BJD
British Journal of Dermatology

British Association of Dermatologists and British Photodermatology Group guidelines for the safe and effective use of psoralen–ultraviolet A therapy 2015

T.C. Ling,[1] T.H. Clayton,[1] J. Crawley,[2] L.S. Exton,[3] V. Goulden,[4] S. Ibbotson,[5] K. McKenna,[6] M.F. Mohd Mustapa,[3] L.E. Rhodes,[7] R. Sarkany[2] and R.S. Dawe[5]

[1]Dermatology Centre and [7]Dermatology Research Centre, Faculty of Medical and Human Sciences, Salford Royal NHS Foundation Trust, Salford, Manchester M6 8HD, U.K.

[2]Department of Dermatology, University College Hospital, 235 Euston Road, London NW1 2BU, U.K.

[3]British Association of Dermatologists, Willan House, 4 Fitzroy Square, London W1T 5HQ, U.K.

[4]Department of Dermatology, Leeds Teaching Hospitals NHS Trust, Leeds LS7 4SA, U.K.

[5]Department of Dermatology, Ninewells Hospital and Medical School, University of Dundee, Dundee DD1 9SY, U.K.

[6]Department of Dermatology, Belfast City Hospital, Belfast BT9 7AB, U.K.

Correspondence

Tsui C. Ling.

E-mail: tsui.ling@srft.nhs.uk

Accepted for publication

19 October 2015

Funding sources

None.

Conflicts of interest

T.H.C. has received an advisory board payment from Johnson & Johnson; and a conference organizing fee from Galderma; S.I. has received travel expenses and honoraria from Galderma, Spirit and Ambicare Health, and research support from Ambicare Health. T.C.L., T.H.C., J.C., V.G., S.I., K.McK, L.E.R., R.S. and R.S.D. are members of the guideline development group with technical support from L.S.E. and M.F.M.M.

This is an updated set of guidelines prepared for the British Association of Dermatologists (BAD) Clinical Standards Unit, which includes the Therapy & Guidelines (T&G) Subcommittee. Members of the Clinical Standards Unit that have been involved are P.M. McHenry (Chairman T&G), J.R. Hughes, M. Griffiths, A.J. McDonagh, D.A. Buckley, I. Nasr, V.J. Swale, C.E. Duarte Williamson, N.J. Levell, T. Leslie, E. Mallon, S. Wakelin, P. Hunasehally, M.J. Cork, S. Ungureanu, J. Donnelly (British National Formulary), K. Towers (British National Formulary), C. Saunders (British Dermatological Nursing Group), R. Davis (British Dermatological Nursing Group), A.G. Brain (BAD Scientific Administrator), L.S. Exton (BAD Information Scientist), M.F. Mohd Mustapa (BAD Clinical Standards Manager).

These guidelines were first produced by the British Photodermatology Group in 1994 (oral psoralen–ultraviolet A) and in 2000 (topical psoralen–ultraviolet A). This update was produced jointly by the British Photodermatology Group and the British Association of Dermatologists.

DOI 10.1111/bjd.14317

NICE has accredited the process used by the British Association of Dermatologists to produce guidelines. Accreditation is valid for 5 years from May 2010. More information on accreditation can be viewed at www.nice.org.uk/accreditation. For full details of our accreditation visit: www.nice.org.uk/accreditation.

1.0 Purpose and scope

The overall objective of the guideline is to provide up-to-date, evidence-based recommendations for the use of psoralen–ultraviolet A (PUVA) photochemotherapy. The document aims to update and expand on the previous guidelines by (i) offering an appraisal of all relevant literature since 1990, focusing on any key developments; (ii) addressing important, practical clinical questions relating to the primary guideline objective; (iii) providing guideline recommendations and, where appropriate, with some health economic implications; and (iv) discussing potential developments and future directions.

The guideline is presented as a detailed review with highlighted recommendations for practical use in the clinic (see section 15.0), in addition to the production of a patient information leaflet [available on the British Association of Dermatologists' (BAD) website, http://www.bad.org.uk].

2.0 Stakeholder involvement and peer review

The initial guideline development group (GDG) consisted of consultant dermatologists, a medical physicist, a nurse phototherapist and a clinical fellow in medical dermatology. The draft document was circulated to the BAD membership, the British Photodermatology Group (BPG) membership, the British Dermatological Nursing Group, the National Eczema Society, the Vitiligo Society, the Psoriasis Association, and the Psoriasis and Psoriatic Arthritis Alliance for comments, which were actively considered by the GDG and peer-reviewed by the Clinical Standards Unit of the BAD (made up of the Therapy & Guidelines Subcommittee) prior to publication.

3.0 Methodology

This guideline has been developed using the BAD's recommended methodology,[1] and with reference to the Appraisal of

Guidelines Research and Evaluation (AGREE II) instrument (www.agreetrust.org).[2] Recommendations were developed for implementation in the National Health Service using a process of considered judgement based on the evidence. The PubMed, MEDLINE and Embase databases were searched up to December 2014 for meta-analyses, randomized and nonrandomized (controlled) clinical trials, case series, case reports, and open and cohort studies involving PUVA therapy, published in the English language; search terms and strategies are detailed in the Supporting Information. Additional relevant references were also isolated from citations in reviewed literature, as well as (independent) targeted searches carried out by the authors. The authors screened the identified titles and those deemed relevant for first-round inclusion were selected for further scrutiny. The abstracts for the shortlisted references were then reviewed and the full papers of relevant material were obtained. The structure of the guidelines published in 2000 was discussed and re-evaluated, and different authors were allocated separate subsections. Each author performed a detailed appraisal of the selected literature with discussions with the entire GDG to resolve any issues, for example with the quality of evidence and making the appropriate recommendations. When considered helpful to assist with comparing study results and to summarize data, forest plots drawn in Excel® (Microsoft, Redmond, WA, U.S.A.) were used,[3] although no formal meta-analyses were performed to prepare this guideline. All subsections were subsequently collated and edited to produce the final guideline.

4.0 Limitations of the guideline

This document has been prepared on behalf of the BAD and is based on the best data available when the document was prepared. It is recognized that under certain conditions it may be necessary to deviate from the guideline and that the results of future studies may require some of the recommendations herein to be changed. Failure to adhere to this guideline should not necessarily be considered negligent, nor should adherence to these recommendations constitute a defence against a claim of negligence. Limiting the review to English-language references was a pragmatic decision but the authors recognize that this may exclude some important information published in other languages.

5.0 Plans for guideline revision

The proposed revision date for this set of recommendations is scheduled for 2020; where necessary, important interim changes will be updated on the BAD website.

6.0 Introduction and history

PUVA has been in use with refined psoralens since the early 1950s.[4] Its use has declined somewhat as narrowband ultraviolet B (NB-UVB) replaced less effective broadband ultraviolet B (BB-UVB) sources to treat psoriasis, and as NB-UVB has been proved more effective than PUVA in treating vitiligo.[5,6] It remains an important treatment, being the first-line phototherapy for pityriasis rubra pilaris and plaque-stage mycosis fungoides (MF), and a good second-line phototherapy for common chronic dermatoses, including psoriasis (for which it may be more effective than other interventions such as the new biological therapies),[7] atopic eczema and chronic urticaria. For phototherapy units serving small populations the availability of NB-UVB should be the first priority, but all larger phototherapy units should be able to offer PUVA.

7.0 Oral and topical psoralen–ultraviolet A: the different forms available

There are many different forms of PUVA. Different psoralens are available [8-methoxypsoralen (8-MOP), 5-methoxypsoralen (5-MOP), trimethylpsoralen (TMP)] and other similar furocoumarin compounds (e.g. khellin) are also used in some areas. The psoralens may be applied topically [as soaks – whole-body, except head and neck, in a bathwater psoralen liquid (bath PUVA); as cream; as gel; as lotion] and by mouth (using different formulations, including microcrystalline tablets and liquid in capsules). Also, different ultraviolet A (UVA) sources are used, including fluorescent BB-UVA lamps, metal halide BB-UVA lamps and sunlight. In the U.K., oral PUVA typically involves administration of microcrystalline tablet 8-MOP dosed according to estimated body surface area followed 2 h later by exposure to fluorescent BB-UVA lamps.[8] Usually, oral 5-MOP (which is more costly and has been less studied) is used if excessive nausea occurs with oral 8-MOP.

8.0 Effective use of psoralen–ultraviolet A: review of the evidence

8.1 When should patients be treated with psoralen–ultraviolet A?

For most indications PUVA is a skin-targeted immunosuppressive treatment; other mechanisms of action are also of likely importance. Many conditions that can be treated with PUVA can also be treated with NB-UVB. NB-UVB is a simpler treatment, with fewer side-effects to consider, so PUVA is generally indicated for chronic plaque psoriasis and atopic eczema if NB-UVB has not been effective. In such cases PUVA is often successful; failure to respond adequately to NB-UVB does not predict failure of response to PUVA. For some indications PUVA is the first-line phototherapy (favoured over NB-UVB). These indications include MF beyond patch stage, pustular psoriasis, pompholyx, hand and foot eczema and, probably, adult generalized pityriasis rubra pilaris.[9]

8.2 Selection of oral or topical psoralen–ultraviolet A

In practice, the choice of route of psoralen administration is usually based on patient preference (Table 1). Many patients prefer oral PUVA as it involves less time in the hospital unit,

Table 1 Advantages of oral vs. topical psoralen–ultraviolet A therapy (PUVA)

Advantages of oral PUVA	Advantages of topical PUVA
Shorter overall outpatient attendance times	No risk of gastrointestinal adverse effects
Less staff involvement	Drug interactions unlikely
Less risk of phototoxic reactions from natural UV exposure (lower concentration of psoralen in the skin after treatment)	Eye protection not always required
Only practical option for whole-body treatment for units with inadequate bath facilities	Shorter periods in treatment cubicle due to smaller dose of UVA

UV, ultraviolet; UVA, ultraviolet A.

but some choose topical PUVA, in particular to avoid the inconvenience of eye protection.

9.0 Psoralen–ultraviolet A for specific dermatoses

9.1 Psoriasis

9.1.1 Is oral psoralen–ultraviolet A therapy more effective than topical psoralen–ultraviolet A therapy in patients with chronic plaque psoriasis?

Two randomized parallel group studies compared oral 8-MOP PUVA with 8-MOP bath PUVA.[10,11] One prospective contemporaneous controlled (but not reported to be randomized) study compared oral 8-MOP PUVA with trioxsalen (TMP) bath PUVA,[12] and another compared oral 8-MOP PUVA with 8-MOP bath PUVA.[13] None of these studies detected a definite difference in efficacy between oral and bath PUVA (Table 2; Fig. 1), although one did show 18% more of the small study sample population clearing with bath PUVA than with oral PUVA (Fig. 1).[11] A recently published randomized study comparing bath 8-MOP PUVA with oral 8-MOP PUVA for psoriasis did not detect a difference in efficacy between these modalities.[14] One study report included a questionnaire administered to 13 patients who had received both oral and bath PUVA. There was a roughly equal split among these patients in which form of PUVA they favoured. A recent questionnaire survey of patients referred to a U.K. phototherapy unit found a similar, roughly equal, split between patients who would choose bath PUVA and those who would choose oral PUVA.[15]

Oral PUVA was not more effective than topical PUVA as a whole-body treatment for psoriasis. The evidence that exists from randomized controlled trials (RCTs) and prospective contemporaneous nonrandomized controlled studies showed that

Table 2 Controlled studies comparing whole-body topical psoralen–ultraviolet A ('bath PUVA') with oral PUVA

First author (year of publication)	Bath psoralen	Oral psoralen	UVA regimen	Randomized?	Blinded?	Proportion (%) cleared with oral PUVA	Proportion (%) cleared with bath PUVA	Difference (% more clearing with oral PUVA); 95% CI for difference
Turjanmaa (1985)[12]	TMP 3 mg L^{-1}	8-MOP 0·6 mg kg^{-1}	Arbitrary starting doses; three times weekly; incremental regimen not reported	No	No	37/43 (86)	42/50 (84)	2; −12 to 17
Lowe (1986)[13]	3·75 mg L^{-1}	8-MOP 0·6 mg kg^{-1}	Skin phototype-based starting dose and incremental regimen	No	No	8/20 (40)	8/20 (40)	0; −30 to 30
Collins (1992)[10]	8-MOP 3·78 mg L^{-1}	8-MOP 0·6 mg kg^{-1}	Skin phototype-based starting doses; three times weekly; no more than 20 treatments	Yes (but allocation not concealed)	No	14/22 (64)	14/22 (64)	0; −28 to 28
Cooper (2000)[11]	8-MOP 2·6 mg L^{-1}	8-MOP 0·6 mg kg^{-1}	70% MPD starting dose; twice weekly; percentage-based incremental regimen	Yes (but allocation not concealed)	No	14/17 (82)	17/17 (100)	−18; −36 to 0·5

UVA, ultraviolet A; CI, confidence interval; TMP, trimethylpsoralen; 8-MOP, 8 methoxypsoralen; MPD, minimal phototoxic dose.

1st Author	Year	n	% more cleared with oral PUVA (95% CI)
Turjanmaa[12]	1985	93	2% (–12% to 17%)
Lowe[13]	1986	40	0% (–30% to 30%)
Collins[10]	1992	44	0% (–28% to 28%)
Cooper[11]	2000	34	–18% (–36% to 0·5%)

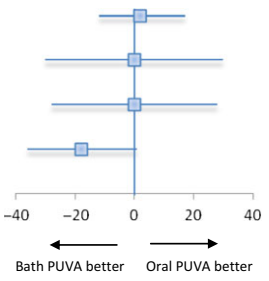

Fig 1. Controlled study (including randomized controlled trials by Collins *et al.* and Cooper *et al.*)[10,11] comparisons of oral psoralen–ultraviolet A (PUVA) with bath PUVA for psoriasis. CI, confidence interval.

bath PUVA works at least as well as oral PUVA. It is of value to be able to offer bath PUVA as well as oral PUVA.

Recommendation [strength of recommendation B; level of evidence 1+ (see Appendix)] All dermatology phototherapy units should offer bath PUVA as well as oral PUVA to treat psoriasis.

9.1.2 Is psoralen–ultraviolet A therapy more efficacious than conventional oral systemic therapies in patients with chronic plaque psoriasis?

There have been no RCTs comparing conventional oral systemic therapies with PUVA to treat chronic plaque psoriasis. An RCT compared PUVA with placebo and showed a similar magnitude of benefit as has been shown with various conventional systemic therapies when compared with placebo (Figs 2 and 3).[16–19] Owing to differences in study methodologies, a meta-analysis comparing PUVA with conventional systemic therapies would not be appropriate. Nevertheless, the information given in these publications concerning baseline psoriasis severity suggests that PUVA was likely to be at least of similar efficacy in the relatively short term as these systemic therapies. As the risks with PUVA are lower than the risks with systemic therapy,[20,21] PUVA should usually be considered first.

Recommendation (strength of recommendation B; level of evidence 1+) PUVA should usually be offered before oral systemic therapy for patients with chronic plaque psoriasis that has not responded adequately to other therapies, including NB-UVB.

9.1.3 Is psoralen–ultraviolet A therapy more efficacious than biologics in patients with chronic plaque psoriasis?

This has not been assessed in any head-to-head comparative studies. However, a retrospective database comparison showed PUVA in the short term to be more effective than most biologicals in improving psoriasis by reducing the Psoriasis Area and Severity Score (PASI) by 75%, and even more so in reducing the PASI by 90% (Figs 4 and 5).[7]

Some national guidelines on the use of biological therapy for psoriasis do not clearly indicate if PUVA should be used before biologics. For example, some guidelines have stated that one of the criterions for using biological therapy was 'where phototherapy and alternative standard systemic therapy are contraindicated or cannot be used due to the development of, or risk of developing, clinically important treatment related toxicity', not clarifying whether phototherapy should be taken to include PUVA or not.[22]

A randomized comparative study of adequate duration comparing PUVA with biological therapy would help guidance with prescribing PUVA before biologicals or not, taking into consideration the relative risks (RR) and efficacy. However, on current evidence it seems appropriate to continue to follow the advice in the *British National Formulary*,[23] where PUVA should be considered before biological therapy.

Recommendation (strength of recommendation C; level of evidence 2+) PUVA should be considered before biological therapy to treat chronic plaque psoriasis.

1st Author	Year	n	% more cleared with oral PUVA (95% CI)
Sivanesan[16]	2009	40	2% (–12% to 17%)

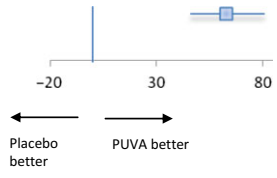

Fig 2. Randomized controlled trial comparing psoralen–ultraviolet A (PUVA) with placebo for psoriasis. CI, confidence interval.

1st Author	Year	Systemic	Outcome	n	% more cleared with systemic (95% CI)
Nugteren-Huying[17]	1990	Fumaric acid esters	'Clear' at 16 weeks	24	42% (9% to 74%)
Ellis[18]	1991	Ciclosporin 7.5 mg/kg/day	'clear or almost clear' by 8 weeks	40	80% (60% to 100%)
Ellis[18]	1991	Ciclosporin 5 mg/kg/day	'clear or almost clear' by 8 weeks	45	65% (44% to 86%)
Ellis[18]	1991	Ciclosporin 3 mg/kg/day	'clear or almost clear' by 8 weeks	50	36% (17% to 55%)
Saurat[19]	2008	Methotrexate	PASI 75% reduction	163	17% (3% to 30%

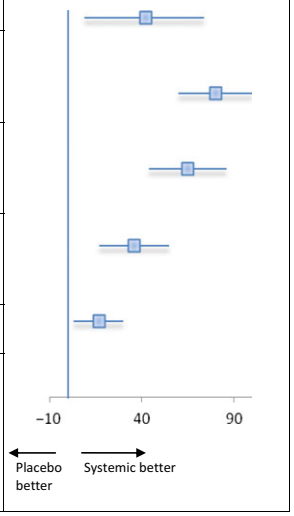

Fig 3. Randomized controlled trials comparing conventional systemic therapies with placebo for psoriasis. CI, confidence interval; PASI 75%, 75% reduction in Psoriasis Area and Severity Index.

