EXPERT REVIEWS

Narrowband ultraviolet B for the treatment of vitiligo

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After its first use in vitiligo in 1997, narrowband ultraviolet B (NBUVB) has been evaluated in the treatment of this condition by several groups of researchers. Its better efficacy and safety compared with psoralen plus ultraviolet A has helped it to be become the preferred modality for use in generalized vitiligo. In this article, we have reviewed the available data pertaining to efficacy and safety issues for NBUVB as monotherapy, its comparison with psoralen plus ultraviolet A and other modes of phototherapy, combination regimens that have been tried and future prospects of NBUVB in vitiligo.

Keywords: combination therapies • comparison • dosimetry • evolution • future prospects • mechanism of action • monotherapy • NBUVB • PUVA

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Learning objectives

Upon completion of this activity, participants should be able to:

- Describe practical considerations regarding use of narrowband ultraviolet B (NBUVB) in generalized vitiligo
- Describe anatomic predictors of response of vitiliginous lesions to NBUVB treatment
- Describe other factors associated with a good response of vitiligo to NBUVB treatment
- Describe the safety of NBUVB treatment in patients with vitiligo

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While ultraviolet A (UVA), along with psoralen plus UVA (PUVA) and broadband ultraviolet B (BBUVB), have been used for various dermatoses, including vitiligo, for quite some time, narrowband ultraviolet B (NBUVB) is a relatively recent development, and was introduced a little over a decade ago for the management of vitiligo. In this article, we will discuss the journey of NBUVB from its earlier days of development until the present day perspective in the management of vitiligo.

Evolution of NBUVB

Photochemotherapy (PUVA) in the form of topical application or ingestion of extracts of the plants *Psoralea corylifolia* (in India) and *Ammi majus linnaeus* (in Egypt), followed by sun exposure, has been in use for more than 2500 years [1]. It was the first treatment found to be effective in vitiligo. In modern medicine, the first clinical studies were performed by El Mofty in 1948 [2]. In 1977, Fischer observed that a NBUVB at a 313-nm wavelength was very effective for clearance of psoriasis, without producing significant erythema [3]. Parrish and Jaenicke subsequently observed that clearance of psoriasis lesions occurred at a wavelength between 296 and 313 nm, with better response at a wavelength of 313 nm [4]. These findings were followed by the development of a fluorescent lamp containing phosphor (TL-01), producing peak emission at narrowband of 311 nm (±2nm). NBUVB was first used clinically in 1988 by two groups for the management of psoriasis: van Weelden *et al.* and Green *et al.* [5,6]. Westerhof and Nieuweboer-Krobotova first used NBUVB in the management of vitiligo in 1997 [7]. Subsequently, several groups have used it for vitiligo in different skin phototypes. The efficacy and safety observed with NBUVB have helped it to supersede PUVA as the treatment of choice in generalized vitiligo.

Mechanism of action of NBUVB pertaining to vitiligo

The exact mechanism of action of NBUVB in vitiligo is unknown. The predominant type of repigmentation after NBUVB is perifollicular. Therefore, it is at least theoretically justified to believe that it has some relation to the melanocyte reserve in the outer root sheath. A two-step effect of NBUVB has been proposed – both of them may occur simultaneously although [8]. Firstly, there is immunomodulation (local as well as systemic), leading to downregulation of immune attack against the melanocytes. Subsequently, the melanocytes are stimulated to migrate to the epidermis and synthesize melanin [9]. NBUVB phototherapy increases synthesis of IL-1, TNF-α and LTC-4, and these cytokines induce melanocyte mitogenesis, melanogenesis and melanocyte migration. However, the roles of IL-1 and TNF-α in melanogenesis are controversial and contradictory, as has been observed in some studies. Englaro *et al.* have proposed that TNF-α inhibits the expression and activity of tyrosinase, the key enzyme in melanin synthesis. This inhibition of melanogenesis induced by TNF-α is secondary to activation of nuclear-factor κB [10]. IL-1 stimulates synthesis of endothelin-1, which is mitogenic and melanogenic. The contradiction is that IL-1α has been found to decrease proliferation of melanocytes and melanogenesis, while IL-1β decreases melanocyte tyrosinase activity without any effect on proliferation [11]. Imokawa *et al.* observed increased expression of endothelin-1, IL-1 and tyrosinase in human keratinocytes *in vivo* and *in vitro* after UVB irradiation, suggesting the possible mechanism of repigmentation [12]. Release of prostaglandins (PGE_2 and PGF_2) is another mechanism of action of phototherapy [13]. PGE_2 is synthesized in the skin and regulates melanocyte and Langerhans cell function, and promotes melanocyte mitogenesis [14].

Dosimetry of NBUVB in vitiligo

As is obvious from Table 1, there are no guidelines for dosimetry of NBUVB in vitiligo as compared with psoriasis, for which NBUVB was originally developed. As vitiliginous skin is akin to type 1 skin, it is natural to believe that the dosimetry should have been uniform across the board, irrespective of the skin phototype of the patient. The starting doses have ranged from as low as 100 mJ/cm^2 or 70% minimal erythema dose (MED) on vitiliginous skin to as high as 740 mJ/cm^2 or 100% MED. The subsequent increments varied between 25 and 50 mJ/cm^2, or 15–40% of the previous dose. The dose increments were carried out as frequently as consecutive sessions until faint pink erythema was achieved, or as sparsely as every other week. The ceiling of maximum dose permissible has been as low as 300 mJ/cm^2 or as high as 910 mJ/cm^2, or of an unspecified permissible maximum upper dose. These wide ranging disparities make it difficult to compare efficacy and safety of NBUVB between the studies. As MED in type 1 skin is 400 mJ/cm^2, the authors use 70% MED or 280 mJ/cm^2 as the standard starting dose in their patients belonging predominantly to skin phototype 4 or 5. Where phototesting is available, the MED can be determined in vitiliginous skin, and 70% of the determined MED is a reasonable starting dose. The subsequent dose is increased by 15–20% until faint pink erythema is achieved or perifollicular repigmentation starts when the dose can be kept constant. If persistent and symptomatic erythema develops, it is prudent to withhold treatment until erythema subsides and the treatment can be restarted with a dose 15–20% lower than the last tolerated dose. The subsequent dose is increased by 10% or as tolerated, with the aim being faint pink erythema or perifollicular repigmentation, following which the dose is to be kept constant.

