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## REVIEW

# Phototherapy with Narrowband vs Broadband UVB

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**Phototherapy with ultraviolet (UV) radiation of wavelengths between 280 and 320 nm (UVB) is a safe and effective treatment for a variety of diseases. In addition to standard broadband UVB (bUVB), narrowband phototherapy with fluorescent bulbs emitting near monochromatic UV around 311 nm (nUVB) has become an important treatment for diseases such as psoriasis, atopic dermatitis and vitiligo. In addition to these indications, the number of diseases for which nUVB phototherapy is reported to be effective is continuously growing. The differential effects of nUVB phototherapy in comparison to other UV wavelengths as well as established and new indications for this treatment modality are reviewed.** *Key words: broadband UVB; narrowband UVB; phototherapy; psoriasis; skin cancer; ultraviolet light.*

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While it has been known for more than 2000 years that several skin diseases improve upon exposure to the sun (heliotherapy), the systematic investigation of photo-therapeutic modalities did not start until the beginning of the twentieth century. In 1903, Niels Finsen received the Nobel Prize for developing phototherapy as a treatment for tuberculosis of the skin and 23 years later Goeckerman (1) showed the beneficial effect of natural sunlight in combination with tar for psoriasis vulgaris. In 1953, Ingram (2) initiated the combination of UVB radiation, dithranol and tar-bathing for psoriasis (2). Data from Fischer & Alsins (3) and Parrish & Jaenicke (4) subsequently showed that wavelengths around 311 nm provoke fewest erythema while being most effective for clearing psoriasis. According to these results a fluorescent bulb was developed (TL-01), emitting a major peak at 311 ($\pm$ 2 nm) and a minor peak at 305 nm. This treatment was later called narrowband UVB (nUVB) and following its introduction several studies were published on its superior efficacy in phototherapy of psoriasis (5–7).

## PHOTOBIOLOGY

### Interaction between UV radiation and the skin

UV radiation that reaches the skin is either reflected or absorbed by structures of the skin. While UVC ($<$ 280 nm) is mostly absorbed in the stratum corneum, UVA (320–400 nm) shows deeper penetration than UVB (280–320 nm) (8–12). Thus, UVB is mainly absorbed by epidermal components including keratino-cytes, melanin and Langerhans' cells (13). Biological effects of UV radiation are generated through interac-tion with absorbing molecules called chromophores. In the case of UVB, the most important chromophores are proteins such as keratin, melanin, collagen and elastin, urocanic acid and DNA (14–16). Ultimately, the interaction of UV with chromophores can lead to a multitude of effects such as induction of oxidative stress and activation of transcription factors, as well as induction of damage to the cell membrane and DNA mutations.

### Induction of DNA damage

UVB radiation leads directly to the generation of pre-mutagenic lesions, so-called photoproducts. Among others, the most prevalent photoproducts induced by UV are cyclobutane pyrimidine dimers (CPD), pyrimidin-(6-4)-photoproducts (6-4PP) and Dewar isomers. Normally these lesions are repaired by a highly conserved repair mechanism called nucleotide excision repair (NER). This mechanism acts in a tightly regulated fashion including recognition and processing of DNA damage, unwinding of DNA by helicases, excision of the damage-containing fragment and re-synthesis by DNA polymerase (17). If UVB-induced lesions are not repaired, C$\rightarrow$T and CC$\rightarrow$TT transitions can occur as DNA mutations (18) representing initial events of multi-step carcinogenesis. These mutations are char-acteristic for UV exposure in potentially relevant genes such as tumour suppressor genes or oncogenes (19). The fact that defective NER in the autosomal recessive disease xeroderma pigmentosum is associated with a strong increase of DNA mutations, photosensitivity and development of skin cancer further underscores the central role of DNA damage and its repair in the process of multi-step photocarcinogenesis (20, 21).