Biological drug	n (number treated with biological)	% more reaching PASI 75 with PUVA than with biological (95% CI)
Adalimumab	18	30% (6% to 54%)
Alefacept	32	60% (44% to 77%)
Efalizumab	17	27% (2·5% to 51%)
Etanercept	38	46% (29% to 63%)
Infliximab	7	−14% (−21% to −8%
Ustekinumab	18	19 (−4% to 42%)

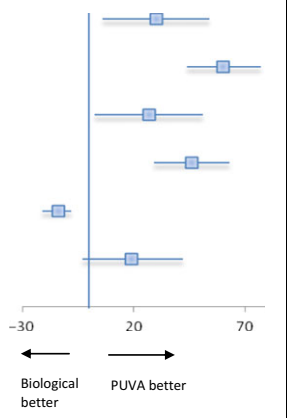

Fig 4. Retrospective comparison of psoralen–ultraviolet A (PUVA) therapy (n = 118 patients) with biologicals (Inzinger *et al.*).[7] Baseline mean Psoriasis Area and Severity Index (PASI) score for PUVA was 15 and for biologicals it was 16·9. Outcome of 75% reduction in PASI (PASI 75). CI, confidence interval.

9.1.4 Is psoralen–ultraviolet A therapy more efficacious than narrowband ultraviolet B in patients with chronic plaque psoriasis?

Ten comparative studies of PUVA with NB-UVB to treat psoriasis have been published (Fig. 6);[24–33] six of these studies were randomized,[26–30,33] with the rest being contemporaneous controlled studies. A study by Dayal *et al.* is not included in Figure 6 because insufficient data were available in the report, although it was reported that all patients (in both groups) reached 'greater than 75% clearance or complete clearance'.[32] One study found that PUVA was more effective the more severe the psoriasis was at baseline,[25] and another showed that PUVA remained more effective than NB-UVB at 6 months after completion of treatment courses.[26] In most (but not all) comparisons involving NB-UVB three times a week there was either little difference or NB-UVB was more effective, whereas in all but one of the studies comparing NB-UVB twice weekly with PUVA, PUVA was more effective (Fig. 6). A randomized study comparing NB-UVB twice weekly with NB-UVB three times weekly found the psoriasis in 11% more patients in the latter group to be clearing;[34] pos-

Biological drug	n (number treated with biological)	% more reaching PASI 90 with PUVA than with biological (95% CI)
Adalimumab	18	47% (26% to 68%)
Alefacept	32	66% (54% to 77%)
Efalizumab	17	64% (50% to 78%)
Etanercept	38	57% (41% to 72%)
Infliximab	7	−2% (−36% to 33%)
Ustekinumab	18	31 (7% to 55%)

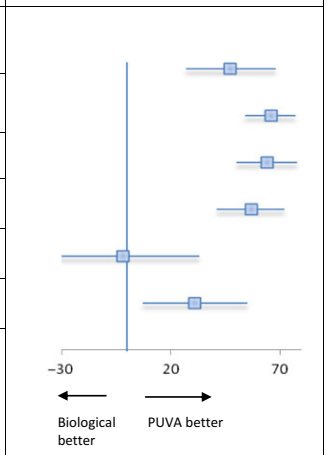

Fig 5. Retrospective comparison of psoralen–ultraviolet A (PUVA) therapy (n = 118 patients) with biologicals (Inzinger *et al.*).[7] Baseline mean Psoriasis Area and Severity Index (PASI) score for PUVA was 15 and for biologicals it was 16·9. Outcome of 90% reduction in PASI (PASI 90) (similar outcome measure to 'clearance' or 'minimal residual activity'). CI, confidence interval.

1st Author	Year	Design	NB-UVB	PUVA	Outcome	Total n	% more cleared with PUVA (95% CI)
Van Weelden[24]	1990	controlled, paired, inpatients	2 times a week	2 times a week, oral 8-MOP	better treatment by 4 weeks	10	10% (−43% to 63%)
Tanew[25]	1999	controlled, paired	3 times a week	3 times a week, oral liquid formulation (rapidly absorbed)	better response	25	28% (−4% to 60%)
Gordon[26]	1999	randomized, parallel group	2 times a week	2 times a week, oral 8-MOP	clearance by end course	100	21% (4% to 38%)
Gordon[26]	1999	randomized, parallel group	2 times a week	2 times a week oral 8-MOP	**still clear at 6 months**	100	21% (5% to 37%)
Dawe[27]	2003	randomized, paired	3 times a week	2 times a week, TMP bath PUVA	clearance/MRA by end course	28	−21% (−6% to−37%)
Markham[28]	2003	randomized, parallel group	3 times a week	2 times a week, oral 8-MOP	clearance by end course	54	1% (−19% to 21%))
Markham[28]	2003	randomized, parallel group	3 times a week	2 times a week, oral 8- MOP	**still clear at 6 months**	54	−3% (−30% to 23%)
Snellman[29]	2004	randomized, paired	3 times a week	3 times a week	excellent clinical response	18	−33% (−6% to −61%)
Yones[30]	2006	randomized, parallel group	2 times a week	2 times a week, oral 8-MOP	clearance at end course	71 (excluded SPT V & VI)	19% (−1% to 39%)
Salem[31]	2010	controlled, parallel group	3 times a week	3 times a week, bath 8-MOP	clearance at end course	34	49% (21% to 76%)
Chauhan[33]	2011	randomized, parallel group	3 times a week	3 times a week, oral 8-MOP	marked improvement	51	1% (−22% to 24%)

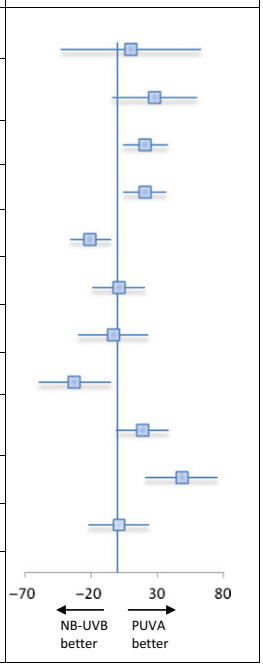

Fig 6. Controlled studies comparing psoralen–ultraviolet A therapy (PUVA) with narrowband ultraviolet B (NB-UVB) for psoriasis. CI, confidence interval; 8-MOP, 8-methyoxypsoralen; TMP, trimethylpsoralen; MRA, minimal residual activity; SPT, skin phototype.

sibly those studies comparing twice weekly NB-UVB regimens were not comparing optimally effective NB-UVB regimens with PUVA. Only two studies showed NB-UVB to be significantly more effective than PUVA: both used a TMP bath PUVA regimen.[27,29]

Overall, in the U.K., PUVA appears to be more effective than NB-UVB for psoriasis. It may work better in those with more severe psoriasis, although only one study showed this to be a significant finding. PUVA can work when NB-UVB has not worked, as found in at least one of the paired comparison studies. The experience of all members of the GDG is that failure to respond adequately (either in initial clearance or maintenance of improvement after a course) to NB-UVB does not mean that PUVA will not prove adequate. An assessment of one region's data corroborates this impression: during the 5 years (2005–2009 inclusive), 128 patients in Tayside had a first course of NB-UVB followed by a first course of PUVA. Of these PUVA courses, subsequent to a course of NB-UVB, 62%

(70/128) were documented to achieve 'clearance' or 'minimal residual activity', and 56% (29/52) of PUVA courses subsequent to a failed NB-UVB course were documented as achieving 'clearance' or 'minimal residual activity'.

We found no studies directly comparing PUVA with NB-UVB in children.[35] It seems likely that the relative efficacy of these treatments will be similar to that found in adults.

There are greater adverse effect concerns with PUVA than with NB-UVB, with particularly long-term skin cancer risks a concern when treating children for what is frequently a lifelong condition. Also, PUVA is more involved, requiring the taking of tablets or attendance for baths in a hospital unit. Therefore, PUVA is not a first-line phototherapy for adults but even less so for children. However, for individuals who have not adequately responded to NB-UVB it is appropriate to consider it, and for many children it is more appropriate than other options, which may include hospital admissions resulting in disruption of school and home life or systemic therapies with their adverse effect risks.

Recommendation (strength of recommendation B; level of evidence 1+) Although PUVA may occasionally be appropriate as a first-line phototherapy treatment for especially thick and/or extensive plaque psoriasis it should usually only be considered in patients with chronic plaque psoriasis if NB-UVB has not been adequately effective.

9.2 Eczema

We did not find any controlled studies investigating the use of PUVA in atopic eczema. The findings of several uncontrolled studies have suggested that PUVA is an effective treatment for severe atopic eczema.[36,37] A more recent randomized crossover trial found 5-MOP plus UVA to be superior to medium-dose UVA1 in the treatment of severe atopic eczema.[38] The authors also found that reductions in an eczema severity score were observed after only 10 irradiations.

A systematic review on the use of photo(chemo)therapy in the management of atopic eczema with PUVA therapy found good-quality RCTs to be limited.[39]

9.2.1 Is psoralen–ultraviolet A therapy more efficacious than narrowband ultraviolet B in patients with atopic eczema?

We found no prospective trials comparing PUVA and NB-UVB. The efficacy of 8-MOP bath PUVA vs. NB-UVB has been studied in a half-side comparison study.[40] The authors of this small study concluded that both regimens were not detectably different in efficacy. In the absence of strong evidence favouring PUVA, NB-UVB should be the first-line phototherapy as a simpler and safer intervention for atopic eczema.

Recommendation (strength of recommendation D; level of evidence 3) PUVA should be considered in patients with atopic eczema only if NB-UVB has not been adequately effective.

9.2.2 Is psoralen–ultraviolet A therapy more efficacious than conventional oral systemic therapies in patients with atopic eczema?

There were no direct comparative trials comparing systemic agents with PUVA in patients with atopic eczema.

9.2.3 Is psoralen–ultraviolet A therapy more efficacious than narrowband ultraviolet B in children (younger than 16 years) with eczema?

While there were several retrospective studies showing efficacy of PUVA in children with atopic eczema, there were no direct comparative studies comparing PUVA with NB-UVB in children. A large study of 113 Japanese patients with severe atopic eczema treated with oral PUVA, which included 18 patients aged 12–19 years, reported that the majority of patients improved with PUVA,[36] although only 31 participants were scored for severity. The efficacy of bath PUVA therapy in severe cases of atopic dermatitis (AD) in adults has been studied in children over the age of 12 years.[41] This small study of 30 participants reported patient evaluations with an overall patient satisfaction score of 8·8 on a scale of 0–10.

The most convincing evidence for the use of PUVA in children with atopic eczema came from a report by Sheehan *et al.*, who found that 32 of 39 children were able to achieve remission.[42] Similar results have been reported for the use of UVB in children with atopic eczema.[43]

9.3 Cutaneous T-cell lymphoma

PUVA remains a major therapeutic modality in the treatment of cutaneous T-cell lymphoma (CTCL). Its use is in the treatment of the most common form of CTCL, MF, where it remains the major therapy for plaque-stage disease. PUVA phototoxicity has been shown to target selectively neoplastic T lymphocytes in the skin.[44–48]

9.3.1 How does psoralen–ultraviolet A therapy compare with other types of phototherapy in cytotoxic T-cell lymphoma?

Narrowband ultraviolet B (TL-01) compared with psoralen–ultraviolet A therapy There are no double-blinded, controlled comparison trials of PUVA vs. NB-UVB for the treatment of early-stage CTCL, and most data are from retrospective studies.

In a retrospective analysis of 56 patients with early-stage (IA and IB) disease, 81% (17 of 21) of patients treated with NB-UVB achieved a complete remission compared with 71% (25 of 35) of those treated with PUVA.[49] In a second retrospective study of 40 patients with early-stage disease, PUVA and NB-UVB were found to be equally effective, with NB-UVB resulting in a 50% complete remission rate and a 33% partial response rate compared with PUVA response rates of 64% and 21%, respectively.[50] A third prospective study also showed no statistically significant difference in the degree of

response obtained with the use of NB-UVB or PUVA in the treatment of 20 patients with early stage MF.[51] Almost complete remission occurred in 70% of participants with either treatment. Remission durations with NB-UVB were assessed in one study which showed that relapse occurred in a mean of 6 months.[52] NB-UVB appears to be as effective as PUVA in patch stage CTCL; remission durations with NB-UVB and PUVA have not been directly compared.

PUVA has long been the first-line phototherapy for plaque-stage MF. PUVA and NB-UVB may work in MF through direct effects on abnormal lymphocytes. If this is part of how it works, it seems unlikely that NB-UVB should penetrate sufficiently to clear plaque-stage MF, as well as PUVA. This is supported by case series of treatment of patch-stage MF, which found that histologically incomplete deep clearance was associated with poorer response.[53] Also, a recent review of how patients who had been receiving PUVA responded when switched to NB-UVB due to a psoralen shortage confirmed that those with more severe disease (that study did not report explicitly on the differences between patch- and plaque-stage MF) were less likely to improve when switched to NB-UVB.[54]

Other types of phototherapy There are no comparative studies of BB-UVB vs. PUVA in CTCL. As with NB-UVB, the role of BB-UVB in CTCL appears to be in early-stage disease.[55,56]

There are no comparative studies of UVA1 vs. PUVA. There are limited data regarding UVA1 therapy in CTCL, and this suggests that it may potentially be a useful treatment in patch-stage disease,[57] and perhaps in more advanced disease as well.[58]

Recommendation (strength of recommendation D; level of evidence 3) For patch-stage CTCL, NB-UVB is as effective as PUVA and is the treatment of choice.

Recommendation (strength of recommendation D; level of evidence 4) For plaque-stage CTCL, PUVA is the treatment of choice.

9.3.2 When should psoralen–ultraviolet A be used in cytotoxic T-cell lymphoma?

PUVA is very effective in clearing lesions of early-stage CTCL, that is, patches and thin plaques. Its effect on infiltrative thick lesions and tumours is more controversial.[59] As patch-stage disease is so responsive to NB-UVB, the role of PUVA is primarily in the treatment of plaque-stage disease. However, one must be aware and use caution in this setting, knowing that there may be an increased risk of other skin tumours if immunosuppressive agents are required later in the disease process (S.J. Whittaker, personal communication). It is not always possible to predict in advance who might require systemic immunosuppressive therapies later and progressing to next-line therapies earlier rather than PUVA is often not appropriate. The issues should be fully discussed with patients.

PUVA was first reported as a treatment for MF in the 1970s. In 1976, Gilchrest *et al.* reported nine patients with MF at a spectrum of stages from plaque stage to erythroderma who had failed to respond to conventional therapies.[60] Two patients were added to this series and reported on in 1979.[47] A course of PUVA, ranging from 16 to 28 months, induced complete clearing in 10 of 11 patients. Long-term outcome was difficult to evaluate as three patients died within the first year and six further patients were lost to follow-up. Roenigk treated 12 patients with plaque-stage MF, a combination of plaques and tumours, or erythrodermic disease.[44] Complete response was observed in the seven patients with plaque-stage disease, with partial response in the four patients with both plaques and tumours, and a poor response in the erythrodermic patient. The mean number of treatments was just 17.

A 15-year prospective study compared PUVA with topical therapies. Eighty-two patients with MF (68 patients at stage I, seven at stage II, six at stage III and one at stage IV) were studied.[61] It was found that 95% (including all stages of disease) of patients had some level of response to PUVA: 65% went into complete remission, 31% had a partial response and 4% showed no response. The medium time to best response for all stages was 3 months. Patients in early-stage disease responded best: 79% of patients with stage 1A disease achieved complete remission, 59% with stage IB, 83% with stage IIA and 33% with stage III.

A smaller case series has shown clinical improvement in six patients with stage II or III MF after PUVA.[62] Remission after PUVA can be long lasting: a single course of PUVA led to remission for up to 79 months in five of nine stage IA patients, and in 10 of 26 stage IB patients.[63]

There has been one randomized crossover study comparing PUVA with extracorporeal photophoresis (ECP) in stage IB disease in patients who had a detectable peripheral T-cell clone. In 16 patients with stage IB disease, skin disease activity scores fell more following 3 months of PUVA than following 6 months of ECP. Neither treatment achieved clearance of T-cell clones from peripheral blood.[64]

Flexural sites ('sanctuary sites') often fail to respond completely – in both patch and plaque stages – and the duration of response varies.[65]

Trial evidence of the role of PUVA in late-stage disease is more limited but nevertheless suggestive that PUVA, as a monotherapy, is not an effective therapy in late-stage disease. This is thought to be because of the failure of UVA to expose significant reservoirs of malignant cells in the lymph nodes and circulation.[44,55,61]

In studies for PUVA, treatment schedules vary from twice to four times a week with varied increment protocols. In the U.K., commonly used schedules are twice or three times weekly treatments until disease clearance or best partial response.[65] Unlike in most other conditions treated with phototherapy, maintenance therapy to prevent disease relapse in patients with quickly recurrent disease is still common practice.[66] However, there is no consensus on this [and a trial comparing maintenance with no maintenance in PUVA for MF is ongoing (clinicaltrials.gov registration NCT01686594)] and the benefits of maintenance therapy are still uncertain. In the

recently published BAD skin lymphoma guidelines, Whittaker *et al.* concluded that maintenance PUVA therapy should be avoided and the cumulative lifetime PUVA exposure should be limited (1200 J cm^{-2} of UVA and/or 250 sessions).