Side effects of NBUVB in vitiligo patients: short & long term

Narrowband ultraviolet B (UVB) is relatively safe, and this is one of the main reasons for it being considered the first choice of treatment of generalized vitiligo in adults, as well as in children.

Erythema is the most significant acute side effect of NBUVB, and the incidence varies between 10 and 94% according to the treatment regimen and definition of erythema [15]. However, asymptomatic faint pink erythema is expected to be common, as this is the end point for NBUVB in vitiligo. A greater proportion of patients develop erythema as compared with PUVA, but they are less likely to miss treatment due to a shorter duration of NBUVB-induced erythema. Pruritus occurs occasionally. Reactivation of orolabial herpes simplex may be problematic and

Table 1. Studies of narrowband ultraviolet B in treatment of vitiligo.

Authors (year)	Study component	Study design	Patients (n)	Mode of each treatment	Number of patients in each arm	Dosimetry	Degree of repigmentation	Color matching	Incidence of side effects	Ref.
Monotherapy										
Njoo *et al.* (2000)	NBUVB	Prospective, open, uncontrolled	51	Twice a week	NA	0.25 J/cm^2 followed by 20% increments until minimal erythema	After a maximum of 1 year treatment: >75% repigmentation in 53%	–	Pruritus: 8%, xerosis: 4%	[34]
Scherschun *et al.* (2001)	NBUVB	Retrospective	7	Three-times a week	NA	280 mJ/cm^2 followed by 15% increments until mild erythema or pruritus	70% patients achieved >75% repigmentation after a mean 19 treatments	–	Mild asymptomatic erythema: 56%, pruritus: 14%	[31]
Hamzavi *et al.* (2004)	NBUVB alone	Randomized, controlled side-to-side comparison	22	Three-times a week	NA	70% of MED on depigmented skin followed by 10% increments until onset of repigmentation	Mean improvement after 6 months or 60 exposures: 42.9% (treatment side) versus 3.3% (control side)	–	–	[25]
Kanwar *et al.* (2005)	NBUVB	Open, uncontrolled	14	Three-times a week	NA	280 mJ/cm^2 followed by 20% increments	After 1 year: >75% repigmentation in 71.4%	–	Burning and pruritus: 28.6%, xerosis and thickening of lesional skin: 21.4%	[23]
Kanwar and Dogra *et al.* (2005)	NBUVB	Prospective, open, uncontrolled	20	Three-times a week	NA	280 mJ/cm^2 followed by 20% increments	After a maximum of 1 year treatment: >75% repigmentation in 75% patients	–	Lesional burning and pruritus: 20%, xerosis and thickening of skin: 15%	[35]
Brazzelli *et al.* (2007)	NBUVB	Open, uncontrolled	60	Twice or three-times a week	NA	180–200 mJ/cm^2 followed by 50 mJ/cm^2 increments until mild erythema	Complete repigmentation or up to maximum 2 years: 68% (face), 57.9% (neck), 50% (trunk), limbs poorer results	–	–	[24]

MED: Minimal erythema dose; NA: Not applicable; NBUVB: Narrowband UVB; PUVA: Psoralen plus UVA.

Table 1. Studies of narrowband ultraviolet B in treatment of vitiligo (cont.).

Authors (year)	Study component	Study design	Patients (n)	Mode of each treatment	Number of patients in each arm	Dosimetry	Degree of repigmentation	Color matching	Incidence of side effects	Ref.
Kishan Kumar *et al.* (2009)	NBUVB	Prospective, open, non-randomized	150	Twice a week	NA	250 mJ/cm^2 (150 mJ/cm^2 for children) followed by 20% increments until perceptible erythema	>75% repigmentation after maximum 1 year treatment: 17.4%	–	Erythema, burning, pruritus: 7%, xerosis: 6%	[26]
NBUVB versus PUVA										
Parsad *et al.* (2006)	NBUVB versus PUVA	Retrospective	69	Both treatments: three-times a week 8-methoxypsoralen: 0.6 mg/kg 2 h before UVA exposure	31/38	280 mJ/cm^2 followed by 20% increments PUVA: 2.5 J/cm^2 followed by 0.5 J/cm^2 increments	Marked to complete response: 41.9 versus 23.6%	–	–	[27]
El Mofty *et al.* (2006)	NBUVB versus PUVA	Side-to-side comparison study	15	Three-times a week 8-methoxypsoralen 0.7 mg/kg 2 h before UV exposure	NA	NBUVB: 0.74 mJ/cm^2 followed by 15% increments UVA: 1 J/cm^2 followed by 0.5 J/cm^2 increments every other session	60–75% repigmentation after 60 sessions: 57.1 versus 57.1%	–	Erythema: 73.3 versus 66.6%, blisters: 6.6 versus 13.3%	[29]
Yones *et al.* (2007)	NBUVB versus PUVA	Randomized double-blind	50	2/2 5-methoxypsoralen 50 mg/m^2 3 h before UVA exposure	25/25	NBUVB: 0.1 J/cm^2 followed by 20% increments till 2 J/cm^2 PUVA: 0.5 J/cm^2 followed by0.25 J/cm^2 increments until 5 J/cm^2	>50% repigmentation after 48 exposures: 53 versus 23%	Excellent in all NBUVB 44% in PUVA	–	[28]

MED: Minimal erythema dose; NA: Not applicable; NBUVB: Narrowband UVB; PUVA: Psoralen plus UVA.

Table 1. Studies of narrowband ultraviolet B in treatment of vitiligo (cont.).