### UV radiation and its effects on the immune system

UV radiation alters immunological function (22) and UVB can increase the production of pro-inflammatory substances like prostaglandins (PG) or tumour necrosis factor (TNF), as well as the production of anti-inflammatory factors like interleukin (IL)-10,

α-melanocyte stimulating hormone (MSH) and PGE2. UVB down-regulates the expression of intercellular adhesion molecule (ICAM)-1 (13). With regard to wavelength, reduction of the density and function of Langerhans' cells in the skin and their migration to the draining lymph nodes is more pronounced with bUVB than with nUVB (23). Infiltrating epidermal T cells as well as mast cells are susceptible to UVB-induced apoptosis (24–26) and depletion of T lymphocytes from psoriatic lesions seems to be greater after nUVB than after bUVB irradiation (27). Moreover, nUVB appears to have a more immunosuppressive effect than bUVB on natural killer cell activity, cytokine responses and lymphoproliferative responses of peripheral blood mononuclear cells (23, 28) and photo-isomerization of trans- to cis-urocanic acid is more effective with nUVB than with bUVB (23), with urocanic acid photoconversion being mainly induced by wavelengths between 310 and 340 nm (29). Therefore, the immunomodulatory effects of nUVB appear to be more pronounced than bUVB.

nUVB suppresses the production of interferon (INF)-γ, IL-2 and IL-12 and increases that of IL-4 and IL-10, which together could account for a shift of the immune response in the direction of T-helper (Th)2-like responses (30–32). The shift from an IFN-γ-dominated Th1 to an IL-4 dominated Th2 response appears to be one of the major factors determining the therapeutic efficacy of nUVB phototherapy as well as that of many systemic treatments such as IL-4 (33), not altering plasma antibody concentrations (34).

In the case of psoriasis, nUVB seems to clear plaques through local rather than systemic effects, as unexposed plaques cleared significantly less than directly exposed plaques (35). However, it has also been hypothesized that clearing of psoriasis is a combination of local and systemic effects (36).

## INDICATIONS FOR NARROWBAND UVB

Phototherapy with bUVB or nUVB has been reported to be effective and safe for the treatment of a large number of skin diseases. In addition to psoriasis, atopic dermatitis (AD) and vitiligo, various other skin diseases can be treated successfully with nUVB phototherapy, like parapsoriasis, initial mycosis fungoides (MF), graft-versus-host disease and pruritus, as well as acquired perforating dermatosis, lichen planus, lichen simplex chronicus, lymphomatoid papulosis, generalized granuloma anulare, nummular dermatitis, pityriasis lichenoides chronica, pityriasis rosea, pityriasis rubra pilaris, pruritic folliculitis of pregnancy, seborrhoeic dermatitis, Schnitzler's syndrome and Sneddon-Wilkinson disease (as reviewed in refs 37, 38). Table I depicts newer studies reporting efficacy and possible combinations of nUVB phototherapy with other treatment modalities.

The most important indications will be discussed in detail below.

*Psoriasis*

*Monotherapy with nUVB.* According to Feldman et al. (39), with regard to efficacy, safety and cost-effectiveness, UVB phototherapy appears to be the best first-line treatment for the control of generalized psoriasis and there is a large body of evidence indicating that nUVB is more effective than bUVB as a monotherapeutic agent in the treatment of psoriasis even in children (5, 40–42). Whereas bUVB is considered to be most effective close to the minimal erythema dose (MED), nUVB has also been shown to be effective in sub-erythemogenic doses (27). However, Diffey (43) could show in a mathematical model that clearance of psoriasis plaques is achieved faster with higher MED rates.

Furthermore, nUVB has been shown to be more effective than bath-PUVA with trimethoxsalen (41, 44), and according to some studies it was as effective as systemic PUVA therapy (45–47), although this evaluation was dependent on the type of psoriasis. In a study by van Weelden et al. (46), the therapeutic result differed depending on the treated body site, with lesions on the trunk responding better to nUVB and lesions on the extremities responding better to PUVA. Other studies showed that PUVA is more effective for psoriasis than nUVB alone (48) and systemic PUVA remains an important therapeutic modality for patients with high PASI scores, especially those who do not respond adequately to nUVB.

For treatment of psoriasis with nUVB, three rather than two or five radiations a week are effective (49, 50) and low incremental regimens are sufficient according to Wainwright et al. (51), who showed this regimen to be as effective as high incremental regimens but less erythemogenic.