Recommendation (strength of recommendation B; level of evidence 1+) PUVA is the first-line treatment for plaque-stage MF.

Recommendation [strength of recommendation D (good practice point); level of evidence 4] Maintenance therapy may be considered to prevent relapse in quickly recurrent disease.

9.3.3 When should psoralen–ultraviolet A be used with other therapies?

In practice, PUVA is often used with other therapies rather than as monotherapy. The choice of therapy will be determined by the disease stage.

Psoralen–ultraviolet A with interferon In early-stage disease the combination of PUVA and interferon (IFN) has been shown to be well tolerated and effective. In a phase II clinical trial, 89 patients with stage IA–IIA disease treated for 14 months with a combination of PUVA and low-dose IFN demonstrated an overall response rate of 98% with complete remission in 84%. The study reported an overall relapse rate of 37% with a median time to relapse of 46 months. Of the relapses, all were local recurrences that further responded to further low-dose IFN therapy.[67]

An RCT comparing PUVA vs. PUVA and IFN-α in early-stage MF found higher remission rates and longer progression-free survival with combination therapy than PUVA monotherapy.[68] In other trials, similar results have been found.[69]

Psoralen–ultraviolet A with retinoids and rexinoids The retinoids acitretin and isotretinoin, and the rexinoid bexarotene have been shown to be effective in combination with PUVA, and may reduce the total cumulative PUVA dose needed to induce and sustain remission. A nonrandomized trial of patients with plaque-stage MF found that combination therapy of isotretinoin or etretinate with PUVA achieved faster remission, with reduced doses of PUVA required. However, the overall remission rate was not increased.[70]

Although data are limited, small studies suggest that PUVA–bexarotene may be an effective combination.[71,72] A larger, phase III RCT (n = 93) reported no significant difference in response rate or response duration between treating with PUVA alone vs. PUVA and bexarotene in stage IB–IIA.[73] However, there was a trend towards fewer PUVA sessions and a lower dose required to achieve complete clinical response in the combination arm but, owing to insufficient power, this did not achieve statistical significance.

Psoralen–ultraviolet A following total skin electron beam therapy A retrospective review found, compared with TSEB alone and with TSEB followed by other forms of adjuvant therapy, that PUVA adjuvant therapy following total skin electron beam therapy (TSEB) increased 5-year survival in patients with early-stage disease.[74] There was a 14% relapse rate at 100 months for patients who had received adjuvant PUVA therapy compared with a 49% relapse rate in those who had not. However, TSEB is not usually appropriate in early disease and that study did not show a difference in survival (as opposed to disease clearance) with TSEB followed by PUVA.

Recommendation (strength of recommendation B; level of evidence 1+) In the treatment of early-stage CTCL, combination therapy with PUVA and IFN or retinoids/rexinoids should be considered if the response to monotherapy is slow.

9.4 Vitiligo

9.4.1 Is psoralen–ultraviolet A more efficacious than narrowband ultraviolet B in patients with vitiligo?

No; NB-UVB is at least as effective as PUVA in treating vitiligo (Fig. 7).[6,75,76] Also, the match of repigmentation to normal skin colour is better with NB-UVB than with PUVA,[6] and NB-UVB is more effective in inducing repigmentation in unstable vitiligo than PUVA.[76,77] These studies involved widespread vitiligo vulgaris; there is no available good quality evidence comparing PUVA and NB-UVB for other patterns of vitiligo, such as segmental vitiligo.

Recommendation (strength of recommendation A; level of evidence 1+) PUVA should only be considered for widespread vitiligo if NB-UVB has not shown to be adequately effective.

9.5 Photodermatoses

Owing to the relative rarity of some idiopathic photodermatoses and paucity of evidence in this area, the literature search was extended to include all papers from 1966. Both oral and topical PUVA have been reported to be used in the following idiopathic photodermatoses: polymorphic light eruption (PLE), chronic actinic dermatitis (CAD), solar urticaria (SU), erythropoietic protoporphyria (EPP) and actinic prurigo (AP). Most papers were found for PLE (n = 15), followed by SU (n = 8), CAD (n = 7), AP (n = 2) and EPP (n = 2).

9.5.1 In the treatment of photodermatoses, what is the efficacy and safety of psoralen–ultraviolet A compared with ultraviolet B?

Polymorphic light eruption In PLE, the reported efficacy of PUVA was a 65–100% photoprotection rate.[78–89] There were five comparative studies with UVB,[78,79,81,83,84] including two RCTs.[81,83]

The only RCT comparing PUVA with NB-UVB did not detect any significant difference in efficacy. In this trial, 12

1st Author	Year	Design	NB-UVB	PUVA	Outcome	Total n	% more cleared with PUVA (95% CI)
Westerhof[75]	1997	controlled (alternate allocation), parallel group	2 times a week	0.005% psoralen gel, 2 times a week	any repigmentation by 4 months	106	−27% (−48% to −6%)
Bhatnagar[77]	2007	controlled ('randomly allocated'), parallel group	3 times a week, reducing to 2 times a week	oral TMP 0.6mg/kg	repigmentation of >50% at end of treatment (up to 1 year therapy)	50	−20% (−47% to 7%)
Yones[6]	2007	randomized, parallel group	2 times a week	oral 8-MOP (or 5-MOP if intolerant of 8-MOP because of nausea) 2 times a week	repigmentation of >50% at end of treatment course	50	−28% (−55% to −1%)
Yones[6]	2007	randomized, parallel group	2 times a week	oral 8-MOP (or 5-MOP if intolerant of 8-MOP because of nausea) 2 times a week	repigmentation of >75% at end of treatment course	50	−12% (−36% to 12%)
Yones[6]	2007	randomized, parallel group	2 times a week	oral 8-MOP (or 5-MOP if intolerant of 8-MOP because of nausea) 2 times a week	repigmentation of still >75% compared with before course on follow-up 12 months after end course	50	−12% (−37% to 13%)

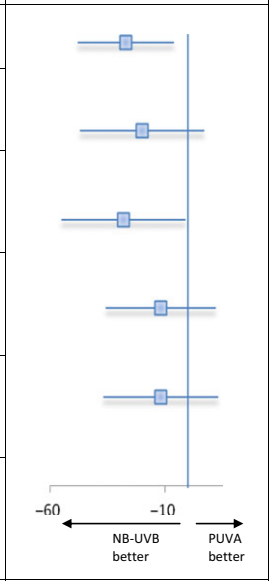

Fig 7. Controlled studies comparing psoralen–ultraviolet A (PUVA) with narrowband ultraviolet B (NB-UVB) for vitiligo. TMP, trimethylpsoralen; 8-MOP, 8-methyoxypsoralen; 5-MOP, 5-methyoxypsoralen; CI, confidence interval.

patients treated with oral 5-MOP or 8-MOP PUVA were compared with 13 patients treated with UVB and placebo tablets [first dose was 70% minimal phototoxic dose (MPD)/minimal erythema dose (MED); 20% increments; three times weekly UV exposures for 5 weeks]. The study found no significant differences between the two forms of phototherapy in reducing the number of episodes of PLE or restriction of outdoor activity.[81]

Two studies compared the efficacy of PUVA with BB-UVB.[83,84] In an RCT, oral 8-MOP PUVA (n = 13) was compared with BB-UVB plus placebo tablets (n = 13) and low-dose UVA plus placebo tablets (n = 12).[83] Using self-assessment of treatment efficacy, 92% of patients considered PUVA successful compared with 62% with BB-UVB. These findings were supported by Addo and Sharma, who reported complete remission in 89% of patients treated with PUVA compared with 69% treated with BB-UVB.[84]

Man *et al.* reported a 10-year retrospective review of 170 patients with moderate-to-severe PLE who attended for PUVA and/or UVB phototherapy.[78] Eight patients received PUVA, 128 NB-UVB, five BB-UVB and 29 patients who failed to respond satisfactorily to NB-UVB were given PUVA the following year. The patients were followed up in autumn or the following spring and self-assessments were made of the severity and frequency of PLE episodes. Two hundred and eighty-one courses of UVB and 99 courses of PUVA were evaluated. At follow-up, 88% of those who received PUVA and 89% who received UVB reported good or moderate improvement, and of the 29 who received both PUVA and NB-UVB, 12 favoured PUVA, four preferred NB-UVB and five liked both equally.[78]

Mastalier *et al.* presented 14-year retrospective data on 79 patients treated with phototherapy; 17 patients with oral 5-MOP or topical 8-MOP PUVA, 56 with BB-UVB and six with UVA alone. The patients were assessed on the first summer after phototherapy for prevention of PLE episodes. The photoprotection rate was complete/partial remission in 65% for PUVA, 82% for BB-UVB and 83% for UVA. However, the authors acknowledged that PUVA was given to patients with more severe symptoms, while BB-UVB and UVA alone were given to patients with milder symptoms.[79]

The latter two studies were retrospective chart review studies, with smaller numbers of patients receiving PUVA compared with UVB; moreover, patients who had more severe PLE, or who had previously failed UVB, tended to receive PUVA.[78,79]

Safety of psoralen–ultraviolet A compared with ultraviolet B in PLE There is an inherent risk of provoking the underlying condition in treating any photodermatosis. There was limited comparative data between the two forms of phototherapy to ascertain which form is more likely to provoke the eruption. Pooling the incidence of adverse events from the small number of PLE studies, the side-effects of rash provocation, erythema and pruritus were found to be common in both forms of phototherapy, although more common with UVB than with PUVA (Table 3). However, as the number of patients in each cohort was small and the severity of the adverse events not directly comparable, the overall percentages should be regarded with caution.

In the treatment of PLE, the side-effects of rash provocation, erythema and pruritus were found to be common in both

Table 3 Incidence of side-effects with different phototherapy

Phototherapy type	Rash provocation (%)	Erythema (%)	Pruritus (%)	Herpes simplex (%)
PUVA	12–50	8–67	18–33	–
NB-UVB	62	54	15	–
BB-UVB	53	27	40	20

PUVA, psoralen–ultraviolet A; NB-UVB, narrowband ultraviolet B; BB-UVB, broadband ultraviolet B.

forms of phototherapy. There was no appreciable difference in the efficacy of PUVA and UVB.

Photodermatoses other than polymorphic light eruption No comparative studies with UVB were identified for the other photodermatoses.

9.5.2 When should psoralen–ultraviolet A be used in preference to other therapies for photodermatoses?

Photodermatoses are chronic conditions requiring ongoing treatment. Photoprotective measures and symptomatic treatment may be adequate in milder cases; however, in more severely affected patients, second-line treatments are often required. First-line treatment may include topical corticosteroids, antihistamines and β-carotene (for EPP), and is not within the scope of this guideline. Second-line treatment may include phototherapy. NB-UVB is generally considered before PUVA because it has the following advantages: lower risk of photocarcinogenesis, no risk of nausea or other side-effects associated with the ingestion of MOP and increased convenience as there is no need to take tablets or use eye protection post-treatment.

Polymorphic light eruption There is good evidence of efficacy with UVB compared with PUVA.[81] There are no other direct comparative studies with other modalities of treatment, which include systemic corticosteroid, azathioprine, ciclosporin, hydroxychloroquine, β-carotene, nicotinamide, omega-3 fatty acids, antioxidants and *Escherichia coli* infiltrate.[90–104] Systemic corticosteroid has been demonstrated to reduce the severity of PLE when used as a short course on sunny holidays.[105] Systemic immunosuppression was found to be effective in a small number of case reports. Efficacy of treatment with hydroxychloroquine, β-carotene, nicotinamide, omega-3 fatty acids, antioxidants, and *E. coli* infiltrate has not been well established in RCTs.

Recommendation (strength of recommendation D; level of evidence 4) In the treatment of PLE, NB-UVB should be considered before PUVA. However, PUVA should be considered if NB-UVB has failed or has previously triggered the eruption, or if there are other practical issues. PUVA should be considered before other systemic treatments.

Chronic actinic dermatitis We found no comparative studies using PUVA in the treatment of CAD. There are a limited number of case reports and small case series reporting the use of PUVA in CAD.[106–112]

The largest case series (only four patients) reported the use of PUVA with topical corticosteroid cover and inpatient supervision in UV-protected rooms (first dose was 0·25 J cm^{-2}, with increments of 0·25–2·50 J cm^{-2}, twice a week; maintenance at 10 J cm^{-2} fortnightly, then monthly). After each of the first six exposures, topical betamethasone or hydrocortisone butyrate was applied immediately to the trunk and 1% hydrocortisone to the face. In two of the patients who were phototested, there was resultant normalization of MEDs to UVB and UVA, and reported normal sun tolerance at 5-year follow-up, with continued monthly maintenance treatment.[108,109]

Treatment with PUVA covered with oral prednisolone and initial inpatient supervision has been reported in three case reports.[111,112] Prednisolone (60–100 mg) was administered daily initially and tapered over 4 weeks, while PUVA was given 3–4 times a week initially and tapered to once or twice weekly. Maintenance PUVA was given for 6–18 months. One patient with a borderline-normal MED to UVB and a low MED to UVA when retested had normal UVA response 4 months after stopping treatment in winter. All reported improvement of sun tolerance during maintenance treatment.

Successful use of ciclosporin, despite concerns about increasing risks of carcinogenesis using it with PUVA, at 5 mg kg^{-1} daily in combination with PUVA and initial prednisolone cover, has also been reported in case reports.[106,110]

Mycophenolate mofetil 1 g twice daily was reportedly effective when administered in combination with PUVA and initial prednisolone cover in two cases, followed by maintenance PUVA once weekly.[107]

One tertiary referral unit in the U.K. routinely treats patients with CAD with PUVA with success (T. Garibaldinos, personal communication). Prednisolone (20–30 mg) is taken on the day of phototherapy; small-dose increments of 0·05 J cm^{-2} are given with each UVA exposure; the course is given three times a week, then reduced to twice weekly and then once weekly. Inpatient supervision is not generally required.

Recommendation (strength of recommendation D; level of evidence 4) In the treatment of CAD, PUVA therapy should be considered in a specialist unit experienced in managing this disease, with full knowledge of the individual patient's action spectrum. Special precautions, including inpatient supervision and topical/oral corticosteroid cover, may be required.

Idiopathic solar urticaria We found no comparative studies with PUVA in the treatment of SU. As would be anticipated in this rare disorder, a limited number of studies report the use of PUVA or other treatment options in SU.

PUVA has been used in small case series as monotherapy (four patients in one study and six in another),[84,113] in

combination with intravenous immunoglobulins (IVIg; single case reports) and with plasmapheresis.[114–116] As monotherapy, PUVA was started at either the MPD, based on an erythema reaction without urticaria, or 0·25 J cm^{-2}, whichever was lower.[84] Treatments were given three times weekly, with gradually increasing areas of skin exposed to UVA. At the end of treatment, a fourfold increase in the minimum urticarial dose (MUD) and improved sun tolerance were reported. In the other case series (n = 6), whole-body PUVA was given with a starting dose of 80% MUD, three times weekly, for 4–8 weeks, with a resultant increase in MUD and sun tolerance (from < 15 min pretreatment to 2–8 h post-treatment).[113] Thus, there is some evidence that PUVA may be beneficial in SU.

Antihistamines are regarded as the standard therapy in SU (other than photoprotection); RCTs are not available in SU itself and it is reported that a substantial proportion of these patients receive only modest benefit.[117–119] High-dose H1 antihistamines are frequently prescribed, in-line with published research and recommendations made in general for other chronic urticarias.[120]

NB-UVB has also been reported to be helpful in SU [Calzavara-Pinton *et al.* (n = 39), Wolf *et al.* (n = 1), Collins and Ferguson (n = 1)].[121–123] In an open trial using two protocols of NB-UVB in patients both with UVB-sensitive (n = 29) and UVB-insensitive SU (n = 10),[121] NB-UVB was well tolerated; 20% of both groups reported SU relapse at 3 months. There are no comparative trials between NB-UVB and PUVA.

A small number of case reports of combination therapy of PUVA with plasmapheresis,[115] and with IVIg,[114] reported an increase in sun tolerance.

There was limited evidence from small case series on the use of UVA, either administered on its own or for pre-PUVA desensitization.[124–127] This has been used in patients who have a very low MUD for UVA, where PUVA was thought to be unsafe. Increased MUDs were reported in all cases (n = 14), and improved sun tolerance in eight of 10 patients, but long-term follow-up was lacking. UVA alone was observed to have the advantage over PUVA of reduced risk of an acute phototoxic reaction and long-term side-effects such as skin cancers, and increased convenience. It was suggested to be worthwhile considering if patients demonstrate a higher MUD with UVA alone compared with PUVA or NB-UVB.[125] Maintenance treatment may be required, although long-term follow-up is lacking to ascertain the frequency and UVA dosage required.

Recommendation (strength of recommendation D; level of evidence 4) In the management of SU (after full assessment, including definition of the action spectrum), PUVA can be considered. The treatment should be carried out with full knowledge of the patient's action spectrum, in a specialist unit experienced in managing this disease.

Erythropoietic protoporphyria We did not find any comparative trials with PUVA in the treatment of EPP.

There was limited evidence in the use of PUVA in EPP.[128,129] Roelandts reported a therapeutic benefit of PUVA in patients who had not responded sufficiently to β-carotene, but did not include data on the number of patients treated or outcomes.[128] Oral 8-MOP was given and whole-body irradiation was administered three times weekly, with 20% increments twice weekly; in total, 26–30 irradiations were given. Another case report showed a threefold increase in MED to UVA with twice-weekly treatment with oral TMP and UVA in comparison with a fourfold increase in MED to UVA with previous β-carotene therapy.[129]

PUVA cannot currently be recommended for the treatment of EPP, owing to lack of evidence and comparative trials with β-carotene or UVB, and the long-term risks associated with the need for annual treatment on a lifelong basis.

