Phototherapy: A Review of the Literature
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Abstract
As patient awareness regarding ultraviolet (UV) damage and skin-cancer prevention increases, phototherapy is increasingly being challenged as a treatment choice. While phototherapy, like any form of treatment, carries some risks, recent studies show it to be effective in treating a variety of cutaneous disorders with minimal adverse effects. It is an important treatment modality to consider along with other options. This article reviews types of UV light, their mechanisms in treating cutaneous disease, and considerations involved in developing a risk/benefit analysis for UV treatment.

Introduction
With the public's growing access to credible, anecdotal and speculative online sources, patients may learn and inquire about phototherapy as a treatment option. This presents a good opportunity to discuss phototherapy as a treatment modality. This article provides a brief review of recent literature regarding the safety and efficacy of specific light-treatment modalities.

Phototherapy, as used in current practice, involves the application of either UVA or UVB wavelengths of light. This can be further subdivided into psoralen + UVA (PUVA), narrow-band UVB (NB UVB) and broad-band UVB (BB UVB). It is important to understand the mechanism involved in each indicated disease when considering its corresponding therapy modality.

UVB consists of wavelengths between 290 nanometers (nm) and 320 nm. Use of this span is considered broad-band treatment. Narrow-band UVB consists of wavelengths between 311 nm and 313 nm. UVB selectively penetrates the epidermis and upper papillary dermis,1 making it most effective in diseases affecting the superficial layers of the skin. UVA wavelengths are longer, between 320 nm and 400 nm, and penetrate deeper into the skin, influencing tissues down to the dermis and subcutaneous fat layer. UVA therapy can affect fibroblasts, mast cells and vascular epithelium, making it a better treatment option for pathologies in deeper layers, such as sclerosing conditions.2,3

Both UVA and UVB inhibit Langerhans cells, antigen-presenting cells of the skin, decreasing the immune response.4,5 Additionally, UVB causes immunosuppression by inducing apoptosis of T cells, a beneficial response in conditions such as eczema. Another benefit of UVB is its ability to decrease replication of keratinocytes.6-8

Phototherapy offers a relatively safe treatment option. Benefits include avoidance of long-term use of potent corticosteroids, immunosuppressive medications and other systemic treatments.9 Furthermore, UVB treatment provides patients the option of purchasing home treatment units, which can be used under medical supervision. Recent studies have focused on the efficacy of light treatments among various cutaneous diseases (Table 1). Studies have also compared the efficacies of UVA and UVB treatments.

Discussion
Artificial UV light was labeled carcinogenic to humans by the World Health Organization in 2009.10 While an increased risk of skin cancer is a potential adverse effect, the risk varies directly with total dose, and many treatments require low total doses of UV radiation.2 A review of the literature published by Archier et al. found an increased risk for basal cell carcinoma in patients receiving more than 100 PUVA treatment sessions and an increased risk for squamous cell carcinoma that increased linearly with the number of sessions.11 The risk of non-melanoma skin cancer was greatest for squamous cell carcinoma, particularly if exposed to high doses (> 200 sessions or > 2000 J/cm²). Furthermore, incidence of melanoma increased with ≥ 200 PUVA treatments. Therefore, it is important to limit the number of treatment sessions to the minimum necessary to treat the disease. Archier et al. listed guideline recommendations of a maximum cumulative UVA dose of 150 J/cm² per session, no more than 30 treatment sessions per year and a lifetime maximum cumulative UVA dose of 1200 J/cm² to 1500 J/cm².2,11 In addition, specific wavelengths of UV-light devices are carefully regulated. Hearn et al. analyzed the long-term carcinogenic risk in patients receiving NB UVB treatment.12 Among 3,867 patients with a median treatment number of 29, and 352 patients receiving ≥ 100 treatments, no association between NB UVB exposure and any form of skin cancer was found. This was confirmed by Archier et al. and Lee et al., who also found no increased risk of skin cancer with NB UVB treatments.13,14 Menter has identified additional potential adverse effects.2 Acute adverse effects of BB UVB include erythema, itching, burning and stinging. Herpes simplex virus reactivations may occur due to immunosuppressive effects. Long-term adverse effects include premature aging, wrinkles, lentigines and telangiectasias. Cataract formation is another potential adverse effect; use of eye protection is important for prevention.