*Combination therapies for psoriasis.* In order to reduce cumulative UV doses and to enhance clearance of psoriasis lesions, combination therapies with topical as well as systemic agents have been established:

*nUVB plus dithranol (Ingram):* In many studies the efficacy of dithranol combined with UVB (broadband or narrowband) could be shown (7, 52, 53). As dithranol is difficult to handle, this therapy is mainly reserved for hospital settings.

*UVB plus vitamin D3 analogues:* Vitamin D3 analogues inhibit proliferation, induce terminal differentiation of human keratinocytes and exhibit immunomodulating properties (54). Several studies showed that calcipotriol as well as calcitriol and tacalcitol are efficacious, safe and can be used on a long-term basis for psoriasis (55–58). Vitamin D3 analogues, when used after nUVB irradiation, reduce the nUVB dose necessary.

Table I. *Recent studies (published since 1999) involving narrowband UVB (nUVB) shown with regard to patient number (n), study design and response rate (in some cases descriptive values in results have been calculated from the studies original data to facilitate comparison between studies)*

| Study (Ref No.) | Therapy regimen | Study design (*n*) | Response | Remarks |
|---|---|---|---|---|
| *Psoriasis* | | | | |
| Pasic (42) | nUVB | Open trial (20) | ≥90% PASI reduction: 45% | Children |
| Gordon (48) | nUVB vs PUVA | Randomized (100) | 84% (PUVA), 63% (nUVB); 6 month remission: 35% (PUVA), 12% (nUVB) | |
| Tanew (45) | nUVB vs PUVA | Half-side, open, non-randomized (25) | PASI reduction: 84% (nUVB); 89% (PUVA) | No significant differences |
| Dawe (41) | nUVB vs TMP-bath-PUVA | Half-side, randomized, observer-blinded (10) | 100% (nUVB), 70% (bath-PUVA) | |
| Snellman (44) | nUVB vs TMP-bath-PUVA | Half-side, randomized (18) | PASI reduction: 77% (nUVB); 45% (bath-PUVA) | |
| Markham (47) | nUVB vs bath-PUVA | Open, randomized, controlled (54) | Treatments to clear: 25; days to clear: 67 (nUVB), 66 (PUVA) | Remission: no difference |
| Calzavara-Pinton (85) | nUVB+bath-PUVA | Half-side, open (12) | PASI reduction: 67.8% (nUVB), 92.4% (PUVA) | |
| Schiffner (75) | nUVB+Dead Sea salt | Multicentre (280) | 71.4% improvement | |
| Carrozza (52) | nUVB+dithranol | Open pilot (13) | PASI reduction: 83.9 ± 15.6% | |
| Woo (59) | nUVB+calcipotriol | Prospective, randomized, controlled (50) | Significant higher PASI reduction with calcipotriol | |
| Rim (61) | nUVB+calcipotriol | Randomized (28) | >95% response: 90.0% (with calcipotriol), 61.1% (no calcipotriol) | |
| Hofmann (66) | nUVB+dithranol vs calcitriol | Half-side, controlled (10) | CR: 100% both groups | PASI only on arms |
| Behrens (68) | nUVB+tazarotene | Half-side, open (10) | PASI reduction 48% (nUVB): 64% (nUVB/tazarotene), | |
| Schiener (71) | nUVB+calcipotriol vs tazarotene | Half-side (10) | CR: after 19 treatments on both sides | No difference |
| Messer (65) | nUVB+tacalcitol | Half-side (24) | >50% response: 38% (tacalcitol) 86% (tacalcitol/nUVB), | After 6 weeks equal response |
| Spuls (77) | nUVB+acitretin | Retrospective (40) | >75% response: 72.5% | Recalcitrant psoriasis |
| *Atopic dermatitis* | | | | |
| Pasic (42) | nUVB+UVA | Open trial (21) | ≥90% SCORAD reduction: 45.4%; 70–90% reduction: 22.7% | Children |
| Hudson-Peacock (87) | nUVB | Open trial (37) | Response: 81%; CR: 43%, | |
| Reynolds (89) | nUVB vs UVA vs visible light | Randomized, controlled (72) | Reduction of activity: 83% (nUVB), 47% (UVA), 47% (Visible light) | |
| Hjerppe (148) | nUVB vs bUVB/UVA | Half-side (10) | Pruritus reduction: significant effect of nUVB | No difference in SCORAD |
| Legat (90) | nUVB vs UVA1 | Half-side, open (9) | Reduction of Costa and Leister score: 40% and 50% (nUVB), 33% and 30% (UVA1); pruritus: 67% (nUVB), 34% (UVA1) | |
| Der-Petrossian (88) | nUVB vs bath-PUVA | Half-side, randomized, investigator-blinded (12) | SCORAD reduction: 65.7% (bath-PUVA), 64.1% (nUVB) | |
| Brazzelli (91) | Cyclosporin A followed by nUVB | Open trial (7) | SCORAD: 63.3% (CsA); relapses treated with nUVB led to further SCORAD-reduction (total 59.9%) | |
| *Mycosis fungoides (MF) and parapsoriasis* | | | | |
| Gathers (93) | nUVB | Retrospective (24) | CR: 54.2%; PR: 29.2%; 30% of CR relapse after 12.5 weeks | Stage IA, IB |
| Clark (96) | nUVB | Open trial (8) | CR: 75%; relapse after 20 months | Patch-stage MF; |
| Hofer (92) | nUVB | Open trial (20) | CR: 95%; relapses: 100% within a mean of 6 months | SPP and early-stage MF |
| Diederen (94) | nUVB vs PUVA | Retrospective (56) | CR: 81% (nUVB), 71% (PUVA); remission in months: 24.5 (nUVB), 22.8 (PUVA) | Early-stage MF |