UVB has been reported in small open studies to be effective in EPP (six patients in one study; one patient in another; and 12 in yet another).[123,130,131]

Recommendation (strength of recommendation D; level of evidence 4) PUVA is rarely appropriate in EPP, in which NB-UVB is the phototherapy of first choice.

Actinic prurigo We found no comparative trials of thalidomide or immunosuppressants with PUVA in the treatment of AP.

There was limited evidence of the use of PUVA in AP. Treatment with PUVA 2–3 times weekly for 15–20 weeks induced normal sun tolerance and increased the MED to UVA immediately post-PUVA, but clinical photosensitivity recurred after 4–6 months' follow-up.[132,133]

UVB has been reported, in a small open study, to be effective in AP (n = 6).[123]

Recommendation (strength of recommendation D; level of evidence 4) NB-UVB may be a safer therapeutic option in terms of phototherapy-associated carcinogenic risk in patients with AP, particularly in children, and should be considered before PUVA.

9.5.3 What special precautions should be undertaken during psoralen–ultraviolet A therapy of photodermatoses?

Photodermatoses run a high risk of provocation with the different forms of phototherapy. Special precautions are required and are described below for the better-reported photodermatoses PLE, CAD and SU. In temperate countries, PUVA is usually administered in early spring. The benefit conferred by phototherapy is diminished or lost several weeks postphototherapy, and post-treatment advice generally includes continued natural sunlight exposure, if tolerable, on an individual basis, to keep resistance to provocation for the rest of summer. As PUVA generally needs to be repeated, the longer-term risk of skin carcinogenesis needs to be weighed against the therapeutic benefit, and annual desensitization is not usually recommended.

Polymorphic light eruption The regimens vary between phototherapy centres; most administer 8-MOP, although 5-MOP, and oral and bath TMP have all been used.[78–89] In most of these studies, 8-MOP PUVA was given three times weekly for 12–20 treatments. Currently in the U.K., a twice-weekly regimen is standard. There are no studies comparing the efficacy and safety of twice- and three times-weekly regimens.

Although there were no studies on the timing of PUVA therapy during the year, this is likely to be an important consideration, particularly in temperate climes. If administered too early in the year, the photoprotective effect may have subsided by mid-summer; administered too late, and the patient may have already suffered an eruption and PUVA may increase the risk of provocation or further aggravation.

The risk of provoking PLE is high, particularly with the first few PUVA exposures. At least one episode was induced during 12–50% of PUVA treatment courses,[78,80–83,86,87,134] which is a little lower than the rates with UVB (48–62%).[78,81] There is evidence that PUVA is as likely as UVB to cause provocation of PLE. Provocation episodes can be managed with potent topical steroid and subsequently lower dose increments, omitting one or two treatments if particularly severe.[78,80,81,86,87] To prevent provocation, one group administered oral prednisolone (40–50 mg) for the first 2 weeks of phototherapy,[85] while another reported routine prophylactic application of a potent topical steroid after each exposure in UVB phototherapy.[78]

Pruritus was also reported in 18–33% of patients,[81,82] with one group managing this with oral corticosteroid.[82]

Post-treatment advice generally includes continued natural sunlight exposure, ranging from 2 h weekly to 'cautious exposure, with sunscreens for extended outdoor stay' to 'expose freely to sun'.[78,83,85,88]

Chronic actinic dermatitis PUVA phototherapy is generally undertaken under close supervision under cover of topical or systemic corticosteroid, as discussed above.[108,109,111,112] Maintenance treatment may be required. Annual repeated courses can be considered but the benefit needs to be balanced against the long-term risk of skin carcinogenicity.

Solar urticaria Treatment of SU with phototherapy can potentially result in provocation, syncope and anaphylaxis. UVA is often, but not always, a wavelength where there is sensitivity in this disease. The choice of PUVA for SU as a therapy, and the protocol used, will be governed by the action spectrum as determined by monochromator phototesting.

Thus, it is important to determine both the action spectrum of the disorder, in a specialized phototesting unit, and the MUD before starting phototherapy, preferably with the UV source to be used for treatment. The initiating dose should be lower than the MUD. In patients with a very low MUD, UVA alone or pre-PUVA UVA has been used.[124–127] The amount of photoprotection will subside, and maintenance treatment with PUVA or UVA has been reported.

9.5.4 Key points

When using prophylactic phototherapy to treat photodermatoses, the risk of rash provocation is high. The use of topical/oral corticosteroids may be used prophylactically or therapeutically in PLE or CAD.

Phototherapy may be given in spring, or before a sunny holiday, before an expected increased natural UV exposure.

Particularly with CAD and SU, the action spectrum should be determined prior to commencement of phototherapy; PUVA should only be carried out in an experienced specialized unit.

With AP and EPP, UVB should be considered before PUVA.

Post-treatment advice of cautious, continued sunlight exposure should be given to maintain the photoprotective effect, but this is dependent on individual tolerance and photoprotection is still needed in very sunny conditions.

9.6 Hand and foot dermatoses

Local PUVA, using oral and topical psoralens, has been widely used to treat hand and foot dermatoses over the last 25 years and is generally considered an effective therapy. Oral psoralen is favoured by some patients for convenience (less time spent in a hospital treatment unit) and because there are lower risks of phototoxic reactions. Topical psoralen is favoured by other patients who prefer not to take oral medication and to avoid the potential risks of systemic side-effects and/or drug interactions. In addition, the use of eye protection outside the UV irradiation period is not required. Different forms of topical psoralen are in use, including soaks, paint, cream, ointment, emulsion and gel. Treatment regimens also vary not only with regard to methods of psoralen application, but also in the time interval between psoralen application and UVA irradiation. It has previously been shown in a small study that, in unaffected skin of the palms and soles, there is a lag time of approximately 40 min between soaking in psoralen solution and maximum UVA sensitivity in the palmar and plantar skin of healthy volunteers.[135] As a result of this, and earlier reports that suggested efficacy in the hand and foot dermatoses of topical psoralens with a 1–2-h delay between psoralen application and UVA exposure but no efficacy in studies with psoralen application immediately before UVA exposure, previous U.K. guidelines have recommended a delay of at least 30 min between immersion and irradiation.[136]

The hand and foot dermatoses comprise three main conditions: eczema, psoriasis and palmoplantar pustulosis.

9.6.1 What is the efficacy of psoralen–ultraviolet A therapy in patients with hand and foot dermatoses compared with placebo or other active treatments?

Palmoplantar eczema Oral PUVA has been compared with UVB in a prospective contemporaneous controlled study of hand eczema ($n = 35$).[137] This showed both treatments to be effective but PUVA was superior to UVB, although the relapse rate

was high. A subsequent smaller study (n = 20) carried out by the same group using a similar design showed similar results.[138] Uncontrolled studies with oral PUVA have shown significant improvement or clearance in 81–86% of patients with hand and foot eczema,[139,140] with similarly good results in smaller case series.[141,142]

Uncontrolled studies of topical PUVA have suggested this to be effective treatment with clearance or considerable improvement reported in 58–81% of dyshidrotic eczema and 50–67% of hyperkeratotic eczema.[143–154] However, evidence from comparative studies was less convincing. A left–right, within-patient study (n = 15) with 8-MOP paint vs. placebo in dyshidrotic eczema found no difference between the two groups, and no patient achieved clearance.[155] The lack of efficacy was supported by a small controlled study (n = 6) with 20% 8-MOP gel in which no patient cleared.[156]

A significant difference between topical PUVA compared with UVB has not been shown. In a nonrandomized, within-patient study (n = 13) of trioxsalen soaks compared with UVB, the reduction of severity scores of 25% and 39%, respectively, was not clinically significant.[157] A further randomized study (n = 15) with 8-MOP PUVA paint and NB-UVB in dyshidrotic eczema showed a reduction in mean severity scores of 75% and 75%, and clearance rates of 8% and 17%, respectively.[158]

Topical 8-MOP cream was compared with high-dose UVA1 in a nonrandomized, within-patient study with dyshidrotic hand eczema (n = 27).[159] No patient obtained clearance.

Topical PUVA paint compared with superficial X-ray showed significant improvement in both groups in a randomized double-blind trial (n = 25) of dyshidrotic hand eczema. At 6 weeks the scores for radiotherapy were significantly better than for PUVA but this was not maintained at follow-up.[160]

For foot eczema, topical PUVA has been compared in a randomized trial to topical PUVA combined with iontophoresis and to potent topical steroid (n = 48) over an 8-week treatment period and at follow-up 8 weeks later. There was no significant difference in eczema and Dermatology Life Quality Index (DLQI) scores between the three groups.[161]

In summary, in hand eczema, evidence from two prospective contemporaneous controlled studies have shown PUVA using oral psoralen to be effective and superior to UVB. Evidence from RCTs and prospective contemporaneous controlled studies has not demonstrated topical PUVA to be more effective than placebo, UVB, UVA1 or superficial X-ray therapy. However, some uncontrolled studies have shown topical PUVA to be associated with good degrees of improvement. All comparative studies lacked the power to detect what might still be important differences between treatments.

Recommendation (strength of recommendation B; level of evidence 2++) PUVA, using oral psoralen, should be considered as a treatment for hand and foot eczema. Although the evidence for topical PUVA in palmoplantar eczema is weak, lack of proof of efficacy does not prove no efficacy and in open discussion with patients it will sometimes be appropriate to consider topical PUVA.

Palmoplantar psoriasis We found no comparative studies comparing oral PUVA with placebo or other active treatments, although a small retrospective study (n = 12)[162] and case series (n = 5)[141] report improvement or clearance.

A large retrospective study (n = 92) compared oral PUVA with NB-UVB and concluded they were equally effective. However, assessment and outcome measures were unclear and no statistical analysis was carried out.[163]

Uncontrolled studies have reported clearance or significant improvement occurring in 58–87% of patients treated with topical psoralen.[143,146–148,150,151,164–167]

In a randomized, left–right, within-patient study in patients with hand and foot dermatoses (psoriasis, n = 11), topical PUVA (20% 8-MOP gel) was compared with UVA, and PUVA was suggested to be more effective overall, but the results were not analysed separately according to the different dermatoses investigated.[156] No patient was reported as being cleared in either group.

Topical PUVA was compared with UVB in two small randomized trials. A left–right, inpatient, observer-blinded study compared PUVA cream with 308-nm UVB excimer laser (n = 10).[168] Both treatments showed similar efficacy, with a mean reduction in modified PASI score of 64% with PUVA and 64% with excimer laser. In a further randomized study (n = 25), local PUVA with 8-MOP paint was compared with NB-UVB, with a reduction in severity scores of 85% compared with 61% with NB-UVB, and clearance rates of 24% and 0%, respectively.[169] The authors of a Cochrane systematic review of NB-UVB phototherapy vs. BB-UVB or PUVA for psoriasis identified only this study for the indication, and concluded no significant difference between treatments.[170]

In summary, for palmoplantar psoriasis there is some randomized study evidence for topical PUVA; however, these studies were underpowered. Oral PUVA for this indication has not been studied adequately.

Recommendations (strength of recommendation C; level of evidence 2++) PUVA using topical or oral psoralen should be considered as a treatment for palmoplantar psoriasis.

Palmoplantar pustulosis A randomized, within-patient study compared oral PUVA with no treatment (n = 22).[171] This showed improvement in 100% of PUVA-treated sites compared with 59% of untreated sites, with 55% and 0% clearance rates, respectively. In a prospective contemporaneous controlled study (n = 14), improvement was recorded in 64% of participants receiving oral PUVA and 14% with no treatment.[172] The clearance rates were 21% and 0%, respectively.

A double-blinded, randomized, left–right, within-patient study compared topical PUVA with placebo (n = 27).[173] The study detected no difference in improvement with topical PUVA compared with placebo. The lack of efficacy of topical PUVA was further supported by smaller randomized studies

(10 and five patients, respectively),[156,174] with clearance rates of only 0–10%.

Two RCTs have compared PUVA with oral retinoids. One study (n = 84) compared two forms of topical PUVA, oral PUVA and etretinate.[175] A total of 12% (4/33) treated with topical methoxsalen cream cleared compared with 70% (14/20) in the etretinate group. None cleared in the oral PUVA and trioxsalen soak group. This suggests etretinate to be more efficacious, but response to PUVA, and, in particular, to oral PUVA, was much lower than in other published studies. Another study comparing oral PUVA to etretinate showed clearance in 21% (3/12) receiving PUVA vs. 17% (3/18) receiving etretinate.[172]

The authors of a Cochrane systematic review of interventions for palmoplantar pustulosis, which included the controlled studies detailed above, concluded that oral PUVA is an effective intervention for this indication, although the combination of retinoids plus oral PUVA is more effective. No proven benefit has been demonstrated with topical PUVA and no definite benefit of retinoid as a monotherapy over PUVA was established.[176]

Recommendations (strength of recommendation C; level of evidence 2++) Oral PUVA should be considered as a treatment for palmoplantar pustulosis.

9.6.2 What is the efficacy of oral psoralen–ultraviolet A therapy compared with topical psoralen–ultraviolet A therapy in patients with hand and foot dermatoses?

Palmoplantar eczema Two RCTs have compared oral and topical PUVA. van Coevorden *et al.* performed an open-label RCT (n = 158) comparing oral methoxsalen (safer for home use than topical psoralens) using a home UVA unit with topical PUVA using trioxsalen soaks in a hospital setting over a 10-week period.[177] The mean hand eczema scores showed a significant reduction of 41% in the oral PUVA group compared with 31% in the topical PUVA group, with no statistically significant difference between the two groups. This improvement was maintained at an 8-week follow-up.

A small RCT compared oral 8-MOP with 8-MOP soak in dyshidrotic eczema (n = 15) and hyperkeratotic eczema (n = 12). This study did not detect a difference in therapeutic efficacy, or that dyshidrotic eczema improved to a greater extent than hyperkeratotic eczema; however, the study was underpowered and does not justify these conclusions.[178]

Palmoplantar psoriasis A retrospective review by Hawk and Grice of oral and topical 8-MOP PUVA in the treatment of patients with hand and foot dermatoses included 18 patients with psoriasis.[179] Fifty per cent (7/14) of patients who received topical PUVA and 50% (2/4) oral PUVA cleared. A small, within-patient, randomized, right–left comparison study compared PUVA using oral oxsoralen with PUVA using 8-MOP soaks in patients with palmoplantar dermatoses but included only three patients with psoriasis. Oral PUVA was reported to be more effective.[180]

Palmoplantar pustulosis Hawk and Grice's retrospective review, which included 15 patients with palmoplantar pustulosis, showed clearance in 67% (4/6) with oral 8-MOP and 33% (3/9) with topical 8-MOP emulsion.[179]

A small, right–left, within-patient comparative study of oral oxsoralen vs. 8-MOP soaks in patients with hand and foot dermatoses included five patients with pustulosis. Oral PUVA was reported to be more effective.[180]

The RCT by Lassus *et al.* of two forms of topical and oral PUVA showed a clearance rate of 8% (4/51) with topical PUVA compared with 0% (0/13) with oral PUVA.[175] PUVA as a whole was disappointing in that study and no difference between the methods of delivering it was detected. A Cochrane review of interventions for palmoplantar pustulosis found only this one direct comparison of topical with oral PUVA for this indication.[176]

Recommendation [strength of recommendation D (good practice point); level of evidence 4] Oral PUVA should usually be considered as the first-line PUVA treatment for patients with palmoplantar dermatoses.

9.6.3 What is the efficacy of psoralen–ultraviolet A therapy alone compared with psoralen–ultraviolet A and adjuvant therapies in the hand and foot dermatoses?

Palmoplantar eczema For foot eczema, topical PUVA has been compared, in a randomized trial, to topical PUVA combined with iontophoresis over an 8-week treatment period and at follow-up 8 weeks later. There was no significant difference in eczema and DLQI scores.[161]

Palmoplantar psoriasis There was only one RCT comparing combination therapy with oral PUVA and etretinate vs. PUVA and placebo but this included only three patients with psoriasis.[181] No other relevant studies were identified.

Palmoplantar pustulosis Three RCTs examined combination therapy with oral PUVA and retinoids compared with PUVA alone. The RCT by Rosén *et al.* showed clearance in 61% (14/23) of patients receiving combination therapy and 21% (three of 14) receiving PUVA alone.[172] A further RCT comparing oral PUVA–etretinate vs. oral PUVA alone showed clearance in 100% (8/8) and 44% (four of nine) of patients, respectively.[181] An RCT using 8-MOP PUVA lotion found 60% (six of 10) of patients clearing with topical PUVA–etretinate compared with 10% (one of 10) receiving topical PUVA alone.[174]

A Cochrane review of the interventions for palmoplantar pustulosis concluded there was evidence for an increased efficacy of retinoids combined with PUVA compared with PUVA used alone.[176]

Recommendation (strength of recommendation 1+; level of evidence A) Unless there are contraindications, the combination of oral PUVA with oral retinoids should be considered as a treatment for palmoplantar pustulosis.