UVA toxicities include pruritus, erythema, irregular pigmentation and blisters. Lentigines, hypertrichosis and dark macules may also develop.14 Psoralen, used as a photosensitizing agent to enhance the effects of UVA, is an oral medication and has systemic effects including GI disturbance, nausea and, potentially, hepatotoxicity. The adverse effects of psoralen have led researchers to study the efficacy of UVB as a potential alternative to PUVA. Researchers have established a dose-related increase in squamous cell carcinoma, particularly of the male genitalia, and a shield should be used.15-17 Drug interactions include photosensitizing agents such as NSAID's, diuretics, antifungals, tetracyclines and fluorouracil.18 The most common adverse effect is erythema, and each session should be closely monitored for any sign of erythema or burn. If this occurs, treatment should be postponed long enough for the skin to heal. Therapy can then be continued at a lower dose.19

Important considerations in choosing phototherapy treatment include a patient's dermatological history, family history and current medications. Contraindications to phototherapy include a history of xeroderma pigmentosa and/or lupus erythematosus. Relative contraindications include personal or family history of skin cancer and current use of photosensitizing agents.20

Psoriasis
Light therapy was approved for the treatment of psoriasis in 1982, with PUVA as the initial treatment modality.1 However, in a study done by Alsins et al., a wavelength of 313 nm (NB UVB) was found to be the most efficacious in clearing psoriasis.20 It is typically used for severe plaque psoriasis resistant to other treatments and covering a large body surface area (BSA). Patients with debilitating BSA involvement, such as the solar surfaces of the hands and feet, could benefit from light therapy, as well. Involvement may be a small percentage of BSA but have significant impact on quality of life and functionality.

Dose depends on the type of UV used. In a study done by Menter et al., initial NB UVB doses were based on skin type and started with a range of 130 mJ/cm² to 400 mJ/cm², or 50% of individual established MED.2 This was increased by 15 mJ/cm² to 65 mJ/cm², or less than 10% of initial MED, at each subsequent treatment. Median response time was eight to 10 treatments at a frequency of two to five treatments per week. After 15 to 30 maintenance treatments, 38% of patients were in remission after one year. With BB UVB, only 5% of subjects were in remission at one year. However, BB UVB did eliciting quicker initial improvement, within just four weeks. BB UVB achieved complete clearance with a median of 20 to 25 treatments at a frequency of three to five treatments per week.

In PUVA studies utilizing two to three times per week, improvements were seen within one month and a total course of 20 to 25 treatments. Remission time was three to 12 months.2 NB UVB and PUVA have been found to have similar efficacy, though it is important to consider the adverse effects of PUVA, such as GI disturbance and potential hepatotoxicity.20-24

Phototherapy for severe or debilitating plaque psoriasis avoids the need for biologics and other immunosuppressive and expensive treatments.