Authors (year)	Study component	Study design	Patients (n)	Mode of each treatment	Number of patients in each arm	Dosimetry	Degree of repigmentation	Color matching	Incidence of side effects	Ref.
Bhatnagar *et al.* (2007)	NBUVB versus PUVA	Prospective, open, randomized	50	Both treatments: three-times a week Trimethylpsoralen: 0.6 mg/kg 2 h before UVA exposure After 75% repigmentation, twice a week	25/25	NBUVB: 280 mJ/cm^2 followed by 20% increments PUVA: 2 J/cm^2 followed by 0.5 J/ cm^2 increments	NBUVB: mean repigmentation 52.24% over mean 6.3 months PUVA:44.7% over mean 5.6 months	–	NBUVB: nine patients (hereps labialis: four, itching: three, urticaria and symptomatic dermographism: one each) PUVA: 13 (Itching: four, sedation, xerosis, exacerbation of acne: three patients each, nausea: two)	[30]
NBUVB versus other modes of phototherapy										
Casacci *et al.* (2007)	NBUVB versus monochromatic excimer light	Randomized, side-to-side comparison	16	Twice a week	16/16	70% of MED followed by 40% increments for treatment 1–4, 30% from 4–8, 20% thereafter	>50–75% repigmentation: 6 versus 37.5% >75% complete repigmentation: 31 versus 25%	–	–	[37]
NBUVB in combination with antioxidants										
Patel *et al.* (2002)	NBUVB plus pseudocatalase mousse	Prospective, open	26	NBUVB: twice a week Psudocatalase mousse: twice-daily and applied well before phototherapy	NA	100 mJ/cm^2 and increased very gradually to minimize likelyhood of erythema		–	–	[42]
Middelkamp-Hup *et al.* (2007)	NBUVB plus *Polypodium leucotomos* extract or placebo	Randomized, double-blind, placebo-controlled	49	NBUVB: Twice a week *Polypodium leucotomos* or placebo: three-times a day	*Polypodium leucotomos* plus NBUVB: 25 Placebo plus NBUVB: 24	210–360 mJ/cm^2 (according to skin type) until faint pink erythema	Head and neck 44 versus 27%, trunk 36 versus 30%, extremities 30 versus 26%, hands and feet 24 versus 19%	–	–	[38]

MED: Minimal erythema dose; NA: Not applicable; NBUVB: Narrowband UVB; PUVA: Psoralen plus UVA.

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Authors (year)	Study component	Study design	Patients (n)	Mode of each treatment	Number of patients in each arm	Dosimetry	Degree of repigmentation	Color matching	Incidence of side effects	Ref.
Del'Anna *et al.* (2007)	NBUVB plus antioxidant pool versus NBUVB alone	Randomized, double-blind, placebo-controlled	28	NBUVB: Twice a week Antioxidant pool (α-lipoic acid – 50 mg, vitamin C – 50 mg, vitamin E – 20 mg): two tablets a day started 8 weeks before beginning of NBUVB	17/11	70% of MED on unaffected skin followed by 30% increments for treatment 1–4, 30% from 4–8, 20% thereafter	75% repigmentation after 6 months: 47 versus 18%	–	–	[39]
Elgoweini and Nour El Din (2009)	NBUVB plus vitamin E versus NBUVB alone	Prospective, randomized	20	NBUVB: Three-times a week Vitamin E: 400 IU once a day started 2 weeks before NBUVB	11/9	0.21 J/cm^2 followed by 20% increments until 10 treatments and 10% increments thereafter	>50% repigmentation after 6 months of treatment: 72.7 versus 55.6%	–	–	[40]
Bakis-Petsoglou *et al.* (2009)	NBUVB plus pseudocatalase cream versus NBUVB plus placebo	Randomized, double-blind, placebo-controlled trial	32	NBUVB: Three-times a week (10–30 min after cream application) Pseudocatalse cream: twice daily	14/18	100% of MED for first three treatments followed by 10–15% increments until 300 mJ/cm^2		–	–	[41]
NBUVB versus vitamin D analogues										
Arca *et al.* (2006)	NBUVB alone versus NBUVB plus topical calcipotriol	Randomized	37	NBUVB: three-times a week Calcipotriol: twice a day	24 versus 13	100 mJ/cm^2 followed by 50 mJ/cm^2 increments until moderate erythema or pruritus	>50% repigmentation: 41.67 versus 45.01%	–	–	[46]
Goktas *et al.* (2006)	NBUVB plus topical calcipotriol versus NBUVB alone	Side-to-side comparison	24	NBUVB: Three-times a week Calcipotriol: twice a day	NA	140 mJ/cm^2 followed by 25 mJ/cm^2 increments until 740 mJ/cm^2 or mild erythema	Overall repigmentation (excluding hands and feet) after 6 months: 51 versus 39%	–	Five patients had mild-to-moderate erythema, itching and xerosis on the calcipotriol applied side	[44]

MED: Minimal erythema dose; NA: Not applicable; NBUVB: Narrowband UVB; PUVA: Psoralen plus UVA.

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Authors (year)	Study component	Study design	Patients (n)	Mode of each treatment	Number of patients in each arm	Dosimetry	Degree of repigmentation	Color matching	Incidence of side effects	Ref.
Leone *et al.* (2006)	NBUVB plus topical tacalcitol versus NBUVB alone	Randomized side-to-side comparison	32	NBUVB: twice a week Tacalcitol ointment (4 µg/g): once a day	NA	70% of MED (on unaffected skin) followed by 30% increments for treatment 1–4, 30% from 4–8, 20% thereafter	Mean grade of repigmentation after 6 months: slightly higher than grade 2 (50–80% repigmentation) versus slightly higher than grade 1 (<50% repigmentation)	–	–	[48]
NBUVB versus topical calcineurin inhibitors										
Mehrabi and Pandya (2006)	NBUVB plus tacrolimus (0.1%) versus NBUVB plus placebo	Randomized double-blind placebo-controlled side-to-side comparison	Nine	NBUVB: three-times a week	NA	196 mJ/cm^2 followed by 15% increments until mild erythma	49.24 versus 41.28%	–	–	[54]
Fai *et al.* (2007)	NBUVB plus topical tacrolimus	Open-label	110	NBUVB: twice a week Topical tacrolimus: 0.03% for face and 0.1% for other areas once a day	NA	0.4 J/cm^2 followed by 0.1 J/cm^2 increments every other week until 0.91 J/cm^2	>75% repigmentation after 16 weeks: 40% in face, 21.5% in trunk, 23% in the limbs, 1% in hands and feet	–	Mild and transient burning: ten, Mild-to-moderate vasodilatory response: eight	[55]
Esfandiarpour *et al.* (2009)	NBUVB plus pimecrolimus versus NBUVB plus placebo	Randomized double-blind placebo-controlled	50	NBUVB: three-times a week Pimecrolimus: twice a day	25/25	280 mJ/cm^2 followed by 15% increments until minimal erythema or 800 mJ/cm^2	>50% repigmentation after 12 weeks: 64.3 versus 25.1% (face), 42.8 versus 47.4% (trunk), 33.3 versus 40% (arms), 25 versus 28.6% (legs)	–	No significant side effects in either group	[56]