10.0 Adverse reactions to psoralen–ultraviolet A therapy

10.1 Acute

10.1.1 Incidence of acute adverse events

Both systemic and topical PUVA are generally well tolerated and the acute adverse effects of PUVA are reasonably well documented. The most common adverse effects are erythema and pruritus, and nausea associated with oral PUVA.[135,182] In one review the rates of acute adverse effects for systemic, bath, and hand and foot PUVA were 1·3% (n = 299 treatments), 1·3% (n = 1675 treatments) and 0·8% (n = 836 treatments), respectively.[183] Importantly, only one severe adverse event (SAE; severe nausea, vomiting and collapse) with oral PUVA was documented in that study (0·3% of treatments), no SAEs were recorded for bath or localized PUVA, and none was attributed to operator error. However, in one review of severe PUVA burns, all four patients had received an accidental overdose of UVA.[184]

In early studies of oral PUVA, reported acute adverse events were uncommon, temporary and generally mild. Melski *et al.* analysed the adverse events from 41 000 oral PUVA treatments given to 1308 patients.[185] The incidence of adverse events was as follows: erythema, 9·8%; pruritus, 14·0%; nausea, 3·2%; headaches, 2·0%; dizziness, 1·5%. Erythema was more likely to occur in lighter skin phototypes and on a three-times-weekly regimen, and resulted in missed treatments in only 1·1%. Pruritus settled, with emollients and antihistamines, in approximately two-thirds of cases. Nausea settled with antiemetics in one-third of cases. The adverse events rarely led to missed treatments. No clinically significant changes in laboratory screening or changes on ophthalmological examination were observed in that study. In later large series (n = 3175), the incidence of adverse events reported were higher: erythema, 32·4%; pruritus, 25·6%; nausea, 13·5%; headaches, 2·0%; Köbner reaction in psoriasis, 2·0%.[186,187] PUVA treatment was interrupted owing to erythema in 6·8%, and only uncommonly discontinued. Nausea with 8-MOP, but not with 5-MOP, is a relatively common occurrence and rarely requires discontinuation of treatment.[188]

Erythema A report in healthy volunteers demonstrated that oral 8-MOP PUVA erythema was evident at 24 h and did not peak until 96 h or later in 75% of participants, based on MPD.[189] Studies of the time course of PUVA erythema following topical delivery of 8-MOP also confirmed the delayed erythemal response, with a broad erythemal peak between 96 and 144 h.[190–192] Oral 5-MOP PUVA erythema shows a similar time course to that of 8-MOP.[193] Thus, as erythema following both topical and systemic 8-MOP PUVA peaks at 96 h or later in the majority of patients, this supports the use of 96-h MPD assessment times and treatment intervals of no less than 2 or 3 days. In practice, many centres use an MPD assessment time of 72 h, and no studies have been undertaken to evaluate whether there are differences in efficacy or adverse effects between treatment regimens based on a 72-h vs. a 96-h MPD assessment. Until such a study has been undertaken, MPD assessment at either 72 or 96 h is appropriate. Most U.K. centres use a twice-weekly regimen for both oral and topical PUVA.

The UVA dose should be delivered within 10 min of an 8-MOP bath as photosensitivity reduces quickly, although there may be a more prolonged effect over 40 min if palmar and plantar skin are being treated.[136,194] The temperature of the bath for PUVA delivery is also important, with photosensitization being optimal at 37 °C and reduced at lower temperatures.[195]

Unusual patterns of erythema and burning have been reported, particularly with TMP bath PUVA, owing to the powder formulation of TMP and the variable distribution within the bath water as it forms a microcrystallized suspension.[196] Frank blisters can also occur either owing to UVA overexposure or to psoralen dose, for example as seen if patients stand in a particular way in the cabinet.[197] Particular care is needed in patients with vitiligo;[198] in one atopic patient with vitiligo, accidental PUVA burning resulted in subsequent development of nodular prurigo at affected sites.[199]

Thus, depending on the methods for reporting erythema, the incidence of PUVA erythema during treatment is between 10% and 32%, requiring treatment interruption in between 1% and 7% of cases. Patients of lighter skin phototype and those treated with more frequent treatment regimens are at greatest risk of developing erythema during treatment. Early recognition of cumulative erythema is important and omission of treatment until this has resolved and adjustment of dose increments may be required. Topical emollients and steroids may offer symptomatic relief.

Pruritus There seems to be a similar incidence of pruritus following oral and bath PUVA, occurring in 10–40% of patients.[135,185,187] The incidence of pruritus is reported to be lower with 5-MOP (43·6%) than with 8-MOP (71·8%).[196] There do not appear to be specific predictors for the likelihood of this adverse effect occurring.

Nausea Nausea is relatively common, occurring in about 3–13% of patients.[185,187,200] This can be helped by taking the psoralen with a light meal or by using an antiemetic. If nausea is significant then 5-MOP or topical psoralen can be used.[200] In one study the incidence of nausea was reported to be much lower with 5-MOP (7·7%) than with 8-MOP (51%).[196]

Induction of photodermatoses Precipitation or aggravation of photodermatoses that are associated with abnormal UVA photosensitivity can occur with PUVA, with reports of CAD and PLE exacerbation having been observed.[81,201] The rate of inducing PLE was estimated to be 50% compared with 62% with NB-UVB in one study.[81] Theoretically, exacerbation or induction

of lupus can occur, and there are case reports of the coincidence of PUVA with the development of lupus.[202–204]

Drug phototoxicity In general, drug phototoxicity is not a major problem because of the overwhelming effect of psoralen photosensitization, and as long as MPD assessment is performed on the patient's drug regimen, this can be largely avoided.[200] However, pseudoporphyria can occur, as with some of the other phototoxic drugs such as the fluoroquinolones, nonsteroidals, tetracyclines and diuretics, and is more likely to occur after minor trauma and on acral sites. Furthermore, enhancement of PUVA phototoxicity has been reported after ingestion of celery and vegetable broths during PUVA therapy and after taking Rutaceae extracts and celery soup.[205,206] Reported phototoxicity rates seem to be similar for oral and bath 8-MOP PUVA,[135] although clinical experience suggests that severe phototoxic reactions are more likely with bath PUVA. In general, avoiding psoralen-containing plants for at least 2 h before treatment, is advised.

Systemic psoralen can interfere with liver metabolism, which results in many potential drug interactions. Psoralens cause liver enzyme inhibition, which, in turn, causes a potential serum increase of the following: warfarin, anticholinergics, antipsychotics, nonsteroidal anti-inflammatories, theophylline and caffeine. More frequent monitoring is advised if a patient is on warfarin. The effects of caffeine are augmented by PUVA,[207–209] and can occasionally cause headaches and 'jitteriness' on treatment days. Advice to reduce caffeinated beverage intake on these days may be required. Systemic psoralen can also cause liver enzyme induction, which may reduce serum concentration of ciclosporin, chemotherapy agents, azole antifungals, macrolides, tricyclics, antidepressants and antipsychotics, benzodiazepines, statins, calcium channel blockers, protease inhibitors and oral contraceptives. Co-administration of potent liver enzyme inducers such as phenytoin and carbamazepine may increase metabolism of psoralen and result in a reduced response to PUVA. The risk of potential drug interactions further underscores the importance of MPD testing to ensure patient safety and also an adequate amount of psoralen in the skin at the correct time to allow the wanted phototoxic responses.

Hepatotoxicity There are case reports of hepatitis following 5-MOP and 8-MOP.[210–215] Importantly, two of the four cases arose in patients who had methotrexate (MTX)-induced liver damage, and the remaining cases resolved once the drug was stopped. In one study of 162 patients receiving PUVA, only three had transient elevations of transaminases, which all reverted to normal after treatment was stopped.[216] The rarity of these cases, that have occurred with bath, as well as oral, PUVA, support the view that routine monitoring of liver function tests is not required. The mechanism is unclear and may be idiosyncratic.[217]

Pain Severe skin pain with PUVA is uncommon and was seen in 4% (eight of 210) of patients in one series treated with oral PUVA.[218] It is characterized by persistent severe prickling, burning or dysaesthesia, which can last from minutes to hours and persist for weeks or months. The risk of developing PUVA pain is unpredictable and does not appear to be related to the patient's skin phototype, PUVA sensitivity or induction of PUVA phototoxicity. An underlying neurogenic mechanism appears most likely.[219–221] Treatment with analgesics, topical anaesthetics and topical or systemic steroids usually has minimal effect. Capsaicin, gabapentin, phenytoin and low-frequency electrotherapy can potentially be of benefit.[220–224] Once PUVA pain has developed it is then a relative contraindication to further PUVA treatment, as pain is likely to recur.

Miscellaneous Allergic and photocontact allergic dermatitis to psoralens have been reported to affect 0·8% (three of 371) of patients treated with topical PUVA.[225] Type I anaphylaxis to both 5-MOP and 8-MOP has also been observed in isolated cases,[226,227] and asthma may be aggravated.[228–231]

Hyperpigmentation is usually a result of repeated PUVA treatments but may occur with the concurrent use of topical vitamin D analogues at treated lesional sites,[232,233] and with concomitant treatment with isotretinoin.[234]

Triggering of herpes simplex virus can occur with PUVA and use of high-factor sunscreen on the lips and prophylactic aciclovir for susceptible subjects is recommended. Eczema herpeticum has been reported in a patient with AD treated with PUVA.[235] Folliculitis can occur and can be managed with applying emollients following the downward direction of the hair.

Onycholysis following ingestion of phototoxic drugs is well documented. Onycholysis following ingestion of psoralens and natural sunlight has been observed and has also been reported following PUVA photochemotherapy.[236] Other associated adverse events include lunular changes, subungual haemorrhage and nail pigmentation.[187,237]

Clinically significant consistent changes in laboratory parameters are rarely observed. However, severe hyperlipidaemia following PUVA treatment for acute skin graft-versus-host disease has been reported.[238]

Other rare acute side-effects of PUVA include bullous pemphigoid,[239–241] lichen planus,[242] lichen planus pemphigoides,[243] polymyositis,[244] influenza-like symptoms,[245] lymphomatoid papulosis in a patient with MF,[246] and neurological disorders such as insomnia, nervousness, headache, migraine, dyssomnia, depression and dizziness.[247,248] The development of hypertrichosis, acne-like eruptions, milia and seborrhoeic-like facial dermatitis can also uncommonly occur, and these changes are usually reversible on stopping treatment.[187,249] An intertriginous, asymptomatic, self-resolving, maculopapular rash was reported in 8% of participants undergoing 5-MOP PUVA and this resolved spontaneously, despite continuation of PUVA.[188] In one report, three patients with MF developed new lesions at sites previously considered to be clear, early in the PUVA course. This might have been due to unmasking of subclinical lesions due to inflammation.[250]

10.1.2 Key points

Relatively common acute adverse effects of PUVA include erythema, pruritus, nausea and polymorphic light eruption.

Uncommon but important acute adverse effects of PUVA include PUVA pain, idiosyncratic hepatitis and psoralen allergy.

10.2 Long term

10.2.1 Psoralen–ultraviolet A therapy-induced skin cancer

PUVA photochemotherapy is mutagenic, carcinogenic and immunosuppressive.[251–260] Skin cancer is a well-recognized side-effect of PUVA and it is well established that the risk of squamous cell carcinoma (SCC) increases in a dose-dependent manner.[261–266] Additional risk factors include exposure to co-carcinogenic therapeutic agents such as UVB therapy, MTX, ciclosporin and X-ray radiation/arsenic.[267–274] The human papilloma virus has also been suggested as a co-carcinogen and has been detected in PUVA-associated nonmelanoma skin cancers (NMSC), especially types associated with epidermodysplasia verruciformis, particularly types 5, 14 and 20.[275–278] More recently, the U.S.A. 16-centre, follow-up study has reported an increased incidence of melanoma in patients treated with PUVA,[279,280] but it remains uncertain that this was a causative association and this association has not been reported by other groups.[265,273,281,282] There is no evidence of either increased incidence of NMSC or melanoma in patients with psoriasis treated by topical PUVA.[283,284] However, the number of patients with high PUVA exposure was low in these studies and many were treated with bath TMP PUVA. It seems likely that any differential risk of carcinogenicity relates more to differences in psoralens than different routes of administration, so it seems reasonable, on the basis of current knowledge, to believe that the risks per phototoxic exposure should be the same for oral 8-MOP PUVA as for bath 8-MOP PUVA.[283] This is a reason why the (mainly historical) use of cumulative UVA dose with PUVA when considering action limits is less useful than considering number of treatments as cumulative UVA dose will always tend to be less with topical PUVA even when the number of phototoxic exposures is the same.

Psoralen–ultraviolet A therapy and nonmelanoma skin cancer The two studies of most value in assessing NMSC risks in humans treated with PUVA were a North American study and a large Swedish study.[263,264,281] The North American study involved the use of maintenance PUVA, and only for one indication (psoriasis) in a fashion rarely used in Europe; the Swedish study used PUVA with a methodology close to that which is used in Europe and for a wide variety of indications. The North American study of necessity (in the absence of good cancer registry data) involved regular follow-up of the patients treated with PUVA without similar follow-up of a control group, whereas the Swedish study relied on cancer registry linkage to identify skin cancers both in patients and in the control population, so comparing better like with like. However, it is still probable that the patients (by definition, having dermatological diseases) were more likely to be diagnosed (ascertainment bias) and diagnosed earlier (lead-time bias) with skin cancers. The North American study demonstrated that patients receiving > 200 treatments have about 30 times the risk of developing a new NMSC per year than the general population.[263] An almost identical risk was found in the highest-risk group (men who had received ≥ 200 PUVA treatments) in the Swedish study.[264] When reporting, RR are typically quoted: it is important to also consider absolute risks. The RR among the highest-risk patients in the Swedish study of 30·7 meant 10 of 180 patients.[264] A meta-analysis reported that the incidence of SCC among patients exposed to high-dose PUVA was 14-fold higher than among patients with low-dose exposure.[285] The risk of skin cancer is persistent, despite discontinuation of PUVA.[286] Other risk factors for patients developing NMSC include having a lighter skin phototype, having skin tumours prior to PUVA and age at starting PUVA, the presence of PUVA keratoses and lentigines.[266,287–289]

PUVA-associated NMSCs show a reversal of the normal ratio of SCC to basal cell carcinoma (BCC) with a marked increase in SCC and these occur in relatively nonsun-exposed sites.[269] Genital SCC in males treated with PUVA has been reported to be substantially increased (95·7 times that of the general population);[290,291] however, a lower incidence was reported in the Swedish study.[264] A retrospective study from France of a cancer registry over 20 years identified only one case, out of 48 cases, of genital SCC in someone with a history of intensive PUVA. In addition, there were no reported cases of genital SCC from 5400 patients who had received PUVA, despite a lack of genital protection during PUVA exposures.[292] Despite reports that SCC occurring in patients receiving PUVA are usually well differentiated and nonaggressive,[263,265,274,287] these tumours can rarely metastasize.[269]

Lim and Stern found high levels of UVB exposure (at least 300 treatments) to be associated with a modest but significant increase in SCC (1·37 times) and BCC (1·45 times) in the U.S.A. PUVA cohort.[267] A high level of exposure to MTX (total of ≥ 4 years of use) has also been found to be a significant independent risk factor in the latter cohort, with an RR of 2·1 for high vs. low, or no exposure.[269] Previously, a synergistic carcinogenic potential between MTX and PUVA had been suggested.[268] Other data from the U.S.A. cohort showed that the risk of SCC in users of ciclosporin was about three times higher than in patients who never used ciclosporin.[270] Patients receiving PUVA who have previously received arsenic or X-ray therapy have an increased incidence of skin cancer than those who have not had such therapy.[271,273,274]

Melanoma Patients who receive high doses of PUVA often develop lentigines that can show cytologically atypical melanocytes.[293] A fivefold increase in the annual incidence of malignant melanoma in the 16-centre PUVA cohort study, using PUVA to treat psoriasis, was initially reported in 1997.[279] Further follow-up showed a ninefold increase.[280] Melanoma

developed after 15 years and was more common in patients of skin types I/II and who had received at least 250 exposures. There have been a number of case reports of melanoma occurring following PUVA,[294–302] but an increased incidence of melanoma has not been observed in European follow-up studies.[265,273,282,303] So, while there is no doubt that an association between PUVA and melanoma was detected in this one study it is uncertain that PUVA causes melanoma. The association could have been because PUVA, as used in that study, did cause melanoma but, equally, the association could have been because of confounding (e.g. patients with psoriasis responsive to PUVA seeking sunlight exposure) or have been due to ascertainment bias (melanomas, and many were early melanomas, some of which might not have progressed, more likely to be diagnosed in a prospectively followed group than in the general population).[304] When it was first reported, the potential risk of melanoma induced by PUVA raised questions as to whether PUVA should be contraindicated in those with a history of > 200 PUVA treatments or those with a personal or family history of melanoma.[303,305]

Noncutaneous cancer risk As PUVA alters immune function, especially that of lymphocytes, there has been continued concern for the potential development of cancer, particularly lymphoma, with long-term use of this therapy. This is particularly relevant in patients with psoriasis, as an association with internal cancer has been found in large cohort studies,[306,307] which includes oral tumours and tumours of the pharynx, lung, liver, pancreas, liver and bladder, and lymphoma.[308–310] However, previous studies have not demonstrated a consistent increase in cancer risk in the central nervous system, thyroid gland, respiratory system, pancreas or kidney.[264,281,311]

Although there are several case reports of leukaemia developing during PUVA therapy,[312–315] Stern and Lange and Stern *et al.* reported no increase in lymphoma or leukaemia in a PUVA cohort, in either 1988 or 1997;[263,279] however, more recent analysis has found the incidence of lymphoma to be increased in this group in those exposed to high levels of MTX (RR 4·39), that is, 36 months of treatment or longer, but not in those exposed to low levels.[316] A study from Finland showed a 2·2-fold increase in non-Hodgkin lymphoma in patients hospitalized for psoriasis.[309]

Noncancerous chronic cutaneous side-effects of psoralen–ultraviolet A therapy Keratoses are typically localized to nonsun-exposed skin; risk factors for their development include increased age, male sex and high cumulative UVA dose.[288] They are reported to occur in 46% of patients receiving high-dose (> 2000 J cm^{-2}) PUVA and show cytological atypia.[266] Disseminated superficial actinic porokeratosis has been reported in association with both oral and topical PUVA.[317–320]

PUVA-induced lentigines are distinct irregular, stellate, darkly pigmented macular lesions and may show cytological atypia.[289,293] Incidence varies from 10% to 53%,[289,321–324] occurring most frequently in those patients exposed to high doses of PUVA and those of skin type I/II.[266,289,321,323]

PUVA-induced mottling consists of hyper- and hypopigmentation associated with atrophy that is mainly localized to areas of overdose.[187,325] Hyperpigmentation has been reported at the lesional sites of patients where calcipotriol ointment has been applied during bath PUVA.[233] Transient hyperpigmentation has also been reported around psoriatic plaques in patients treated with calcipotriol ointment and PUVA.[234] Acquired dermal melanocytosis typically affecting the back of Japanese patients treated with PUVA has been reported.[326,327]

PUVA can result in dose-related premature ageing of the skin, manifesting as wrinkling, xerosis, loss of elasticity, freckling, telangiectasia, mottled pigmentation, yellowing of the skin and comedones. More marked changes are seen in those of skin type I/II. Both epidermal and dermal changes have been reported with chronic PUVA exposure, including skin atrophy, focal epidermal and elastosis.[328,329]

Free 8-MOP can be detected in human lenses for at least 12 h after 8-MOP dosing.[330] Previous guidelines from the BPG recommend that protective eyewear be worn for 12–24 h after PUVA and for 24 h in high-risk individuals, for example patients with atopic eczema, children or those with pre-existing cataracts.[331] Previous clinical studies (involving patients advised on eye protection), including the 16-centre prospective cohort study of American patients with psoriasis,[332–334] have not detected an association between the use of PUVA and cataract development. A follow-up study of 82 patients who declined to wear UVA-blocking sunglasses after PUVA treatments over 2–4 years found no evidence of the development of cataracts.[335]

10.2.2 Key points

PUVA is associated with a significant dose-dependent risk of SCC, and PUVA keratoses, pigmentary changes and photoageing.