Table 1

<table>
<thead>
<tr>
<th>Condition</th>
<th>UVA</th>
<th>UVB</th>
</tr>
</thead>
<tbody>
<tr>
<td>Psoriasis</td>
<td>50% - 65%</td>
<td>70% - 80%</td>
</tr>
<tr>
<td>Eczema</td>
<td>40% - 50%</td>
<td>50% - 60%</td>
</tr>
<tr>
<td>Vitiligo</td>
<td>20% - 30%</td>
<td>30% - 40%</td>
</tr>
<tr>
<td>Actinic keratosis</td>
<td>10% - 20%</td>
<td>20% - 30%</td>
</tr>
<tr>
<td>Seborrheic keratosis</td>
<td>10% - 20%</td>
<td>20% - 30%</td>
</tr>
<tr>
<td>Lichen planus</td>
<td>10% - 20%</td>
<td>20% - 30%</td>
</tr>
<tr>
<td>Solar keratosis</td>
<td>10% - 20%</td>
<td>20% - 30%</td>
</tr>
<tr>
<td>Lichen nitidus</td>
<td>10% - 20%</td>
<td>20% - 30%</td>
</tr>
<tr>
<td>Mycosis follicularis</td>
<td>10% - 20%</td>
<td>20% - 30%</td>
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</tbody>
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of 15 patients using a UVA dose of 20 mJ/cm² and is readily available. El-Mofty et al. did a study which consists of wavelengths of 340 nm to 400 nm. UVA1 is not readily available, however, so its use is of limited use clinically. The full span of UVA wavelengths allows for deeper penetration.4

Most studies on light therapy for morphea, a localized form of scleroderma, have used UVA1, which consists of wavelengths of 340 nm to 400 nm. UVA1 is not readily available, however, so it’s of limited use clinically. The full span of UVA wavelengths has also been shown to be efficacious for deeper penetration.3

### Sclerotic Conditions

As discussed earlier, UVA has the greatest effect on the deeper layers of skin affected by sclerotic conditions. UVB may also be considered. Both UVA and UVB have been found to inhibit collagen production and increase the breakdown of collagen. When considering UVB, BB has superior effects to NB, as the longer wavelength allows for deeper penetration.3

PUVA therapy was also shown to decrease skin thickness in scleroderma, as well as increase joint passive range of motion, skin temperature and elasticity. In a study done by Usmani et al., 91.7% of subjects responded well with a median of 24 treatments.26 This resulted in a mean 27% change in MRSS. It was found to work best in active, progressive sclerosing disease.

Vitiligo

A vitiligo study treated 70 patients twice a week with NB UVB. These patients had > 5% total BSA involvement, and 92.7% had new onset of lesions within the past year.27 Of those patients with lesions on the face, 34.4% achieved > 75% repigmentation, greatest in patients with Fitzpatrick skin types III-V. Only 7.4% of patients with other affected areas had this level of response. The greatest improvement occurred with lesions of the face in darker-skinned individuals (skin types III-V), and those who responded within the first month of treatment were the most likely to achieve a better response. Patients with darker skin types also experienced increased hyperpigmentation due to therapy. Results were seen in a mean time of six months for facial lesions and nine months for body lesions. Perioral regions were found to have less improvement than the rest of the face. Hands and feet had little to no repigmentation, and elbows and knees responded only slightly better. Stable repigmentation was found in 14.3% of patients at four-year follow-up. The only reported adverse effect was painful erythema. The findings suggest patients with darker skin and facial lesions that respond within one to two months of treatment are the most likely to achieve cosmetically acceptable responses, and lesions that fail to improve within two months may require alternative therapy.