Table I. *(Continued.)*

| Study (Ref No.) | Therapy regimen | Study design (*n*) | Response | Remarks |
|---|---|---|---|---|
| *Vitiligo* | | | | |
| Scherschun (99) | nUVB | Retrospective (7) | 75% response: 71.4%; rest: 50–40% response | Response depended on duration |
| Njoo (102) | nUVB | Open trial (51) | 75% response: 53%; stable disease: 80%; | Children; localization dependence |
| Tjioe (100) | nUVB+folic acid (FA)+vitamin B12 | Randomized, controlled (27) | ⩽100% repigmentation: 92%; equal response with FA and vitamin B12 | Localization dependence |
| *Pruritus* | | | | |
| Baldo (107) | nUVB | Open trial (10) | CR: 80% | Polycythaemia+pruritus |
| *Polymorphous light eruption* | | | | |
| Dummer (113) | nUVB and UVA/bUVB | Open trial (25) | Response: 80% (nUVB), 66.6% (UVA/UVB) | nUVB effective after ineffective UVA/UVB |
| Gupta (111) | nUVB in hidroa vacciniforme | Retrospective (5) | Response: 60% | Spontaneous clearing: 60% |
| *Graft-versus-host disease* | | | | |
| Grundmann-Kollmann (114) | nUVB | Open trial (10) | CR: 70%; significant improvement: 30% | Recalcitrant |
| *Pityriasis lichenoides* | | | | |
| Pasic (42) | nUVB | Open trial (9) | ⩾90% reduction: 33.3%; 70–90% reduction: 33.3% | Children |
| *Lichen planus* | | | | |
| Saricaoglu (123) | nUVB | Open trial (10) | CR: 100% (30–51 radiations) | |
| Taneja (122) | nUVB | Open trial (5) | CR: 100%; Remission: ⩾5–21 months | Oral lesions: no response |
| *Seborrhoeic dermatitis* | | | | |
| Pirkhammer (124) | nUVB | Open trial (18) | CR: 33.3%, PR: 66.6%; pruritus: 100% | All relapsed after 21 d |

CR, complete remission; PR, partial remission; MF, mycosis fungoides; SPP, small plaque parapsoriasis; SCORAD, Severity Scoring of Atopic Dermatitis; PUVA, psoralen with UVA; PASI, Psoriasis Area and Severity Index.