PUVA has not been consistently shown to be associated with melanoma, internal malignancy or cataracts.

10.3 How do we identify those who are susceptible to the side-effects of psoralen–ultraviolet A therapy?

To prevent side-effects being encountered, particularly skin cancer, careful patient selection is essential. PUVA should be used with care (generally only if the alternatives are treatments carrying greater risks, such as systemic immunosuppressives) in children, owing to the risk of causing UV cutaneous damage at a young age.

There is concern that PUVA therapy may lead to worsening of HIV status or may increase risk of skin cancer in people with HIV,[336–338] particularly as SCC and melanoma have been reported to be more aggressive in HIV.[339,340] The risk of Merkel cell carcinoma of the skin was increased by 100 times in the U.S.A. PUVA cohort,[341] and is also increased in patients with HIV.[342] However, studies to date of PUVA use in patients with HIV have not demonstrated a deterioration in HIV status

or immune function,[343–345] and it has been suggested that, in fact, PUVA might be preferable to UVB therapy in patients infected with HIV.[346]

Patients who are at risk of ocular toxicity are those with pre-existing cataracts, patients who have AD or who are aphakic.

10.3.1 Risk factors associated with psoralen–ultraviolet A therapy-induced skin cancer

Risk factors include a history of the following: sun-reactive skin phototype I/II; previous history of skin cancer; personal/family history of skin cancer or dysplastic naevus syndrome; previous exposure to ionizing radiation, arsenic or excessive sunbed exposure; history of xeroderma pigmentosum or other genetic disorders associated with skin cancer; immunosuppressive drug therapy; HIV. Look out for the following on examination: multiple freckles/moles; dysplastic naevi/solar keratoses/SCC *in situ* (Bowen disease); solar elastosis; skin cancer.

10.4 How can side-effects be prevented in patients receiving psoralen–ultraviolet A therapy?

Important measures to reduce skin cancer risk include the shielding of high-risk areas on the genitalia and face, education of patients regarding sun-protective measures with sunscreen use and protective clothing, and monitoring for premalignant or malignant skin lesions. Patients who have received > 150–200 PUVA treatments should be offered an annual skin examination to ensure no premalignant or malignant skin lesions have developed,[187,331] and as a component to education of patients and their primary care doctors that they might be at increased risk of skin cancer as a result of medical treatment. Patients should be advised to wear protective UVA-blocking glasses from the time they ingest psoralen until 12 h following PUVA therapy (24 h for high-risk individuals, e.g. patients with atopic eczema, children or those with pre-existing cataracts). Sunglasses or opaque UV protective glasses should be used,[347,348] and these can be tested for suitability.[347,349] Uncoloured glasses are, if there are any uncertainties about their ability to stop UVA transmission, more suitable than tinted glasses as the latter result in dilation of the pupil, potentially allowing more UVA to reach the lens.[350] Protective eyewear should be of sufficient size to reduce peripheral UV exposure, and additional side protection is recommended. Most contact lenses have little or no UVA protection and are not recommended.[351]

UVA-blocking goggles should be worn during PUVA therapy. As studies have not shown an increased incidence of cataracts, it has been suggested that an examination by an ophthalmologist should usually be considered only if the patient is at increased risk of cataracts,[331] that is, patients with pre-existing cataracts, who have atopic eczema or who are aphakic.

As the risk of PUVA-induced skin cancer is related to the cumulative exposure, attempts should be made to reduce this exposure. This can be done in a number of ways, including more efficient dosimetry using less intense PUVA treatment regimens,[352,353] the avoidance of maintenance treatment, following guidelines on action limit the number of treatment exposures (e.g. 150–200 treatments),[331] consideration of periods of breaks from PUVA with rotational therapy,[354] and the use of combination therapy with retinoids or topical vitamin D analogues.[355] Retinoids not only increase the efficacy of PUVA, but also have a skin cancer prophylactic action.[356,357] Concurrent use of PUVA with ciclosporin should be avoided as it can significantly accelerate skin cancer development in patients receiving such treatment.[270] Topical vitamin D analogues and tazarotene have also been used as dose-sparing agents combined with PUVA.[358,359] There may also be a role of potentially safer photosensitizers such as trimethylangelicin.[360] Photochemotherapy using potentially safer wavelengths of radiation, for example NB-UVB, requires further research.[361,362] Agents that may protect against PUVA-induced photochemical damage, for example green tea or *Polypodium leucotomos* extract, may decrease long-term carcinogenesis.[363,364]

Recommendation (strength of recommendation D; level of evidence 2+) Concurrent use of PUVA with ciclosporin should be avoided. Post-PUVA ciclosporin is associated with increased risks of NMSC and should be avoided when possible. However, previous use of ciclosporin should not preclude consideration for PUVA.

10.5 How are the side-effects managed in patients receiving psoralen–ultraviolet A therapy?

Premalignant and malignant skin lesions are treated in the same way as patients not receiving PUVA. PUVA must be discontinued if neoplastic lesions develop and alternative therapy should be considered, but ciclosporin should be avoided.[270] Introduction of acitretin can be helpful in the management of patients with multiple keratoses and skin cancer following PUVA.[356,357,365] These individuals will require careful follow-up as they are at increased risk of further skin cancers developing with time.

10.6 Psoralen–ultraviolet A therapy and pregnancy

As PUVA therapy is mutagenic there is concern regarding potential teratogenicity of this treatment. Oral psoralen is associated with reduced birth rate and teratogenicity in animal studies,[366–368] but this is not found in humans.[369–371] One study observed a marked increase in infants with low birth weights when pregnancy occurred after treatment.[370] It was thought that this may be an effect of the underlying disease rather than the treatment itself. Recently, it has been reported that pregnant women with severe psoriasis have a 1·4-fold increased risk of giving birth to infants with low birth weights.[372] It has been suggested that local topical PUVA may

be relatively safe in pregnancy as it does not give rise to detectable levels of psoralen.[373] It was recommended that PUVA therapy should be avoided during pregnancy whenever possible as it is mutagenic.[369,374]

There is no evidence that PUVA is a significant teratogen (level of evidence 2++).

Recommendation (strength of recommendation D; level of evidence 4) It is recommended that women should avoid conception during PUVA therapy and that, if despite this advice, pregnancy does occur, PUVA should be discontinued.

11.0 Protocols and practical considerations

11.1 What is the optimum protocol for the delivery of psoralen–ultraviolet A therapy to optimize outcome in patients with psoriasis, eczema and polymorphic light eruption?

Examples of treatment schedules commonly used in the U.K. can be accessed at the following websites: http://www.bad.org.uk/healthcare-professionals/clinical-services/service-standards/phototherapy; http://www.photonet.scot.nhs.uk (the National Managed Clinical Network for Phototherapy in Scotland website); http://www.phototherapysupport.net (the South-east of England Phototherapy Network website).

These may be used as guidance to the phototherapist in determining the optimum protocol.

11.2 How should a psoralen–ultraviolet A therapy clinic be set up?

Taking account of equipment; staffing/training; support (e.g. medical physics, servicing); dosimetry/quality assurance; and records/database, a Phototherapy Working Party Report has been produced by the BAD on the minimum standards for phototherapy services, and includes a phototherapy service review toolkit. It is available at: http://www.bad.org.uk/healthcare-professionals/clinical-services/service-standards/phototherapy.

In addition, the BPG has also published guidelines for dosimetry and calibration in UV radiation therapy.[375] A joint BAD and BPG update of these guidelines has recently been published in the BJD.[376] Please visit http://www.bpg.org.uk/index.asp?SID=7&PID=13 for published BPG workshop reports and http://www.bad.org.uk/healthcare-professionals/clinical-standards/clinical-guidelines for BAD clinical guidelines.

12.0 Pretreatment assessment

12.1 Risk assessment and patient counselling

Prior to phototherapy, a formal risk assessment, which can be made by a nurse or a doctor, should include assessment of skin cancer risk, use of concomitant topical and systemic drugs, drug allergies, photosensitivity, liver or kidney disease, and history of cataracts.

All patients who have had > 150–200 exposures of PUVA should be offered annual assessment for any premalignant or malignant skin lesions.

Advice should be given on eye protection to be worn for 12–24 h after oral PUVA, and considered for bath PUVA for widespread dermatoses, and for 24 h in high-risk individuals, for example patients with atopic eczema, children or those with pre-existing cataracts or who are aphakic. Eye protection should be worn when outdoors, when exposed to sunlight transmitting through window glass and if exposed to indoor lighting capable of emitting UVA (including 'energy saving' compact fluorescent lamps).

Advice should be given on photoprotection following each PUVA session, especially over the 12 h after each treatment.

Informed consent should be taken and appropriate patient information leaflet provided.

Some examples of patient information leaflets can be viewed at the following websites: http://www.bad.org.uk/shared/get-file.ashx?itemtype=document&id=1644 (pp. 35–8); http://www.phototherapysupport.net/view-document.asp?FileID=40 (Appendix 2, pp. 44–9); http://www.photonet.scot.nhs.uk/professionals-area/patient-information-sheets/.

12.2 Baseline investigations

In view of the minimal risk of hepatotoxicity, routine liver function tests are unnecessary, but should be performed to establish baseline levels in cases where there is known or suspected pre-existing liver dysfunction.

There is no definite evidence that lupus can be induced or exacerbated by PUVA. The routine checking of antinuclear antibodies is unnecessary unless there is history of photosensitivity.

If the patient is at an increased risk of cataracts (e.g. children with atopic eczema), a baseline assessment by an ophthalmologist should be considered.

The MPD should be established to avoid phototoxicity and also, importantly, to ensure sufficient psoralen in the skin at the correct time.[377]

13.0 Future directions

We have presented updated evidence to assist in the safe and effective use of PUVA therapy, although gaps still remain in direct evidence of comparison. Suggested areas for future research include: (i) a randomized comparative study comparing PUVA with biological therapy for chronic plaque psoriasis – this would help with guidance on whether to prescribe PUVA before biological therapies, taking into consideration the RR and efficacy; (ii) a study to investigate whether or not there is an effect of MPD measurement at 72 and 96 h on erythemal episodes during PUVA and efficacy outcome measures.

Table 4 Recommendations in particular clinical situations

Psoriasis	All dermatology phototherapy units should offer bath PUVA, as well as oral PUVA to treat psoriasis (strength of recommendation B) PUVA should usually be offered before oral systemic therapy for patients with chronic plaque psoriasis that has not responded adequately to other therapies, including narrowband UVB (strength of recommendation B) PUVA should be considered before biological therapy to treat chronic plaque psoriasis (strength of recommendation C) Although PUVA may occasionally be appropriate as a first-line phototherapy treatment for especially thick and/or extensive plaque psoriasis it should usually only be considered in patients with chronic plaque psoriasis, if NB-UVB has not been adequately effective (strength of recommendation B)
Atopic eczema	PUVA should be considered in patients with atopic eczema only if NB-UVB has not been adequately effective (strength of recommendation D)
CTCL of the MF type	PUVA is the first-line treatment for plaque-stage CTCL (strength of recommendation B) Maintenance therapy may be considered to prevent relapse in quickly recurrent plaque-stage CTCL (strength of recommendation D) NB-UVB is as effective as PUVA and is the treatment of choice for patch-stage CTCL (strength of recommendation D) Combination therapy with PUVA and IFN or retinoids/rexinoids should be considered in the treatment of early stage MF, if the response to monotherapy is slow (strength of recommendation B)
Vitiligo	PUVA should only be considered for widespread vitiligo if NB-UVB has been not shown to be adequately effective (strength of recommendation A)
PLE	PUVA should be considered if UVB has failed, or has previously triggered the eruption sufficiently to compromise a course of therapy, or if there are other practical issues. PUVA should be considered before other systemic treatments (strength of recommendation D)
CAD	In the treatment of CAD, PUVA should be considered in a specialist unit experienced in managing this disease, with full knowledge of the individual patient's action spectrum. Special precautions, including inpatient supervision and topical/oral corticosteroid cover, may be required (strength of recommendation D)
Idiopathic SU	In the management of SU (after full assessment, including definition of the action spectrum), PUVA can be considered. The treatment should be carried out with full knowledge of the patient's action spectrum, in a specialist unit experienced in managing this disease (strength of recommendation D)
EPP	PUVA is rarely appropriate in EPP; NB-UVB is the phototherapy of first choice (strength of recommendation D)
AP	NB-UVB may be a safer therapeutic option in terms of phototherapy-associated carcinogenic risk in patients with AP, particularly in children, and should be considered before PUVA (strength of recommendation D)
Hyperkeratotic palmoplantar eczema	Oral PUVA should usually be considered as the first-line PUVA treatment for patients with palmoplantar dermatoses [strength of recommendation D (GPP)]
Palmoplantar psoriasis	PUVA using topical or oral psoralen should be considered as a treatment for palmoplantar psoriasis (strength of recommendation C)
Palmoplantar pustulosis	PUVA using oral psoralen should be considered as a treatment for palmoplantar pustulosis (strength of recommendation C) Unless there are contraindications, the combination of oral PUVA with oral retinoids should be considered as a treatment for palmoplantar pustulosis (strength of recommendation A)
Pregnancy	It is recommended that female patients should avoid conception during PUVA therapy and that if despite this advice pregnancy does occur, PUVA should be discontinued (strength of recommendation D)

PUVA, psoralen–ultraviolet A; UVB, ultraviolet B; NB-UVB, narrowband UVB; CTCL, cutaneous T-cell lymphoma; MF, mycosis fungoides; IFN, interferon; PLE, polymorphic light eruption; CAD, chronic actinic dermatitis; SU, solar urticaria; EPP, erythropoietic protoporphyria; AP, actinic prurigo; GPP, good practice point.

14.0 Recommended audit points

Is there a system in place to record and recall episodes of 'burning' which clearly:

1 Grades each episode;
2 Reviews all episodes at 6-monthly intervals;
3 Interprets the result in the context of the total number of treatments and total number of patients treated?

Over the last 12 months:

1 Was there clear documentation of instances of painful erythema?
2 Was there clear documentation of staff training records for topical and/or oral PUVA therapy?
3 Was a patient information leaflet provided to (i) the last 20 consecutive patients receiving topical PUVA therapy; (ii) the last 50 consecutive patients receiving oral PUVA therapy?
4 Was there clear documentation on advising patients on the risk of skin carcinogenicity on sun-exposed skin for (i) the last 20 consecutive patients receiving topical PUVA therapy; (ii) the last 50 consecutive patients receiving oral PUVA therapy?
5 Was there clear documentation on advising patients on eye protection and UV protection following each oral PUVA treatment for the last 50 consecutive patients?

The audit recommendation of 20 or 50 cases per department is to reduce variation in the results due to a single patient, and to allow for benchmarking between different units. However, departments unable to achieve this recommendation may choose to audit all cases seen in the preceding 12 months.

15.0 Summary

Please see the summary of recommendations for the safe and effective use of PUVA therapy in particular clinical situations (Table 4).

Acknowledgments

We are very grateful to Professor Alex Anstey (University of Cardiff and Ysbyty Gwynedd), Dr J.J. Lloyd (University of Newcastle and Royal Victoria Infirmary) and Ms Trish Garibaldinos (St. John's Institute of Dermatology), as well as everyone who commented on the draft during the consultation period.