MED: Minimal erythema dose; NA: Not applicable; NBUVB: Narrowband UVB; PUVA: Psoralen plus UVA.

precautionary measures are prudent in those who are prone to frequent relapses of orolabial herpes. Exposure keratitis and conjunctivitis can occur following NBUVB [16]. The eye protection protocol during UV exposure should be stringently followed even though cataract is not a problem with NBUVB. NBUVB-induced tanning has been observed to increase gradually during treatment, and post-treatment recovery requires at least 10 weeks [17].

The long-term risk remains unclear, and questions regarding the risk of carcinogenecity of UVB remain unanswered. Induction of photodegenerative changes by UVB is well established. UVB is a complete carcinogen and TL-01 has been shown to induce DNA damage in human skin cells and animal models. In a knockout mice model, development of malignant skin tumors was significantly higher for NBUVB than BBUVB following equivalent dose exposure [18]. The formation of cyclobutane pyrimidine dimers (CPD) was significantly higher with NBUVB, while that of photoproduct and 8-oxoguanine was significantly higher following BBUVB. These findings suggested the close correlation between CPD and the higher carcinogenic potential of NBUVB. At least in the setting of psoriasis, it is proposed that this disadvantage of NBUVB *vis-à-vis* BBUVB can be offset by the fact that the total dose required for clearance of psoriasis is lower than that for BBUVB. The only available human data has a mean follow-up of 5 years [19]. No significant increase in squamous cell carcinoma or melanoma was observed, and there was only a small increase in basal cell carcinoma. This marginal increase in the incidence of basal cell carcinoma is unlikely to be related to treatment, as it appeared during the first 3 months of therapy. Until further data becomes available it is desirable to keep the number of treatment sessions to a minimum. Most of these safety data have been derived from psoriasis patients. Theoretically, absence of functional melanocytes can place patients at a greater risk for development of skin cancers following NBUVB. As the development of skin cancer in vitiligo patients appears to be rare, it is a rational expectation that NBUVB in vitiligo patients would not predispose them to a higher risk of malignancy compared with other indications in which it is used [20].

Clinical experience with NBUVB in vitiligo has generally been for a short duration, and there is currently no established safe limit for its maximum duration of use in treatment of this condition. Njoo *et al.* recommend that a responsive patient can be given therapy for 24 months at a maximum, and a resting period of 3 months should be advised after 1 year of treatment [21]. In children the maximum period recommended is 12 months. If there is no response at 6 months of treatment, further therapy is discouraged. In view of the greater susceptibility of vitiliginous skin to sunburn and photodamage due to lack of melanin, Gawkrodger *et al.* recommends that safety limits for NBUVB in vitiligo should be more stringent, with an arbitrary limit of 200 exposures in those with the fair-skinned 1–3 skin phototype [22].

NBUVB as monotherapy in vitiligo

The results of monotherapy with NBUVB have been better in Asian skin. Approximately three-quarters of patients in the series by Kanwar *et al.* achieved greater than 75% to complete repigmentation after NBUVB treatment for a maximum period of 1 year [23]. The mean duration of disease was significantly shorter in those who had marked to complete pigmentation compared with those who had poorer response. As with any treatment modality for vitiligo, the best results were observed in lesions on the face and neck, followed by the proximal limbs and trunk. Perifollicular pigmentation was the most common type of initial repigmentation that was observed in approximately three-quarters of patients.

Brazzelli *et al.* have studied the effect of NBUVB in vitiligo and the influence of body sites, age of the patients and duration of disease on clinical response [24]. Complete repigmentation was more commonly observed in lesions located on the face, neck and trunk in decreasing order of frequency (68, 57.9 and 50%, respectively). Age of the patients did not influence the response to treatment for facial lesions, while in other areas complete repigmentation was much more commonly observed in younger patients (<20 years). As far as the duration of disease is concerned, lesions over the neck, upper and lower limbs showed the best rate of complete repigmentation (83.3, 33.3 and 28.5%, respectively) in patients with disease of recent onset (<2 years), while for the lesions over the face, long-standing vitiligo patients responded better. The authors recommend early treatment, as the best results were achieved by young patients with recent-onset vitiligo.

In a randomized, controlled, side-to-side comparison study, mean improvement in the NBUVB was 42.9% compared with 3.3% in the untreated control side, with the severity of disease having been assessed by Vitiligo Area Scoring Index (VASI) [25]. Response to treatment varied greatly between different anatomic sites, with the best response seen over the lower extremities and worst response on the feet. Whereas all patients did not receive treatment for their face, 37.5% of those who opted for treatment of their face had more than 75% repigmentation.

In a recent large, open, prospective study from India, only approximately a quarter of patients could achieve more than 75% repigmentation [26]. This poor result in Indian patients can be attributed to lower initial dose and twice-weekly treatment. In those patients who had significant pigmentation, it was attributed to good compliance, a greater number of treatments and increasing cumulative dose. Although initial repigmentation was darker, good color matching could be achieved with continued treatment.