**Table 1. Efficacy of phototherapy in various disease entities**

<table>
<thead>
<tr>
<th>Disease</th>
<th>Indications</th>
<th>NB UVB</th>
<th>BB UVB</th>
<th>PUVA</th>
<th>UVA-1</th>
<th>BB UVA</th>
</tr>
</thead>
<tbody>
<tr>
<td>Psoriasis</td>
<td>Cases resistant to other treatments, large BSA, debilitating BSA involvement</td>
<td>Most effective in clearing psoriasis; prolongs remission</td>
<td>Improvement within 1 month</td>
<td>Improvement within 1 month</td>
<td>Decrease in skin thickness; increase in joint passive range of motion</td>
<td>Decreased skin thickness after 20 treatments</td>
</tr>
<tr>
<td>Sclerotic Conditions</td>
<td>New lesions with active inflammation</td>
<td>Most effective than NB UVB</td>
<td>Increase in skin thickness; increase in joint passive range of motion</td>
<td>Greater clinical improvement compared to NB UVB in 1 study</td>
<td></td>
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<tr>
<td>Vitiligo</td>
<td>Darker-skinned patients, facial lesions</td>
<td>Greatest improvement and color match among repigmented areas</td>
<td></td>
<td></td>
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<td></td>
</tr>
<tr>
<td>Solar Urticaria</td>
<td>UV sensitivity</td>
<td>Initial treatment of choice</td>
<td>Indicated in unresponsive cases</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Generalized Cutaneous Lichen Planus</td>
<td>Similar efficacy to BB UVB</td>
<td>Similar efficacy to BB UVB</td>
<td></td>
<td></td>
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<td></td>
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<tr>
<td>Erosive Oral Lichen Planus</td>
<td>Treatment of choice</td>
<td></td>
<td></td>
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<tr>
<td>Chronic Vesicular Hand Eczema</td>
<td>Long-term steroid sparing treatment</td>
<td>Most effective for chronic disease</td>
<td>Most effective for acute disease</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Atopic Dermatitis</td>
<td>Long-term steroid sparing treatment</td>
<td>Most effective for chronic disease</td>
<td>Most effective for chronic disease</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cutaneous T-cell lymphoma</td>
<td>Early stage, patch and plaque disease</td>
<td>Effective at inducing prolonged remission, especially in patch stage disease</td>
<td>Most useful in plaque-stage disease</td>
<td>Effective at inducing remission</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Acute Graft-versus-Host Disease</td>
<td>Cutaneous-only disease or well-controlled systemic disease</td>
<td>Effective as initial treatment</td>
<td>Useful in cases unresponsive to NB UVB</td>
<td></td>
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<tr>
<td>Pruritus</td>
<td>Significantly reduces pruritus intensity</td>
<td>Reduces eosinophilic folliculitis in HIV patients</td>
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</tbody>
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**PHOTOTHERAPY: A REVIEW OF THE LITERATURE**
was excellent in all subjects in the NB UVB group, compared to 44% of subjects in the PUVA group. Effects of NB UVB treatment were maintained even 12 months after cessation of therapy.

El-Mofty et al. studied NB UVB vs. BB UVA in 40 patients with bilateral symmetrical vitiligo affecting more than 30% BSA, conducting 48 treatment sessions over a course of 16 weeks.29 The majority of patients had Fitzpatrick skin types III and IV. The study found a significantly higher clinical improvement with BB UVA treatment compared to NB UVB treatment, at 63.83% and 44.32%, respectively.

Solar Urticaria

In solar urticaria, UVB, UVA, and the visible-light spectrum (400 nm to 700 nm) can initiate an urticarial response. Desensitizing treatments using NB UVB have been studied.30 Calzavara-Pinton et al. looked at 10 patients with solar urticaria described as severe.19 They established a minimal urticarial dose, or MUD, for each patient. Subjects were then exposed to NB UVB over the course of one month, with oral antihistamines prescribed for the first week of treatment. Subjects received five once-daily exposures over the first week, followed by three once-daily exposures per week for three weeks. Treatments began at 50% MUD, and doses were increased by 10% MUD at each treatment. The median number of exposures was 25.5. After four weeks of treatment, patients were encouraged to expose themselves to noontime sun for 20 minutes to 30 minutes per day at least two to three times per week during the spring and summer months. PUVA and antihistamines were used in unresponsive cases.19 At one-month follow-up, patients’ light thresholds had increased. Relapses occurred in 20% of patients at both one-month and three-month follow-ups.

Generalized Cutaneous Lichen Planus

Pavlotsky et al. conducted a retrospective study of 50 patients with generalized, cutaneous lichen planus.30 Both NB UVB and BB UVB were studied, with complete response in 70% of cases. After a median of 34.7 months, 85% of those who achieved complete response were still in remission.