References

1 Bell HK, Ormerod AD. Writing a British Association of Dermatologists clinical guideline: an update on the process and guidance for authors. *Br J Dermatol* 2009; **160**:725–8.
2 Brouwers MC, Kho ME, Browman GP *et al.* AGREE II: advancing guideline development, reporting and evaluation in health care. *Can Med Assoc J* 2010; **182**:E839–42.
3 Neyeloff JL, Fuchs SC, Moreira LB. Meta-analyses and Forest plots using a microsoft excel spreadsheet: step-by-step guide focusing on descriptive data analysis. *BMC Res Notes* 2012; **5**:52.
4 Hönigsmann H. History of phototherapy in dermatology. *Photochem Photobiol Sci* 2013; **12**:16–21.
5 Dawe RS. A quantitative review of studies comparing the efficacy of narrow-band and broad-band ultraviolet B for psoriasis. *Br J Dermatol* 2003; **149**:669–72.
6 Yones SS, Palmer RA, Garibaldinos TM *et al.* Randomized double-blind trial of treatment of vitiligo: efficacy of psoralen-UV-A therapy vs narrowband-UV-B therapy. *Arch Dermatol* 2007; **143**:578–84.
7 Inzinger M, Heschl B, Weger W *et al.* Efficacy of psoralen plus ultraviolet A therapy vs. biologics in moderate to severe chronic plaque psoriasis: retrospective data analysis of a patient registry. *Br J Dermatol* 2011; **165**:640–5.
8 Sakuntabhai A, Matthews JN, Farr PM. Improved prediction of the minimal phototoxic dose in PUVA therapy. *Br J Dermatol* 1994; **130**:604–9.
9 Gemmeke A, Schonlebe J, Koch A *et al.* Pityriasis rubra pilaris – a retrospective single center analysis over eight years. *J Dtsch Dermatol Ges* 2010; **8**:439–44.
10 Collins P, Rogers S. Bath-water compared with oral delivery of 8-methoxypsoralen PUVA therapy for chronic plaque psoriasis. *Br J Dermatol* 1992; **127**:392–5.
11 Cooper EJ, Herd RM, Priestley GC *et al.* A comparison of bathwater and oral delivery of 8-methoxypsoralen in PUVA therapy for plaque psoriasis. *Clin Exp Dermatol* 2000; **25**:111–14.
12 Turjanmaa K, Salo H, Reunala T. Comparison of trioxsalen bath and oral methoxsalen PUVA in psoriasis. *Acta Derm Venereol* 1985; **65**:86–8.
13 Lowe NJ, Weingarten D, Bourget T *et al.* PUVA therapy for psoriasis: comparison of oral and bath-water delivery of 8-methoxypsoralen. *J Am Acad Dermatol* 1986; **14**:754–60.
14 Berneburg M, Herzinger T, Rampf J *et al.* Efficacy of bath psoralen plus ultraviolet A (PUVA) vs. system PUVA in psoriasis: a prospective, open, randomized, multicentre study. *Br J Dermatol* 2013; **169**:704–8.
15 Alshiyab D, Chin MF, Edwards C *et al.* An evaluation of the preferences of patients with psoriasis between systemic psoralen plus ultraviolet A and bath psoralen plus ultraviolet A. *Br J Dermatol* 2015; **172**:1457–8.
16 Sivanesan SP, Gattu S, Hong J *et al.* Randomized, double-blind, placebo-controlled evaluation of the efficacy of oral psoralen plus ultraviolet A for the treatment of plaque-type psoriasis using the Psoriasis Area Severity Index score (improvement of 75% or greater) at 12 weeks. *J Am Acad Dermatol* 2009; **61**:793–8.
17 Nugteren-Huying WM, van der Schroeff JG, Hermans J *et al.* Fumaric acid therapy for psoriasis: a randomized, double-blind, placebo-controlled study. *J Am Acad Dermatol* 1990; **22**:311–12.
18 Ellis CN, Fradin MS, Messana JM *et al.* Cyclosporine for plaque-type psoriasis. Results of a multidose, double-blind trial. *N Engl J Med* 1991; **324**:277–84.
19 Saurat JH, Stingl G, Dubertret L *et al.* Efficacy and safety results from the randomized controlled comparative study of adalimumab vs. methotrexate vs. placebo in patients with psoriasis (CHAMPION). *Br J Dermatol* 2008; **158**:558–66.
20 Kuitunen T, Malmstrom J, Palva E *et al.* Pancytopenia induced by low-dose methotrexate. A study of the cases reported to the Finnish Adverse Drug Reaction Register From 1991 to 1999. *Scand J Rheumatol* 2005; **34**:238–41.
21 Souto A, Maneiro JR, Salgado E *et al.* Risk of tuberculosis in patients with chronic immune-mediated inflammatory diseases

treated with biologics and tofacitinib: a systematic review and meta-analysis of randomized controlled trials and long-term extension studies. *Rheumatology (Oxford)* 2014; **53**:1872–85.
22 Smith CH, Anstey AV, Barker JN *et al.* British Association of Dermatologists' guidelines for biologic interventions for psoriasis 2009. *Br J Dermatol* 2009; **161**:987–1019.
23 Joint Formulary Committee. *British National Formulary* (BNF) 69. London: BMJ Publishing Group Ltd and Royal Pharmaceutical Society, 2015.
24 Van Weelden H, Baart de la Faille H, Young E *et al.* Comparison of narrow-band UV-B phototherapy and PUVA photochemotherapy in the treatment of psoriasis. *Acta Derm Venereol* 1990; **70**:212–15.
25 Tanew A, Radakovic-Fijan S, Schemper M *et al.* Narrowband UV-B phototherapy vs photochemotherapy in the treatment of chronic plaque-type psoriasis: a paired comparison study. *Arch Dermatol* 1999; **135**:519–24.
26 Gordon PM, Diffey BL, Matthews JN *et al.* A randomized comparison of narrow-band TL-01 phototherapy and PUVA photochemotherapy for psoriasis. *J Am Acad Dermatol* 1999; **41**:728–32.
27 Dawe RS, Cameron H, Yule S *et al.* A randomized controlled trial of narrowband ultraviolet B vs bath-psoralen plus ultraviolet A photochemotherapy for psoriasis. *Br J Dermatol* 2003; **148**:1194–204.
28 Markham T, Rogers S, Collins P. Narrowband UV-B (TL-01) phototherapy vs oral 8-methoxypsoralen psoralen-UV-A for the treatment of chronic plaque psoriasis. *Arch Dermatol* 2003; **139**:325–8.
29 Snellman E, Klimenko T, Rantanen T. Randomized half-side comparison of narrowband UVB and trimethylpsoralen bath plus UVA treatments for psoriasis. *Acta Derm Venereol* 2004; **84**:132–7.
30 Yones SS, Palmer RA, Garibaldinos TT *et al.* Randomized double-blind trial of the treatment of chronic plaque psoriasis: efficacy of psoralen-UV-A therapy vs narrowband UV-B therapy. *Arch Dermatol* 2006; **142**:836–42.
31 Salem SA, Barakat MA, Morcos CM. Bath psoralen + ultraviolet A photochemotherapy vs. narrow band-ultraviolet B in psoriasis: a comparison of clinical outcome and effect on circulating T-helper and T-suppressor/cytotoxic cells. *Photodermatol Photoimmunol Photomed* 2010; **26**:235–42.
32 Dayal S, Mayanka , Jain VK. Comparative evaluation of NBUVB phototherapy and PUVA photochemotherapy in chronic plaque psoriasis. *Indian J Dermatol Venereol Leprol* 2010; **76**:533–7.
33 Chauhan PS, Kaur I, Dogra S *et al.* Narrowband ultraviolet B versus psoralen plus ultraviolet A therapy for severe plaque psoriasis: an Indian perspective. *Clin Exp Dermatol* 2011; **36**:169–73.
34 Cameron H, Dawe RS, Yule S *et al.* A randomized, observer-blinded trial of twice vs. three times weekly narrowband ultraviolet B phototherapy for chronic plaque psoriasis. *Br J Dermatol* 2002; **147**:973–8.
35 de Jager MEA, de Jong EMGJ, van de Kerkhof PCM *et al.* Efficacy and safety of treatments for childhood psoriasis: a systematic literature review. *J Am Acad Dermatol* 2010; **62**:1013–30.
36 Uetsu N, Horio T. Treatment of persistent severe atopic dermatitis in 113 Japanese patients with oral psoralen photo-chemotherapy. *J Dermatol* 2003; **30**:450–7.
37 Hannuksela M, Karvonen J, Husa M *et al.* Ultraviolet light therapy in atopic dermatitis. *Acta Derm Venereol Suppl* 1985; **114**:137–9.
38 Tzaneva S, Kittler H, Holzer G *et al.* 5-Methoxypsoralen plus ultraviolet (UV) A is superior to medium-dose UVA1 in the treatment of severe atopic dermatitis: a randomized crossover trial. *Br J Dermatol* 2010; **162**:655–60.
39 Garritsen FM, Brouwer MW, Limpens J *et al.* Photo(chemo) therapy in the management of atopic dermatitis: an updated systematic review with implications for practice and research. *Br J Dermatol* 2014; **170**:501–13.
40 Der Petrossian M, Seeber A, Hönigsmann H *et al.* Half-side comparison study on the efficacy of 8-methoxypsoralen bath- PUVA versus narrow-band ultraviolet B phototherapy in patients with severe chronic atopic dermatitis. *Br J Dermatol* 2000; **142**:39–43.
41 de Kort WJ, van Weelden H. Bath psoralen-ultraviolet A therapy in atopic eczema. *J Eur Acad Dermatol Venereol* 2000; **14**:172–4.
42 Sheehan MP, Atherton DJ, Norris P *et al.* Oral psoralen photochemotherapy in severe childhood atopic eczema: an update. *Br J Dermatol* 1993; **129**:431–6.
43 Clayton TH, Clark SM, Turner D *et al.* The treatment of severe atopic dermatitis in childhood with narrowband ultraviolet B phototherapy. *Clin Exp Dermatol* 2007; **32**:28–33.
44 Roenigk HH. Photochemotherapy for mycosis fungoides. *Arch Dermatol* 1977; **113**:1047–51.
45 Cox NH, Turbitt ML, Ashworth J *et al.* Distribution of T cell subsets and Langerhans cells in mycosis fungoides, and the effect of PUVA therapy. *Clin Exp Dermatol* 1986; **11**:564–8.
46 Okamoto H, Takigawa M, Horio T. Alteration of lymphocyte functions by 8-methoxypsoralen and longwave ultraviolet radiation. I. Suppressive effects of PUVA on T-lymphocyte migration *in vitro*. *J Invest Dermatol* 1985; **84**:203–5.
47 Gilchrest BA. Methoxsalen photochemotherapy for mycosis fungoides. *Cancer Treat Rep* 1979; **63**:663–7.
48 Gasparro FP, Dall'Amico R, O'Malley M *et al.* Cell membrane DNA: a new target for psoralen photoadduct formation. *Photochem Photobiol* 1990; **52**:315–21.
49 Diederen PV, van Weelden H, Sanders CJ *et al.* Narrowband UVB and psoralen-UVA in the treatment of early-stage mycosis fungoides: a retrospective study. *J Am Acad Dermatol* 2003; **48**:215–19.
50 Ahmad K, Rogers S, McNicholas PD *et al.* Narrowband UVB and PUVA in the treatment of mycosis fungoides: a retrospective study. *Acta Derm Venereol* 2007; **87**:413–17.
51 El Mofty M, El Darouty M, Salonas M *et al.* Narrow band UVB (311 nm), psoralen UVB (311 nm) and PUVA therapy in the treatment of early-stage mycosis fungoides: a right–left comparative study. *Photodermatol Photoimmunol Photomed* 2005; **21**:281–6.
52 Hofer A, Cerroni L, Kerl H *et al.* Narrowband (311-nm) UV-B therapy for small plaque parapsoriasis and early-stage mycosis fungoides. *Arch Dermatol* 1999; **135**:1377–80.
53 Clark C, Dawe RS, Evans AT *et al.* Narrowband TL-01 phototherapy for patch-stage mycosis fungoides. *Arch Dermatol* 2000; **136**:748–52.
54 Drucker AM, Baibergenova A, Rosen CF *et al.* Narrowband UVB as an effective substitute for psoralen plus UVA: lessons from a psoralen shortage. *Photodermatol Photoimmunol Photomed* 2012; **28**:267–8.
55 Ramsay DL, Lish KM, Yalowitz CB *et al.* Ultraviolet-B phototherapy for early-stage cutaneous T-cell lymphoma. *Arch Dermatol* 1992; **128**:931–3.
56 Resnik KS, Vonderheid EC. Home UV phototherapy of early mycosis fungoides: long-term follow-up observations in thirty-one patients. *J Am Acad Dermatol* 1993; **29**:73–7.
57 Plettenberg H, Stege H, Megahed M *et al.* Ultraviolet al (340–400 nm) phototherapy for cutaneous T-cell lymphoma. *J Am Acad Dermatol* 1999; **41**:47–50.
58 Zane C, Leali C, Airo P *et al.* 'High-dose' UVA1 therapy of widespread plaque-type, nodular, and erythrodermic mycosis fungoides. *J Am Acad Dermatol* 2001; **44**:629–33.
59 Pothiawala SZ, Baldwin BT, Cherpelis BS *et al.* The role of phototherapy in cutaneous T-cell lymphoma. *J Drugs Dermatol* 2010; **9**:764–72.
60 Gilchrest BA, Parrish JA, Tanenbaum L *et al.* Oral methoxsalen photochemotherapy of mycosis fungoides. *Cancer* 1976; **38**:683–9.
61 Herrmann JJ, Roenigk HH, Hurria A *et al.* Treatment of mycosis fungoides with photochemotherapy (PUVA): long- term follow-up. *J Am Acad Dermatol* 1995; **33**:234–42.

62 Hodge L, Warin AP, Gange RW *et al.* Photochemotherapy in mycosis fungoides. *Br Med J* 1977; **2**:1257–9.
63 Hönigsmann H, Brenner W, Rauschmeier W *et al.* Photochemotherapy for cutaneous T cell lymphoma. A follow-up study. *J Am Acad Dermatol* 1984; **10**:238–45.
64 Child FJ, Mitchell TJ, Whittaker SJ *et al.* A randomized cross-over study to compare PUVA and extracorporeal photopheresis in the treatment of plaque stage (T2) mycosis fungoides. *Clin Exp Dermatol* 2004; **29**:231–6.
65 Whittaker SJ, Marsden JR, Spittle M *et al.* Joint British Association of Dermatologists and U.K. Cutaneous Lymphoma Group guidelines for the management of primary cutaneous T- cell lymphomas. *Br J Dermatol* 2003; **149**:1095–107.
66 Carter J, Zug KA. Phototherapy for cutaneous T-cell lymphoma: online survey and literature review. *J Am Acad Dermatol* 2009; **60**:39–50.
67 Rupoli S, Goteri G, Pulini S *et al.* Long-term experience with low-dose interferon-alpha and PUVA in the management of early mycosis fungoides. *Eur J Haematol* 2005; **75**:136–45.
68 Stadler R. Optimal combination with PUVA: rationale and clinical trial update. *Oncology* 2007; **21**:29–32.
69 Roenigk HH Jr, Kuzel TM, Skoutelis AP *et al.* Photochemotherapy alone or combined with interferon alpha-2a in the treatment of cutaneous T-cell lymphoma. *J Invest Dermatol* 1990; **95**:198S–205S.
70 Thomsen K, Hammar H, Molin L *et al.* Retinoids plus PUVA (RePUVA) and PUVA in mycosis fungoides, plaque stage. A report from the Scandinavian Mycosis Fungoides Group. *Acta Derm Venereol* 1989; **69**:536–8.
71 Singh F, Lebwohl MG. Cutaneous T-cell lymphoma treatment using bexarotene and PUVA: a case series. *J Am Acad Dermatol* 2004; **51**:570–3.
72 Talpur R, Ward S, Apisarnthanarax N *et al.* Optimizing bexarotene therapy for cutaneous T-cell lymphoma. *J Am Acad Dermatol* 2002; **47**:672–84.
73 Whittaker S, Ortiz P, Dummer R *et al.* Efficacy and safety of bexarotene combined with psoralen-ultraviolet A (PUVA) compared with PUVA treatment alone in stage IB-IIA mycosis fungoides: final results from the EORTC Cutaneous Lymphoma Task Force phase III randomized clinical trial (NCT00056056). *Br J Dermatol* 2012; **167**:678–87.
74 Quirós PA, Jones GW, Kacinski BM *et al.* Total skin electron beam therapy followed by adjuvant psoralen/ultraviolet-A light in the management of patients with T1 and T2 cutaneous T-cell lymphoma (mycosis fungoides). *Int J Radiat Oncol Biol Phys* 1997; **38**:1027–35.
75 Westerhof W, Nieuweboer Krobotova L. Treatment of vitiligo with UV-B radiation vs topical psoralen plus UV- A. *Arch Dermatol* 1997; **133**:1525–8.
76 Bhatnagar A, Kanwar AJ, Parsad D *et al.* Comparison of systemic PUVA and NB-UVB in the treatment of vitiligo: an open prospective study. *J Eur Acad Dermatol Venereol* 2007; **21**:638–42.
77 Bhatnagar A, Kanwar AJ, Parsad D *et al.* Psoralen and ultraviolet A and narrow-band ultraviolet B in inducing stability in vitiligo, assessed by vitiligo disease activity score: an open prospective comparative study. *J Eur Acad Dermatol Venereol* 2007; **21**:1381–5.
78 Man I, Dawe RS, Ferguson J. Artificial hardening for polymorphic light eruption: practical points from ten years' experience. *Photodermatol Photoimmunol Photomed* 1999; **15**:3–4.
79 Mastalier U, Kerl H, Wolf P. Clinical, laboratory, phototest and phototherapy findings in polymorphic light eruptions: a retrospective study of 133 patients. *Eur J Dermatol* 1998; **8**:554–9.
80 Berg M, Ros AM, Berne B. Ultraviolet A phototherapy and trimethylpsoralen UVA photochemotherapy in polymorphous light eruption – a controlled study. *Photodermatol Photoimmunol Photomed* 1994; **10**:139–43.
81 Bilsland D, George SA, Gibbs NK *et al.* A comparison of narrow band phototherapy (TL-01) and photochemotherapy (PUVA) in the management of polymorphic light eruption. *Br J Dermatol* 1993; **129**:708–12.
82 Leonard F, Morel M, Kalis B *et al.* Psoralen plus ultraviolet A in the prophylactic treatment of benign summer light eruption. *Photodermatol Photoimmunol Photomed* 1991; **8**:95–8.
83 Murphy GM, Logan RA, Lovell CR *et al.* Prophylactic PUVA and UVB therapy in polymorphic light eruption – a controlled trial. *Br J Dermatol* 1987; **116**:531–8.
84 Addo HA, Sharma SC. UVB phototherapy and photochemotherapy (PUVA) in the treatment of polymorphic light eruption and solar urticaria. *Br J Dermatol* 1987; **116**:539–47.
85 Molin L, Volden G. Treatment of polymorphous light eruption with PUVA and prednisolone. *Photodermatol* 1987; **4**:107–8.
86 Ortel B, Tanew A, Wolff K *et al.* Polymorphous light eruption: action spectrum and photoprotection. *J Am Acad Dermatol* 1986; **14**:748–53.
87 Jansén CT, Karvonen J, Malmiharju T. PUVA therapy for polymorphous light eruptions: comparison of systemic methoxsalen and topical trioxsalen regimens and evaluation of local protective mechanisms. *Acta Derm Venereol* 1982; **62**:317–20.
88 Parrish JA, Le Vine MJ, Morison WL *et al.* Comparison of PUVA and beta-carotene in the treatment of polymorphous light eruption. *Br J Dermatol* 1979; **100**:187–91.
89 Gschnait F, Hönigsmann H, Brenner W *et al.* Induction of UV light tolerance by PUVA in patients with polymorphous light eruption. *Br J Dermatol* 1978; **99**:293–5.
90 Patel GK, Harding KG, Millis CM. Severe disabling Koebnerizing ulcerated necrobiosis lipoidica successfully managed with topical PUVA (18). *Br J Dermatol* 2000; **143**:668–9.
91 Norris PG, Hawk JL. Successful treatment of severe polymorphous light eruption with azathioprine. *Arch Dermatol* 1989; **125**:1377–9.
92 Shipley DR, Hewitt JB. Polymorphic light eruption treated with cyclosporin. *Br J Dermatol* 2001; **144**:446–7.
93 Murphy GM, McCann P, O'Leary A *et al.* Guidelines for the use of phototherapy and photochemotherapy in Ireland. *Ir J Med Sci* 1997; **166**:92–7.
94 Corbett MF, Hawk JL, Herxheimer A *et al.* Controlled therapeutic trials in polymorphic light eruption. *Br J Dermatol* 1982; **107**: 571–81.
95 Jansén CT. Beta-carotene treatment of polymorphous light eruptions. *Dermatologica* 1974; **149**:363–73.
96 Mathews-Roth MM, Pathak MA, Fitzpatrick TB *et al.* Beta carotene therapy for erythropoietic protoporphyria and other photosensitivity diseases. *Arch Dermatol* 1977; **113**:1229–32.
97 Jansén CT. Oral carotenoid treatment in polymorphous light eruption: a cross-over comparison with oxychloroquine and placebo. *Photodermatol* 1985; **2**:166–9.
98 Neumann R, Rappold E, Pohl-Markl H. Treatment of polymorphous light eruption with nicotinamide: a pilot study. *Br J Dermatol* 1986; **115**:77–80.
99 Ortel B, Wechdorn D, Tanew A *et al.* Effect of nicotinamide on the phototest reaction in polymorphous light eruption. *Br J Dermatol* 1988; **118**:669–73.
100 Rhodes LE, Durham BH, Fraser WD *et al.* Dietary fish oil reduces basal and ultraviolet B-generated PGE2 levels in skin and increases the threshold to provocation of polymorphic light eruption. *J Invest Dermatol* 1995; **105**:532–5.