Furthermore, clearing of plaques occurs faster if vitamin D is applied (59–61). Vitamin D3 derivatives may be used up to 2 h before phototherapy (62, 63) or after UV application, as they are unstable under UV irradiation (64). One study showed that pretreatment with tacalcitol accelerated the response to nUVB (65).

Hofmann et al. (66) found no difference in the efficacy of the combination of nUVB with dithranol versus nUVB with calcipotriol in a half-side trial. However, studies with higher patient numbers are necessary to confirm this finding.

*UVB plus topical retinoids:* In clinical studies, tazarotene 0.1% gel in combination with nUVB showed faster and significantly greater reduction of psoriasis plaques with significantly lower median cumulative UV exposure than UVB alone (67, 68). Mild irritations like erythema, peeling, dryness, burning and pruritus do occur but photosensitivity is not observed (69, 70). Comparison of tazarotene plus nUVB versus calcipotriol plus nUVB in clinical studies revealed no significant therapeutic difference (71). However, reduction of stratum corneum by retinoids increases UV erythemogenicity and a more cautious increment of UV is recommended when combined with tazarotene (72).

*UVB plus salt:* Balneophototherapy is a widely applied treatment modality in combination with bUVB or nUVB (73, 74). A multicentre study with 280 psoriasis patients describes a PASI reduction of 71.4% when patients are irradiated with nUVB in the presence of Dead Sea salt solution (75). These are encouraging data, but controlled comparative trials are needed to support these results.

*Combination of UVB and systemic therapy:* UVB plus systemic retinoids (isotretinoin and acitretin) can improve the efficacy of nUVB, almost reaching the effectiveness of PUVA (76). In patients refractory to other treatments, the combination of low-dose acitretin and nUVB results in greater improvement than monotherapy with either acitretin or nUVB (77) and retinoids may protect against development of squamous skin cancer (78–81). Thus, combination of nUVB with systemic retinoids is a possible alternative to avoid large cumulative PUVA doses.

*UVB plus psoralen:* Psoralen is normally combined with UVA (PUVA). Anecdotal reports describe equal efficacy of psoralens in combination with nUVB when compared to PUVA, although it is unclear to what extent improvement was due to nUVB radiation alone (82–84). The combination of bath-PUVA plus additional nUVB has also been described with nUVB enhancing the phototoxic and therapeutic activities of bath-PUVA (85).

## Atopic dermatitis

There is a large body of evidence indicating that nUVB is effective in the treatment of atopic dermatitis (86). In a recent study, Pasic et al. (42) combined nUVB with UVA for AD in children and showed ≥90% reduction of the SCORAD index in 45.4% and 70–90% reduction in another 22.7% of patients. Hudson-Peacock et al. (87) described a response rate of 81% with complete clearance in 43% for nUVB twice weekly. The first randomized investigator-blinded, half-side comparison study on the efficacy of 8-methoxypsoralen bath-PUVA versus nUVB in patients with severe chronic AD found equal effectiveness after a mean duration of 40 days when used three times a week in equi-erythemogenic doses (88). Another randomized, controlled, double-blind study with 73 patients treated with nUVB, bUVB/UVA or visible light twice a week showed nUVB to be most effective with respect to the following end points: disease activity and ability to sleep for up to 3 months after cessation of therapy (89). Furthermore, nUVB was shown to be as effective as medium-dose UVA1 in clearing chronic AD and better in reducing pruritus (90).

Combination of nUVB phototherapy with cyclosporin A (CsA) has been reported to be effective in the treatment of AD. Patients with severe AD were treated with oral short-term CsA for 4 weeks. Then CsA was washed out for 4–6 weeks followed by nUVB phototherapy applied three times a week for up to 2 months. This regimen showed good clinical response. However, the study did not investigate long-term effects of this protocol (91) and this combination has to be viewed critically.