Comparison with PUVA

In Westerhof and Nieuweboer-Krobotova's study comparing twice-weekly topical PUVA versus NBUVB, it was observed that 67% of patients achieved repigmentation in the NBUVB group compared with 46% in the topical PUVA group after 4 months of treatment [7]. After 3 months of NBUVB treatment, 8% of patients showed more than 75% repigmentation, whereas after 12 months of NBUVB treatment, 63% had such repigmentation. In the first retrospective analysis of comparison between NBUVB and PUVA by Parsad *et al.*, 41.9% of patients in the NBUVB group and 23.6% in the PUVA group had marked to complete repigmentation after a maximum treatment for 1 year. Color matching was observed in 86% of the

NBUVB-treated patients and only 35% in the PUVA group. Stable repigmentation after 1 year of treatment completion was observed in 78.5% of patients in the NBUVB group and 60% in the PUVA group [27]. In the first randomized, double-blind, placebo-controlled trial, the improvement in body surface area affected by vitiligo was greater with NBUVB than placebo after 48 sessions ($p = 0.007$) [28]. While 53% of evaluable patients in the NBUVB group achieved more than 50% repigmentation, 23% in the PUVA group achieved similar repigmentation. After 12 months of cessation of therapy, the superiority in terms of efficacy for NBUVB was maintained, although it was not statistically significant. No association between duration of disease and success of treatment was observed. Although some degree of repigmentation was observed in all patients in the NBUVB group and 92% patients in the PUVA group, color match was excellent in all patients in NBUVB, while it was much poorer with PUVA. The cosmetically unacceptable color matching tended to persist even after a year of treatment cessation.

In a side-to-side comparison study involving 15 patients, an exactly equal number of patients achieved 0–40, 40–60 and 60–75% repigmentation after 60 sessions [29]. The difference in the incidence of side effects such as erythema and blistering was not siginificant between the groups.

In our center, Bhatnagar *et al.* compared NBUVB versus PUVA in vitiligo in a prospective, open, randomized study [30]. Mean degree of repigmentation observed was 67.5% over a mean treatment period of 6.3 months with NBUVB, while the corresponding figures in the PUVA group were 54.2% over 5.6 months (excluding hands and feet). The mean time to initial repigmentation was 33.6 days in both the groups. After excluding the treatment-resistant sites, more than 75% repigmentation was observed in 52 and 20% of patients in the NBUVB and PUVA groups, respectively. The best response was seen over the face in both the groups. Statistically better improvement with NBUVB was seen over the upper limbs and posterior trunk. In a small retrospective analysis by Scherschun *et al.*, five of their seven patients (70%) achieved more than 75% repigmentation after a mean of 19 treatment sessions. They observed that longer disease duration correlated negatively with response to treatment [31]. In the same setting, NBUVB was found to be more effective compared with PUVA in imparting stability in vitiligo and in repigmentation in both active and stable disease [32].

Vitiligo usually begins in childhood in a proportion of patients, with half of the patients having disease onset before 20 years of age [33]. However, experience of NBUVB in childhood vitiligo is limited. This issue is of particular importance because the long-term effect on the general skin condition of vitiligo patients treated with NBUVB is not known, and exposing children to NBUVB at an earlier age may expose them to an increased risk of chronic photodamage and skin cancers. In probably the first study meant for assessment of the role of NBUVB in childhood vitiligo, 82% of patients achieved more than 25% repigmentation, while 53% of patients achieved more than 75% repigmentation [34]. The best responses were seen for the lesions on the neck and face, followed by the abdomen, back, breast, legs and arms, in decreasing order of frequency. Before treatment, 96 patients had active disease, while the disease activity stabilized in 80% of patients after treatment. Pretreatment activity of disease did not significantly influence the final outcome of treatment. Demographic variables such as age, sex and skin type, and other factors, such as family history, duration of disease and body surface area affected by vitiligo, did not influence the degree of repigmentation. In a prospective study, Kanwar and Dogra recruited 26 children, of whom 20 completed the study. After treatment for a maximum of 1 year, 75% of patients had more than 75% repigmentation [35]. After a mean exposure of 34 times, 50% repigmentation was achieved. Mean duration of disease prior to treatment initiation was less for patients who had marked to complete repigmentation compared with those who had minimal or moderate improvement. The best responses were observed on the face and neck, followed by the proximal limbs and trunk. Although the authors concluded that NBUVB is effective and well-tolerated in children with vitiligo, the long-term outcome for skin conditions in general is not known.

Comparison with other modes of phototherapy

Targeted phototherapy devices were developed for psoriasis. The main advantages of these devices are that they target the affected area only, sparing the surrounding normal skin. Consequently, higher doses of irradiation can be applied, resulting in earlier and better response. Monochromatic excimer light (MEL) is a relatively new development. The basic difference between monochromatic excimer light and MEL is that the former produces incoherent and continuous emission, even though the wavelength is the same, at 308 nm. A higher number of apoptotic T cells are produced by the 308-nm excimer laser, compared with fluorescent NBUVB at the same dose in an *in vitro* model [36]. In equivalent dosages, monochromatic excimer devices are expected to impart better clinical response than NBUVB.

In a side-to-side randomized comparison model involving 16 patients with phototype 2–4, it took fewer exposures in the MEL group compared with the NBUVB group for initial perifollicular and peripheral repigmentation, as well as to achieve up to 50% overall repigmentation [37]. The percentage of lesions achieving more than 50% repigmentation was 63% in the MEL group, compared with 38% in the NBUVB group. The mean repigmentation grade was higher for MEL (2.68 vs 2.12). The cumulative UV dose was also significantly lower for MEL.