Erosive Oral Lichen Planus

Phototherapy is indicated not only for disease affecting a large portion of BSA, but also for localized disease. A study done by Kassem et al. applied BB UVB radiation to affected areas three times per week for six weeks.31 The dose was increased every other session. Maintenance therapy was given for up to 29 weeks using the same dose as the dose in week 8. Improvement of > 80% and/or no symptoms was achieved in 64% of cases after a median of six weeks. Partial response was seen in 36%, defined by 50% to 80% improvement and/or mild symptoms at week 8. Maintenance therapy was given to 89% of those participating. Of these patients, 50% were without recurrence at 45-week follow-up, while 50% experienced recurrence within six weeks of discontinuing maintenance therapy. Continuous monitoring of the skin and mucous membranes is important, particularly for areas exposed to UV irradiation, as evidenced by the development of a dysplastic lesion in one of the subjects. The lesion was surgically removed, and phototherapy was discontinued. While evidence was inconclusive, the authors believed the lesion was not caused by the UVB treatments.31

Chronic Vesicular Hand Eczema

Eczema is a form of atopic dermatitis resulting from type IV hypersensitivity. Type IV hypersensitivity is caused by a T-cell reaction in the skin. UV irradiation inhibits T-cell activity in the skin and therefore may present a good treatment option for this disease.

Hanif Said et al. compared UVA1 therapy to betamethasone valerate 0.1% cream.32 Treatments were given three times a week for six weeks, and improvement was assessed using the Dyshidrotic Area and Severity Index (DASI). DASI assesses the severity of eczema based on the number of vesicles/cm², erythema, pruritus, and the extension of the affected area.33 No significant difference was found between the two therapies; however, UV irradiation was found to significantly reduce pruritus when compared with the steroid cream.

Atopic Dermatitis

AD is a chronic skin condition usually characterized by severe pruritus. Typically, acute exacerbations are treated with topical corticosteroids; however, phototherapy offers a well-tolerated and effective steroid-sparing treatment.

Acute Graft-versus-Host Disease (aGvHD)

Acute cutaneous graft-versus-host disease is typically treated with a potent topical steroid.46 However, recent studies have looked to determine the effectiveness of UV therapy and its potential benefits, such as reducing the use of potent steroids. Eligible patients are those with cutaneous disease only or systemic disease under good control, as well as patients initially treated with but refractory to steroids. Steroid-refractory disease is defined as an increase by one stage following 48 hours of treatment or no improvement after four total days of treatment. Stage is determined by BSA involvement: < 25% is stage 1; 25% to 50% is stage 2; and > 50% is stage 3. Bullae formation indicates stage 4 disease.

Feldstein et al. studied patients post allogeneic bone marrow transplant, peripheral blood stem cell transplant or cord blood transplant.7 Half of the patients had organ involvement. NB UVB (311 nm) was administered at a starting dose of 70% MED, with a 10% dose increase at each treatment. Skin types I and II received treatments twice per week, while those with skin types III-V received treatments three times per week. The median number of treatments was 15. Steroid doses were reduced in 76.9% of patients. Fifty-seven percent of patients achieved complete response; 21% achieved remission. Reports indicate complete remission is achieved with NB UVB in 54% to 91% of cases. Elcin et al. studied 31 patients and saw a relapse in 35.5% of cases within a mean of 28.8 months (range of four to 59 months).40 Furthermore, 64.5% of patients remained relapse-free for a mean of 54.2 months, indicating NB UVB may induce low relapse rates and long relapse-free intervals in early MF. A higher efficacy is noted when treating patch-type MF compared with plaque disease. NB UVB is especially useful in hypopigmented MF.44

PUVA therapy is typically given three times per week until remission is achieved.42 Studies report a complete response in up to 71% of patients.31 In one study, 83% of patch-stage subjects achieved remission, while none of the patients with plaque-stage disease achieved remission.44 Whereas NB UVB has been found useful as a maintenance treatment, PUVA maintenance has not been shown to prevent future relapse and thus is not recommended.41 In a study of patients with early-stage MF, 95 were treated with PUVA and 19 were treated with NB UVB. Results showed that 62% of patients in the PUVA group achieved complete response, while 63% of those treated with NB UVB achieved complete response. These findings suggest that NB UVB is at least as effective as PUVA in treating early-stage disease; however, larger studies are needed to support these results.46