## Early stage mycosis fungoides and parapsoriasis en plaques

Several studies indicate the beneficial effect of nUVB for patch-stage MF (Ia/Ib) and parapsoriasis (92, 93). Times to reach complete remissions range from 6 weeks (92) up to 66 months (94). The time to relapse after complete responses after photochemotherapy with PUVA ranges between 6 and 43 months (95). For nUVB prolonged remission up to 20 months has been described (96). Diederen et al. (94) describes even higher complete remissions rates and longer mean relapse-free intervals when comparing nUVB with PUVA (81% vs 71% resp. 24.5 vs 22.8 months). Some authors propose a maintenance phototherapy once a week after complete clearing of MF. As p53 mutations were described in tumour stage MF with a mutation spectrum strikingly similar to that reported in non-melanoma skin cancer and characteristic for DNA damage caused by UVB radiation, precautions regarding long-term phototherapy have to be taken (97). Even though treatment of MF with UVB still raises the issue of carcinogenicity, until now there has been no clinical evidence suggesting that UVB treatment promotes progression of MF.

## Vitiligo

No randomized controlled trials investigating the efficacy of nUVB in the treatment of vitiligo have been published so far. However, several clinical studies report that nUVB can achieve up to >75% repigmentation in about two-thirds of patients after at least 1 year of treatment (98, 99). Repigmentation >90% can even be observed (100). nUVB seems to be more effective than bUVB, local steroids or PUVA (101) and this wavelength also appears to be effective in children (102). Body areas with good responses (>75%) include face, neck, trunk and proximal extremities, whereas distal extremities as well as genital areas respond very modestly (<25%) or not at all. nUVB seems to be safe as regards photocarcinogenicity, as up to now only two patients with vitiligo have been reported to develop squamous cell carcinoma after prolonged PUVA therapy (103, 104).

## Pruritus

Phototherapy of pruritus can be effective due to treatment of the underlying disease, such as AD, lichen planus or lymphoma. Symptomatic improvement can also be achieved by phototherapy in pruritus associated with uraemia, primary biliary cirrhosis, macular amyloidosis and Hodgkin's lymphoma (105). According to Hsu & Yang (106) uraemic pruritus responds only to bUVB but not to nUVB. Baldo et al. (107) showed nUVB to be effective for treatment of pruritus associated with polycythaemia vera. One open trial study showed that the combination of initial thalidomide followed by nUVB for prurigo nodularis leads to an excellent response after an average of 12 weeks (108).

## Polymorphous light eruption

Polymorphous light eruption (PLE) is mainly provoked by UVA and to a lesser extent by a combination of UVA/UVB or UVB alone and a light-hardening effect can be seen. For patients with severe forms of PLE effective photo-hardening in spring with nUVB has been described as equally effective as with PUVA, UVA1 or bUVB (109, 110). Photohardening with nUVB has also been used for actinic prurigo, idiopathic solar urticaria, erythropoietic protoporphyria, amiodarone photosensitivity, congenital erythropoietic protoporphyria, homozygous variegate porphyria or hydroa vacciniforme, even when patients showed abnormal photosensitivity in the UVB spectrum (86, 111, 112). PLE lesions provoked by UVA and UVB may respond to photohardening with nUVB, even in patients where UVA/UVB treatment was inefficient. On the other hand, if PLE lesions are induced by bUVB, correct application of nUVB might be

impossible. In these very rare cases PUVA therapy has been reported to be a valid alternative (113).

### Graft-versus-host disease

The first-line treatment for graft-versus-host disease (GvHD) is photochemotherapy (PUVA), especially when the skin involvement is severe. Moreover, Grundmann-Kollmann et al. (114) reported 10 patients, resistant to combinations of immunosuppressive drugs, of which seven patients showed complete clearance after treatment with nUVB five times a week over 3–5 weeks. After clearing of cutaneous GvHD, radiation was continued as maintenance therapy for at least 4 weeks and no patient relapsed during a follow-up of 4–18 months. As nUVB phototherapy is a non-aggressive treatment that may be of benefit for patients who are receiving higher doses of immunosuppressive drugs, including CsA or FK506, this form of photo-therapy may be an alternative to systemic and topical PUVA in mild cases or during onset of the disease (115).

### Rare diseases and other indications

There are anecdotal reports of using nUVB in various other diseases. Thus nUVB has been successfully used for subcorneal pustular dermatosis (Sneddon-Wilkinson disease) (116, 117), acquired perforating dermatosis (118) and pruritic folliculitis of pregnancy (119).

