88%, but the relapse rate was 43% in the first 6 months. Phototherapy may also be useful in children, but the most common indications among these patients are psoriasis and atopic dermatitis (50).

PRP is clinically characterized by follicular keratotic plugs, red to orange plaques and palmoplantar hyperkeratosis (2). NB-UVB can be a very effective therapy in this case as well (51).

Lymphomatoid papulosis is a chronic papulonecrotic or papulonodular skin disease and a rare form of indolent cutaneous T cell lymphoma characterized by crops of recurrent self-healing papules (2). PUVA-Bath photochemotherapy is associated with satisfactory results and along with topical corticosteroid therapy and methotrexate, are among the first-line therapies for this disease (52-54).

PLCA is the deposition of amyloid in an apparently normal skin without affecting the internal organs (2). A variety of treatment options for PLCA have been reported, including retinoids, corticosteroids, cyclophosphamide, cyclosporine, amitriptyline, colchicine, catharanthine, tacrolimus, dimethyl sulfoxide, vitamin D₃ analogs, capsaicin, menthol, hydrocolloid

dressings, surgical modalities, laser treatment and among phototherapy types, NB-UVB is considered to be very useful for prurigo (55,56).

Studies have shown the short-term efficacy of NB-UVB in the treatment of parapsoriasis (57,58).

HV is a rare, chronic photodermatosis of unknown origin that can occur in childhood (2). It is frequently associated with Epstein-Barr infection (2). Among oral antimalarials, such as hydroxychloroquine, and oral antioxidants, such as β -carotene, phototherapy NB-UVB or PUVA may be considered (59,60).

SPD is a rare neutrophilic dermatosis with a largely unknown etiology. PUVA, BB-UVB and NB-UVB alone or in combination with dapsone and/or retinoids can be efficient (61-63).

Scleredema is a rare form of disease characterized by excessive mucin deposits among the collagen fibers in the dermis, which determines the skin induration (64-67). Among the therapies used in this condition (systemic steroids, cyclosporine, methotrexate, high-dose penicillin, penicillamine, electron beam, and glycemic control with prostaglandin E1), UVA, PUVA and NB-UVB may be associated with good results, but most authors prefer UVA and PUVA for this condition as UVA radiation penetrates more deeply into the dermis, while UVB radiation reaches the epidermis and the upper dermis (68-76).

7. Side effects and complications

Phototherapy is associated with a series of side effects. Short-term side effects include: i) Erythema; ii) xerosis; iii) pruritus; iv) skin hyperpigmentation; v) blistering; vi) worsening skin disease; and v) photoconjunctivitis or photokeratitis (eye protection is mandatory). The long-term side effects include: i) Photoaging, such as wrinkling, freckling, xerosis, telangiectasia, elastosis and atrophy; and ii) photocarcinogenesis, such as actinic keratoses, squamous cell carcinoma, basal cell carcinoma, melanoma, genital skin cancer [the risk of which is very high (x286), especially after PUVA phototherapy, which is why shields are mandatory] and cataracts (77).

8. Contraindications

The contraindications for phototherapy, according to Coelho and Apetato (77) and Krutmann *et al* (78), are as follows: i) Systemic diseases with a photosensitive component, such as systemic lupus erythematosus or dermatomyositis; ii) photodermatoses, such as xeroderma pigmentosum and basal cell nevus syndrome; iii) Fitzpatrick skin type 1 and 2 (PUVA phototherapy); iv) past excessive exposure to natural sun light or phototherapy; v) immunosuppressive medication; vi) photosensitizing creams or medication; vii) past skin cancer, especially melanoma; viii) pregnancy and breastfeeding (PUVA); ix) immobility or inability to stand unassisted for ≥ 10 min; and x) congenital erythropoietic porphyria, or a family history of porphyria.

9. Conclusions

Overall, phototherapy is a useful therapeutic method in the management of numerous dermatological maladies and lately it is starting to gain widespread acceptance. The studied articles

demonstrated that NB-UVB seems to be the best alternative for psoriasis vulgaris, vitiligo, lichen planus, chronic eczema and annular granuloma, while PUVA phototherapy is useful for localized scleroderma (UVA 1 sessions can also be performed), psoriasis vulgaris (the remission rate is similar to the rate after NB-UVB phototherapy), vitiligo (NB-UVB is preferred), cutaneous T cell lymphoma (another alternative is NB-UVB, but it is associated with poorer results) and acute atopic dermatitis. As long as the protocols and treatment guidelines are followed, favorable results should be obtained and the potential risk of side effects will be minimized. Most of the dermatological conditions listed above have a significant remission rate after a variable number of phototherapy sessions, which is why this therapeutic method should be taken into consideration more often.

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DEB, DCB and MPT contributed to the study design, participated in the entire review process and prepared the manuscript. DSD, DCB, ACN and IB contributed to collecting the relevant literature and critical interpretation. ACN, IB, CMB, GB, AD, NA and EAP conceived the concept of the review and modified the manuscript. All authors have read and approved the final manuscript. Data authentication is not applicable.

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Competing interests

The authors declare that they have no competing interests.

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