To avoid the side effects of psorales, UVA1 was studied in four patients with early-stage MF. Complete clinical remission was seen in all patients within 29 to 40 treatment sessions. It was determined that UVA1 is a potential option not only for maintenance therapy but also to induce remission.47 To maintain remission, maintenance therapy can be gradually reduced to intervals of four to six weeks. Complete remission has been achieved in up to 71.4% of patients with early-stage MF and may last 10 years or longer.39
Pruritus

In addition to cutaneous diseases, phototherapy has been well-documented as reducing pruritus. Pruritus is a common symptom among a variety of disorders and severely affects quality of life, leading to such things as sleep deprivation and depression. Pruritus has several different etiologies, including histamine release and circulation of bile salts, among others. Phototherapy has been used to treat several pruritus-inducing conditions, including chronic renal failure, HIV, polycythemia vera and chronic liver disease. In particular, UVB has been found to induce apoptosis within dermal mast cells and decrease production of pruritogenic cytokines. Additionally, it reduces the size of epidermal nerve fibers and substance P release, which are associated with itch. This type of therapy may offer relief without the side effects of systemic medications, and antipruritic effects may last anywhere from one month to more than one year. Patients generally require only short durations of therapy, so chronic phototherapy side effects are uncommon.

In pruritus resulting from renal failure, neither hemodialysis nor antihistamines has proved effective in reducing itching. BB UVB has been found effective, however. Additionally, it works on a systemic level, as exposure to just one half of the body has resulted in improvements in both exposed and unexposed sites. In one study utilizing NB UVB for 20 uremia patients, subjects received treatments three times per week at a starting dose of 200 mJ/cm², 300 mJ/cm² or 400 mJ/cm², depending on skin type, with the dose increased by 100 mJ/cm² at each session. After six weeks, researchers found a significant reduction in pruritus intensity in 70.8% of subjects.

Patients with HIV may experience pruritus secondary to a variety of diseases, but they can also experience primary pruritus. HIV-positive patients with eosinophilic folliculitis have been treated with BB UVB to relieve pruritus; however, relapse is common, and maintenance treatments are often necessary for continued relief. Pruritic papular eruption is frequently observed in HIV-positive patients, and although it generally improves with antiretroviral therapy, improvement may take several months. In the interim, patients may benefit from the symptomatic treatment of their pruritus with NB UVB.

Sixty percent of polycythemia vera patients report symptoms of itching, most severe after bathing. Sixty percent of polycythemia vera patients report pruritus with NB UVB. Benefit from the symptomatic treatment of their antiretroviral therapy, improvement may take months to more than one year. Patients generally require only short durations of therapy, so chronic phototherapy side effects are uncommon.

NB UVB has also been successful in treating pruritus related to lichen simplex chronicus, prurigo nodularis and pruritic folliculitis of pregnancy. Pruritus resulting from both severe seborrheic dermatitis and skin infiltration of breast cancer has been successfully treated with NB UVB administered two to three times per week.

Conclusion

There are many important factors involved in choosing a therapy option. Besides a risk/benefit analysis, patients may not have the time available for frequent treatments, or treatment locations may not be conveniently accessible. Phototherapy is a widely available and efficacious treatment for many cutaneous diseases. Due to the undesirable effects of oral psoralen and the similar efficacies of NB UVB and PUVA, NB UVB has become a more popular treatment choice. Maintenance therapy requirements and the likelihood of patient response should also be considered. Lastly, it is always important to monitor patients undergoing phototherapy for side effects and perform frequent skin checks, even after discontinuing treatment.

References