Combination treatment with NBUVB

Among different proposed pathomechanisms of vitiligo, oxidative stress is a relatively recent one. It has been suggested that cytotoxic metabolites of melanogenesis are originated by oxidative stress. *Polypodium leucotomos* has immunomodulatory and oxidative properties; it quenches free radicals and reactive oxygen species, as well as prevents lipid peroxidation [38]. In addition, it has been found that *P. leucotomos* downregulates the Th1 response, while upregulating the Th2 response, thus acting as an immunomodulating agent. In a randomized, double-blind, placebo-controlled trial, it was observed that the *P. leucotomos* group showed a trend towards greater repigmentation compared

with placebo in all body areas [38]. In the head and neck area the difference achieved near statistical significance (p = 0.06), while it was nonsignificant in other areas. The mean cumulative doses were similar in both the groups. The repigmentation was significantly higher in the head and neck area in light skin-type patients in the *P. leucotomos* group, while no such effect was seen in the darker skin group due to a low number of patients. According to physician global assessment, 72% of patients in the *P. leucotomos* group achieved clinically relevant repigmentation, while that in the placebo group was 43%. The role of antioxidants in conjunction with NBUVB in vitiligo has also been assessed by Del'Anna *et al.,* where they started administering an antioxidant pool containing α-lipoic acid, vitamin E and vitamin C 8 weeks before commencing phototherapy [39]. While α-lipoic acid is known to be a fatty acid peroxyl and hydroxyl radical scavenger, vitamin C is a hydrophilic antioxidant and vitamin E a is free-radical scavenger that inhibits lipid peroxidation. A significantly greater number of patients in the combination group (47%) achieved more than 75% repigmentation compared with the placebo group (18%). The average number of exposures required for 50% repigmentation was 18 in the combination and 23 in the placebo group. The clinical improvement in the combination group compared with the placebo group was also substantiated by improved redox status characterized by increased catalase activity and decreased intracellular reactive oxygen species production and reduced membrane peroxidation. The beneficial role of oral antioxidants in conjuncttion with NBUVB has also been substantiated by Elgoweini and Nour El Din [40]. In the patients who received oral vitamin E starting 2 weeks before initiating phototherapy, 72.7% achieved more than 50% repigmentation after 6 months of treatment, while it was 55.6% in the NBUVB monotherapy group. The lipid peroxidation product malondialdehyde, assessed in patients' plasma, decreased significantly post-treatment in the combination group. UVB radiation is known to cause lipid peroxidation and impairment of the antioxidant defence system. The decrease in malondialdehyde in plasma indicates that vitamin E can reduce NBUVB-induced cellular damage, and can thus augment its efficacy. However, topical antioxidants do not seem to work. In a randomized, placebo-controlled trial, topical pseudocatalase was used in conjunction with NBUVB [41]. Pseudocatalse presumably replenishes catalase that is known to be deficient in vitiligo patients, resulting in diminution in degradation of hydrogen peroxide. Moreover, it corrects calcium homeostasis known to occur in vitiligo. No significantly increased repigmentation was observed on the face and hands in the pseudocatalase group compared with the placebo group. In both the groups, there was significant reduction in the area of depigmentation after treatment, signifying that topical pseudocatalse does not have an additional role beyond NBUVB to play. Similar was the finding by Patel *et al.,* where no benefit of the combination of pseudocatalse mousse and NBUVB was observed [42].

The role of vitamin D analogues in the management of vitiligo was discovered serendipitously when hyperpigmentation was observed in psoriatic patients who had been treated with a combination of topical calcipotriol and PUVA or NBUVB. Formally, the combination of vitamin D analogue and NBUVB was used first by Dogra and Parsad [43]. The proposed mechanism for vitamin D analogues in vitiligo is two-fold: it repairs defective calcium uptake in melanocytes and activates vitamin D receptors. Activation of vitamin D receptors leads to stimulation of tyrosinase activity and consequent melanogenesis. Moreover, decreased levels of intracellular Ca^{2+}, as observed in vitiligo, leads to high levels of intracellular reduced thioredoxin, the substrate for thioredoxin reductase and consequent inhibition of tyrosinase activity [44]. As the mechanism of action of NBUVB is different from that of topical vitamin D analogues, hypothetically the combination might be better than either agent alone. Many subsequent trials have shown contradicting results with this combination. In a side-to-side comparison study assessing the combination of NBUVB and topical calcipotriol compared with NBUVB alone, involving patients with type 2–3 skin, 66.7% of patients had perifollicular pigmentation earlier in the combination side [44]. The treatment sessions (18 vs 24) and cumulative dose (6345 vs 8867 mJ/cm^2) required for induction of initial repigmentation was significantly less in the combination side. Overall repigmentation (excluding hands and feet) was 51 versus 39%. Kullavanijaya and Lim observed appreciably better response with the combination compared with NBUVB alone (although not significant) in a side-to-side comparison study [45]. Although the combination of topical vitamin D analogues with NBUVB was found to be beneficial, Arca *et al.* could not find encouraging differences in the percentage of repigmentation [46]. In their study, mean repigmentation was 41.6% in the NBUVB-alone group and 45% in the combination NBUVB and calcipotriol group. More than 50% repigmentation was observed in 41% of patients in the NBUVB alone group, and 46% in the combination group after a mean exposure of 30 times. Hartmann *et al.* also did not find the combination of calcipotriol and NBUVB to be superior to the combination of NBUVB plus placebo [47]. In the same study, BBUVB was found to be ineffective in vitiligo. The combination of tacalcitol with NBUVB was found to be effective [48]. The mean time to initial repigmentation in lesions that had a good response (50–80% repigmentation) was significantly shorter in the combination treatment side compared with monotherapy (55 vs 130 days). In other grades of repigmentation, the mean time to initial repigmentation was shorter in the combination treatment side. The final repigmentation was significantly better with the combination. In the patients with disease of shorter duration, the combination treatment side imparted significantly better response. No such effect was seen in patients with long-duration disease. The interesting finding of this study was the efficacy of the combination in treating lesions in sites traditionally considered as resistant, such as elbows and knees. The better response with combination has been attributed to upregulation of c-Kit mRNA expression by NBUVB-irradiated melanocytes consequent to tacalcitol application [49]. In addition to the clinical benefit as suggested by some studies, the added advantage of the combination of NBUVB with vitamin D analogues is protection against NBUVB-induced carcinogenesis. 1,25-dihydroxyvitamin D3 has been shown to protect human keratinocytes against the induction of CPDs by UVB [50]. Studies

in a mouse model suggest that the vitamin D receptor, instead of 1,25-dihydroxyvitamin D3 itself, is more important in providing protection against UV-induced skin carcinogenesis [51].