For classical juvenile pityriasis rubra pilaris (PRP), a good clinical result was observed with nUVB in combination with acitretin (120). Notably, PRP can be provoked by UV irradiation and painful and tense lesional blistering has been described under nUVB. Thus, phototesting prior to initiation of nUVB as well as discrete dose increments are mandatory (121). Patients with lichen planus have successfully been treated with nUVB: pruritus responded early and a complete flattening occurred within 30–51 radiations and no relapse was seen during follow-up of 20 months. Again, photoaggravated lichen planus should be kept in mind (122, 123).

Other diseases responding to treatment with nUVB include chronic pityriasis lichenoides in children, but not pityriasis lichenoides et varioliformis acuta (42) and seborrhoeic dermatitis (124).

## ADVERSE EFFECTS OF NUVB

### Early side effects

Early side effects of nUVB include erythema and dryness of the skin. The maximum erythema occurs 8–24 h after irradiation (125, 126). As patients over 70 years show a prolonged nUVB-induced erythema, a more cautious approach to dose increases is recommended in the elderly (127).

### Late side effects

Chronic exposure to UV radiation induces premature aging (photoaging) of the skin, showing typical clinical signs of leathery appearance, wrinkling, reduced recoil capacity and increased fragility of the skin (128, 129). Both wavelengths UVA and UVB are capable of inducing the different metabolic changes that result in enhanced skin aging (128, 130). The relative influence of nUVB in comparison to UVA or bUVB has not yet been investigated.

More important than photoaging after chronic UVB exposure is the risk of skin tumour induction. While the role of PUVA in the induction of skin tumours is undisputed, in humans the role of UVB phototherapy in skin carcinogenesis is less clear. No significant increase in the risk of developing squamous cell carcinoma or basal cell carcinoma has been associated with long-term exposure of patients with psoriasis to bUVB phototherapy in older and recent studies (131–133), even in combination with crude coal tar over 25 years (134). At present it is not clear whether nUVB or bUVB is more carcinogenic. Several animal studies found that nUVB has a higher carcinogenic potency than bUVB (135–137), while others did not confirm this (4, 5, 138–140). Macve & Norval (141) showed that tumour outgrowth is enhanced by bUVB, but not by nUVB or UVA1. Remarkably, cis-urocanic acid seemed not to be important for tumour induction, although it is recognized as an initiator of UV-induced immunosuppression.

Throughout the UVB spectrum, the first DNA lesions induced are pyrimidine dimers, but the number of dimers produced decreases dramatically with longer UV wavelengths. For example, irradiation of human fibro-blasts with equal UVB energy produces 100 pyrimidine dimers at 302 nm, but only 1 dimer at 312 nm. Similarly, 60 functional mutations of the hypoxanthine phosphoribosyltransferase gene are produced at 302 nm, but only one is produced at 312 nm (142). These data were confirmed by Tzung & Runger (143) and Budiyanto et al. (144), who showed 10-fold higher doses of nUVB yielding a similar amount of CPD and also a 1.5–3 times higher amount of oxidative DNA damage compared with bUVB.

Data investigating the carcinogenic risks of nUVB and bUVB are limited. When used in humans nUVB seems not to be associated with a higher carcinogenic risk when compared with bUVB, but a significantly reduced risk compared with PUVA (145, 146). A first long-term retrospective study by Weischer et al. (147) during a follow-up of 10 years further supports the view that neither nUVB nor bUVB significantly increase the risk of skin cancer. Nevertheless, phototherapy must be applied with due caution and patients possibly receiving long-term phototherapy should be followed-up by a dermatologist on a regular basis.

## CONCLUSION

Phototherapy with nUVB is a safe and effective treatment modality for a continuously increasing number of skin diseases. In addition to its low erythemogenicity and high therapeutic efficacy, its major advantages are possible combination with other topical or systemic treatment modalities and cost-effectiveness. More clinical trials are needed to investigate important issues such as carcinogenicity and effectiveness in skin diseases other than psoriasis.

## ACKNOWLEDGEMENTS

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