Autoimmunity is probably the first etiology proposed for vitiligo. The role of autoimmunity in vitiligo is substantiated by detection of organ-specific autoantibodies in vitiligo patients, antibodies directed to melanocytes and a decrease in T-helper cells, amongst other factors [52]. Topical calcineurin inhibitors having immunomodulatory properties have been found useful in vitiligo as monotherapy, as well as in combination with NBUVB. Direct interaction between pimecrolimus and keratinocytes, creating a favorable atmosphere for melanocyte growth and migration, has been proposed [53]. Mehrabi and Pandya assessed the efficacy of the combination of tacrolimus with NBUVB in a side-to-side comparison study [54]. There was no significant difference between the NBUVB plus placebo and NBUVB plus tacrolimus 0.1% ointment group in terms of treatment response after 12 weeks of three-times a week exposure. The average percentage of repigmentation in the target lesions was 49% in the active group and 41% in the placebo group. The finding by Fai *et al.* was similar, as they observed more than 75% repigmentation after 16 weeks of treatment (NBUVB twice a week in combination with 0.03% topical tacrolimus for face and 0.1% for other areas once at night time) in only 40% of facial lesions, while the results were far worse in the trunk and limbs and worst on the hands and feet [55]. In a double-blind, randomized, placebo-controlled trial, the combination of topical pimecrolimus twice a day and three-times a week exposure to NBUVB resulted in a statistically better rate of clinical improvement (>50% repigmentation) in facial lesions after only 3 months of treatment, while in other areas the results were comparable [56]. The conclusion that can be drawn from the majority of the studies combining topical calcineurin inhibitors with NBUVB is that the combination may increase the efficacy, and probably hasten the response, only for facial lesions.

Oral psoralen in combination with NBUVB has been used in vitiligo. In the initial study by El Mofty *et al.*, it was found to be equally effective as PUVA, with 50–60% improvement being observed in both sides in the side-to-side comparison study [57]. However, time to initial perifollicular repigmentation was earlier in the PUVA group. In the subsequent study, no appreciable statistical difference was observed in the percentage of patients achieving 60–75% repigmentation after 48 sessions between the NBUVB group and the NBUVB plus psoralen group [7]. The incidence of phototoxic reaction, and erythema, was significantly increased in the combination group compared with NBUVB alone (85 vs 60%, 75 vs 55%). The time taken to initial perifollicular repigmentation and to 40–60% repigmentation was earlier in the psoralen in combination with NBUVB group.

Although not tried in human subjects, the combination of $PGF_{2\alpha}$ analogues with NBUVB has demonstrated promising results in animal studies [58]. The combination induced marked pigmentation, while moderate pigmentation was seen when either of the agents were used alone. The authors speculated that supplementation of NBUVB-induced prostaglandin synthesis with extraneous prostaglandin resulted in better effects.

Predictors of response & persistence of repigmentation

It is always difficult to predict whether a particular treatment strategy is going to work in every patient with vitiligo and in all lesions of a particular patient. Nicolaidou *et al.*, in a study involving 70 patients, exposed patients to NBUVB twice a week and observed cosmetically acceptable repigmentation – that is, more than 75% repigmentation – in 34.4% of patients with lesions on the face, while only 7.4% of patients with lesions on the body had a similar degree of repigmentation [59]. For facial lesions, skin phototypes 3–5 and duration of treatment were important in determining cosmetically acceptable repigmentation. For lesions over the body, only duration of treatment was important. The earlier a patient developed a repigmentation, the greater the chance for cosmetically acceptable repigmentation on the face and more than 50% repigmentation on the body. Overall, they observed that good predictors of repigmentation are lesions on the face, skin phototypes 3–5, and early initial response within the first month of treatment. No significance of pretreatment body surface area involvement with response to treatment was observed. Other factors, such as the age of the patients, sex, family history of vitiligo, presence of autoimmune thyroid disease, pretreatment body surface area involvement, duration of disease or activity of disease, did not influence the degree of repigmentation. The better outcome in terms of final degree of repigmentation correlated with early repigmentation in the study by Chen *et al.* also [60]. In contradiction to the report of Nicolaidou *et al.*, Njoo *et al.* [61] and Scherschun *et al.* [31] observed that the earlier the NBUVB treatment is initiated, the higher is the chance of successful repigmentation. Anbar *et al.* also corroborated this proportionate association between early treatment initiation and degree of repigmentation for the lesions on the face, trunk and limb, while such an association was not observed for acral lesions [62]. Hamzavi *et al.* did not observe the influence of patient demographic characteristics such as age, sex, skin phototype, ethnicity and other factors such as duration of vitiligo, prior vitiligo treatment with either steroids or UV therapy and pretreatment extent in the treatment outcome of vitiligo [25].

While studying the persistence of repigmentation during post-treatment follow-up over a 2-year period in patients who had achieved more than 75% repigmentation following NBUVB treatment, Sitek *et al.* observed around half of the patients to relapse during the follow-up period [63]. The patients who remained in remission were likely to have received a lower cumulative dose of NBUVB for a satisfactory response and stable, nonprogressive disease before treatment initiation. However, no definative conclusions can be drawn from this study, as it involved only 11 patients.

Narrowband UVB is not effective in the management of segmental vitiligo. Anbar *et al.* treated 15 patients with segmental and 135 patients with nonsegmental vitiligo [62]. Nothing greater than mild repigmentation was observed in the segmental vitiligo patients. Approximately half of the patients in the nonsegmental group had marked response and, a quarter each had moderate and mild responses. The face was the area to achieve the fastest repigmentation. The less hairy areas of the face, namely the periauricular areas, the lips and the angles of the mouth, were resistant to treatment.

What happens to the quality of life after NBUVB phototherapy

Vitiligo is a disease with profound cosmetic and consequent psychological impact, rather than physical disability. The majority of the studies performed so far have assessed the efficacy of NBUVB in the improvement of cosmetic disfigurement – that is, a decrease in the area of depigmentation. Although it is natural to believe that repigmentation following NBUVB would improve the quality of life in vitiligo patients, there is minimal objective assessment to such an effect. In a study of retrospective design, Tjioe *et al.* assessed the quality of life in vitiligo patients after treatment with NBUVB [64]. Although the patients rated their health to be generally good to excellent, phototherapy accounted for only a small improvement in a minority of patients in general well-being. The main problem of phototherapy in fair-skinned individuals is prominence of the vitiligo lesions consequent to tanning of the surrounding normal skin requiring a greater degree of camouflaging until complete repigmentation is achieved in the lesions. In a study in children, quality of life assessed by the Children's Dermatology Life Quality Index did not diminish significantly in children having less than 25% repigmentation, while the reduction was significant in those who had more than 25% pigmentation with a proportional decrease in Children's Dermatology Life Quality Index with improvement grade of repigmentation [34].

Expert commentary

Narrowband UVB is the first-line treatment of vitiligo in adults and children alike due to its better efficacy when compared with PUVA. It is reasonably safe in the short term, although long term complications in vitiligo patients are yet to be determined. The logistic advantages with NBUVB over PUVA include no need to ingest oral drug with its associated side effects, no need to observe photoprotection protocol after phototherapy, lesser chance of eye complications and safety in pregnancy/lactation. NBUVB is particularly effective in treating lesions on the face (excluding non-hair-bearing areas) and neck, followed by the trunk and proximal extremities. NBUVB is not effective for lesions on the palms, soles, elbows and knees. The indicators for good response to treatment are early treatment, compliance to treatment, skin phototype 4–5, prolonged treatment, early onset of repigmentation and nonsegmental vitiligo. The combination of NBUVB and oral antioxidants seems to have a synergistic effect. The beneficial role of vitamin D analogues and calcineurin inhibitors in conjunction with NBUVB in vitiligo treatment remains controversial as a result of contradictory results projected by different studies.

Five-year view

Although NBUVB has become the first-line treatment for generalized vitiligo, the medium- and long-term risk of NBUVB in vitiligo patients is yet to be determined. Combination therapy is a reasonable approach for decreasing the side effects of individual agents, as has been proven in psoriasis. Although the combination of prostaglandin analogues and NBUVB has been found to be very effective in melanogenesis in an animal model, the role of this combination in human subjects has yet to be determined. Apparently, there should not be any safety problem, and thus ethical issues in trying such a combination. A major problem that still persists is lack of uniform dosimetry and objective tools to measure response to treatment. These deficiencies have led to widespread discrepancies in results of various studies performed so far. VASI has been developed by Hamzavi *et al.* [25]. For calculation of the VASI score, the body is divided into five regions, and for each region the VASI score is determined by the product of the area of vitiligo in hand units (1 hand unit = 1% body surface area) and extent of depigmentation in each hand unit. Adding up the scores of all regions provides a composite VASI score. For the assessment of response to treatment in vitiligo, the Vitiligo European Task Force proposed a system that takes into account the extent, stage of disease and disease progression [65]. The practical experiences with these tools are limited, and a component of subjectivity still remains with these tools. Planimetric computer software providing accurate measurement of vitiligo area will be a welcome addition.

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Key issues

- Narrowband ultraviolet B (NBUVB) is the first-line management of choice for generalized vitiligo.
- The initial dose should be ascertained by determining minimal erythema dose in vitiliginous skin, and 70% of minimal erythema dose is a reasonable starting dose. Subsequent increments may be 15–20% of the previous dose till faint pink erythema develops or perifollicular pigmentation appears.
- The long-term risk of NBUVB in vitiligo remains unclear and questions as to the carcinogenecity of UVB remain unanswered.
- The best response is observed in lesions over the face and neck, and the least response is seen over the hands and feet – the degree of repigmentation is proportional to the density of pigmented hair in a particular anatomical area.
- The combination of NBUVB with oral antoxidants appears to have an additive effect, while the combination with topical vitamin D analogues and calcineurin inhibitors does not impart additional advantage.
- The indicators for good response to treatment are early treatment, compliance to treatment, skin phototype 4–5, prolonged treatment, early onset of repigmentation and nonsegmental vitiligo.

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CME Narrowband ultraviolet B for the treatment of vitiligo

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Activity Evaluation
Where 1 is strongly disagree and 5 is strongly agree

	1	2	3	4	5
1. The activity supported the learning objectives.					
2. The material was organized clearly for learning to occur.					
3. The content learned from this activity will impact my practice.					
4. The activity was presented objectively and free of commercial bias.					

1. You are considering NBUVB treatment for your patient, a 54-year-old white man with generalized vitiligo and skin phototype 4–5. Past history is positive for an episode of a herpetic lesion on the lip 3 years previously. Based on the above review, which of the following considerations is *most likely* to apply to his treatment?

- ☐ **A** Ultraviolet A (UVA), along with psoralen, is the treatment of choice
- ☐ **B** A reasonable starting dose for NBUVB is 70% of the minimal erythema dose in vitiliginous skin
- ☐ **C** Subsequent dose increments for NBUVB should be 50% of the previous dose
- ☐ **D** Combination therapy with topical vitamin D analogues and calcineurin inhibitors is recommended in addition to NBUVB

2. Based on the above review, in which area is the patient in question 1 *least likely* to have a good response to NBUVB treatment?

- ☐ **A** Face
- ☐ **B** Neck
- ☐ **C** Hands
- ☐ **D** Areas with a high density of pigmented hair

3. Based on the above review, which of the following is *most likely* to predict a good response to NBUVB treatment for the patient described in questions 1 and 2?

- ☐ **A** Delaying treatment until later in the course
- ☐ **B** Later onset of repigmentation
- ☐ **C** Segmental vitiligo
- ☐ **D** Skin phototype 4–5

4. Based on the above review, which of the following adverse effects is *least likely* to develop in the patient described in questions 1–3?

- ☐ **A** Erythema
- ☐ **B** Reactivation of orolabial herpes simplex
- ☐ **C** Exposure keratitis and conjunctivitis
- ☐ **D** Cataract