101 Hadshiew I, Stäb F, Untiedt S *et al.* Effects of topically applied antioxidants in experimentally provoked polymorphous light eruption. *Dermatology* 1997; **195**:362–8.

102 Rippke F, Wendt G, Bohnsack K *et al.* Results of photoprovocation and field studies on the efficacy of a novel topically applied antioxidant in polymorphous light eruption. *J Dermatolog Treat* 2001; **12**:3–8.

103 Eberlein-König B, Fesq H, Abeck D *et al.* Systemic vitamin C and vitamin E do not prevent photoprovocation test reactions in polymorphous light eruption. *Photodermatol Photoimmunol Photomed* 2000; **16**:50–2.

104 Przybilla B, Heppeler M, Ruzicka T. Preventive effect of an *E. coli*-filtrate (Colibiogen) in polymorphous light eruption. *Br J Dermatol* 1989; **121**:229–33.

105 Patel DC, Bellaney GJ, Seed PT *et al.* Efficacy of short-course oral prednisolone in polymorphic light eruption: a randomized controlled trial. *Br J Dermatol* 2000; **143**:828–31.

106 Marguery MC, Montazeri A, El Sayed F *et al.* Chronic actinic dermatitis: a severe case responding to cyclosporin- bath-PUVA therapy. *J Dermatolog Treat* 1997; **8**:281–3.

107 Nousari HC, Anhalt GJ, Morison WL. Mycophenolate in psoralen-UV-A desensitization therapy for chronic actinic dermatitis. *Arch Dermatol* 1999; **135**:1128–9.

108 Hindson C, Downey A, Sinclair S *et al.* PUVA therapy of chronic actinic dermatitis: a 5-year follow-up. *Br J Dermatol* 1990; **123**:273.

109 Hindson C, Spiro J, Downey A. PUVA therapy of chronic actinic dermatitis. *Br J Dermatol* 1985; **113**:157–60.

110 Gardeazábal J, Arregui MA, Gil N *et al.* Successful treatment of musk ketone-induced chronic actinic dermatitis with cyclosporine and PUVA. *J Am Acad Dermatol* 1992; **27**:838–42.

111 Burke DA, Corey G, Storrs FJ. Psoralen plus UVA protocol for Compositae photosensitivity. *Am J Contact Dermat* 1996; **7**:171–6.

112 Yokel BK, Hood AF, Morison WL. Management of chronic photosensitive eczema. *Arch Dermatol* 1990; **126**:1283–5.

113 Parrish JA, Jaenicke KF, Morison WL *et al.* Solar urticaria: treatment with PUVA and mediator inhibitors. *Br J Dermatol* 1982; **106**:575–80.

114 Adamski H, Bedane C, Bonnevalle A *et al.* Solar urticaria treated with intravenous immunoglobulins. *J Am Acad Dermatol* 2011; **65**:336–40.

115 Hudson-Peacock MJ, Farr PM, Diffey BL *et al.* Combined treatment of solar urticaria with plasmapheresis and PUVA. *Br J Dermatol* 1993; **128**:440–2.

116 Leenutaphong V, Hölzle E, Plewig G *et al.* Plasmapheresis in solar urticaria. *Dermatologica* 1991; **182**:35–8.

117 Bilsland D, Ferguson J. A comparison of cetirizine and terfenadine in the management of solar urticaria. *Photodermatol Photoimmunol Photomed* 1991; **8**:62–4.

118 Diffey BL, Farr PM. Treatment of solar urticaria with terfenadine. *Photodermatol* 1988; **5**:25–9.

119 Grundmann SA, Ständer S, Luger TA *et al.* Antihistamine combination treatment for solar urticaria. *Br J Dermatol* 2008; **158**:1384–6.

120 Grattan CE, Humphreys F. Guidelines for evaluation and management of urticaria in adults and children. *Br J Dermatol* 2007; **157**:1116–23.

121 Calzavara-Pinton P, Zane C, Rossi M *et al.* Narrowband ultraviolet B phototherapy is a suitable treatment option for solar urticaria. *J Am Acad Dermatol* 2012; **67**:e5–9.

122 Wolf R, Herzinger T, Grahovac M *et al.* Solar urticaria: long-term rush hardening by inhibition spectrum narrow-band UVB 311 nm. *Clin Exp Dermatol* 2013; **38**:446–7.

123 Collins P, Ferguson J. Narrow-band UVB (TL-01) phototherapy: an effective preventative treatment for the photodermatoses. *Br J Dermatol* 1995; **132**:956–63.

124 Bernhard JD, Jaenicke K, Momtaz-T K *et al.* Ultraviolet A phototherapy in the prophylaxis of solar urticaria. *J Am Acad Dermatol* 1984; **10**:29–33.

125 Dawe RS, Ferguson J. Prolonged benefit following ultraviolet A phototherapy for solar urticaria. *Br J Dermatol* 1997; **137**:144–8.

126 Beissert S, Ständer H, Schwarz T. UVA rush hardening for the treatment of solar urticaria. *J Am Acad Dermatol* 2000; **42**:1030–2.

127 Roelandts R. Pre-PUVA UVA desensitization for solar urticaria. *Photodermatol* 1985; **2**:174–6.

128 Roelandts R. Photo(chemo)therapy and general management of erythropoietic protoporphyria. *Dermatology* 1995; **190**:330–1.

129 Ros AM. PUVA therapy for erythropoietic protoporphyria. *Photodermatol* 1988; **5**:148–9.

130 Warren LJ, George S. Erythropoietic protoporphyria treated with narrow-band (TL-01) UVB phototherapy. *Australas J Dermatol* 1998; **39**:179–82.

131 Sivaramakrishnan M, Woods J, Dawe R. Narrowband ultraviolet B phototherapy in erythropoietic protoporphyria: case series. *Br J Dermatol* 2014; **170**:987–8.

132 Farr PM, Diffey BL. Treatment of actinic prurigo with PUVA: mechanism of action. *Br J Dermatol* 1989; **120**:411–18.

133 Lee DY, Youn JLI, Park MH *et al.* Actinic purigo: limited effect of PUVA. *Br J Dermatol* 1997; **136**:972–3.

134 Gschnait F, Schwarz T, Ladich I. Treatment of polymorphous light eruption. *Arch Dermatol Res* 1983; **275**:379–82.

135 Halpern SM, Anstey AV, Dawe RS *et al.* Guidelines for topical PUVA: a report of a workshop of the British photodermatology group. *Br J Dermatol* 2000; **142**:22–31.

136 Konya J, Diffey BL, Hindson TC. Time course of activity of topical 8-methoxypsoralen on palmoplantar skin. *Br J Dermatol* 1992; **127**:654–6.

137 Rosén K, Mobacken H, Swanbeck G. Chronic eczematous dermatitis of the hands: a comparison of PUVA and UVB treatment. *Acta Derm Venereol* 1987; **67**:48–54.

138 Rosén K, Jontell M, Mobacken H *et al.* Epidermal Langerhans' cells in chronic eczematous dermatitis of the palms treated with PUVA and UVB. *Acta Derm Venereol* 1989; **69**:200–5.

139 Mobacken H, Rosén K, Swanbeck G. Oral psoralen photochemotherapy (PUVA) of hyperkeratotic dermatitis of the palms. *Br J Dermatol* 1983; **109**:205–8.

140 Tegner E, Thelin I. PUVA treatment of chronic eczematous dermatitis of the palms and soles. *Acta Derm Venereol* 1985; **65**:451–3.

141 Morison WL, Parrish JA, Fitzpatrick TB. Oral methoxsalen photochemotherapy of recalcitrant dermatoses of the palms and soles. *Br J Dermatol* 1978; **99**:293–302.

142 LeVine MJ, Parrish JA, Fitzpatrick TB. Oral methoxsalen photochemotherapy (PUVA) of dyshidrotic eczema. *Acta Derm Venereol* 1981; **61**:570–1.

143 De Rie MA, Van Eendenburg JP, Versnick AC *et al.* A new psoralen-containing gel for topical PUVA therapy: development, and treatment results in patients with palmoplantar and plaque-type psoriasis, and hyperkeratotic eczema. *Br J Dermatol* 1995; **132**:964–9.

144 Schempp CM, Müller H, Czech W *et al.* Treatment of chronic palmoplantar eczema with local bath-PUVA therapy. *J Am Acad Dermatol* 1997; **36**:733–7.

145 Gritiyarangsan P, Sukhum A, Tresukosol P *et al.* Topical PUVA therapy for chronic hand eczema. *J Dermatol* 1998; **25**:299–301.

146 Behrens S, von Kobyletzki G, Gruss C *et al.* PUVA-bath photochemotherapy (PUVA-soak therapy) of recalcitrant dermatoses

of the palms and soles. *Photodermatol Photoimmunol Photomed* 1999; **15**:47–51.
147 Davis MD, McEvoy MT, el-Azhary RA. Topical psoralen-ultraviolet A therapy for palmoplantar dermatoses: experience with 35 consecutive patients. *Mayo Clin Proc* 1998; **73**:407–11.
148 Taylor CR, Baron ED. Hand and foot PUVA soaks: an audit of the Massachusetts General Hospital's experience from 1994 to 1998. *Photodermatol Photoimmunol Photomed* 1999; **15**:188–92.
149 Douwes KE, Karrer S, Abels C *et al.* Does smoking influence the efficacy of bath-PUVA therapy in chronic palmoplantar eczema? *Photodermatol Photoimmunol Photomed* 2000; **16**:25–9.
150 O'Kane D, McLoone NM, Jenkinson H *et al.* Efficacy of topical PUVA soaks for palmoplantar dermatoses: an audit. *Photodermatol Photoimmunol Photomed* 2008; **24**:279–84.
151 Riad K, Felix P, Dorit S *et al.* The use of topical PUVA for palmoplantar dermatoses. *J Dermatolog Treat* 2006; **17**:304–7.
152 Grundmann-Kollmann M, Behrens S, Peter RU *et al.* Treatment of severe recalcitrant dermatoses of the palms and soles with PUVA-bath versus PUVA-cream therapy. *Photodermatol Photoimmunol Photomed* 1999; **15**:87–9.
153 Shephard SE, Schregenberger N, Dummer R *et al.* Comparison of 8-MOP aqueous bath and 8-MOP ethanolic lotion (Meladinine) in local PUVA therapy. *Dermatology* 1998; **197**:25–30.
154 Schiener R, Gottlöber P, Müller B *et al.* PUVA-gel vs. PUVA-bath therapy for severe recalcitrant palmoplantar dermatoses. A randomized, single-blinded prospective study. *Photodermatol Photoimmunol Photomed* 2005; **21**:62–7.
155 Grattan CE, Carmichael AJ, Shuttleworth GJ *et al.* Comparison of topical PUVA with UVA for chronic vesicular hand eczema. *Acta Derm Venereol* 1991; **71**:118–22.
156 Engin B, Oguz O. Evaluation of time-dependent response to psoralen plus UVA (PUVA) treatment with topical 8-methoxypsoralen (8-MOP) gel in palmoplantar dermatoses. *Int J Dermatol* 2005; **44**:337–9.
157 Simons JR, Bohnen IJ, van der Valk PG. A left-right comparison of UVB phototherapy and topical photochemotherapy in bilateral chronic hand dermatitis after 6 weeks' treatment. *Clin Exp Dermatol* 1997; **22**:7–10.
158 Sezer E, Etikan I. Local narrowband UVB phototherapy vs. local PUVA in the treatment of chronic hand eczema. *Photodermatol Photoimmunol Photomed* 2007; **23**:10–14.
159 Petering H, Breuer C, Herbst R *et al.* Comparison of localized high-dose UVA1 irradiation versus topical cream psoralen-UVA for treatment of chronic vesicular dyshidrotic eczema. *J Am Acad Dermatol* 2004; **50**:68–72.
160 Sheehan-Dare RA, Goodfield MJ, Rowell NR. Topical psoralen photochemotherapy (PUVA) and superficial radiotherapy in the treatment of chronic hand eczema. *Br J Dermatol* 1989; **121**:65–9.
161 Tupker RA, Coenraads PJ, Zanen P *et al.* Randomized controlled observer-blinded treatment of chronic foot eczema with iontophoresis and bath-PUVA. *Acta Derm Venereol* 2013; **93**:456–60.
162 Adişen E, Tekin O, Gulekon A *et al.* A retrospective analysis of treatment responses of palmoplantar psoriasis in 114 patients. *J Eur Acad Dermatol Venereol* 2009; **23**:814–19.
163 Redon E, Bursztejn AC, Loos C *et al.* [A retrospective efficacy and safety study of UVB-TL01 phototherapy and PUVA therapy in palmoplantar psoriasis]. *Ann Dermatol Venereol* 2010; **137**:597–603. (in French).
164 Wilkinson JD, Ralfs IG, Harper JI *et al.* Topical methoxsalen photochemotherapy in the treatment of palmoplantar pustulosis and psoriasis. *Acta Derm Venereol Suppl* 1979; **59**:193–8.
165 Abel EA, Goldberg LH, Farber EM. Treatment of palmoplantar psoriasis with topical methoxsalen plus long-wave ultraviolet light. *Arch Dermatol* 1980; **116**:1257–61.
166 Coleman WR, Lowe NJ, David M *et al.* Palmoplantar psoriasis: experience with 8-methoxypsoralen soaks plus ultraviolet A with the use of a high-output metal halide device. *J Am Acad Dermatol* 1989; **20**:1078–82.
167 Gómez MI, Pérez B, Harto A *et al.* 8-MOP bath PUVA in the treatment of psoriasis: clinical results in 42 patients. *J Dermatolog Treat* 1996; **7**:11–12.
168 Neumann NJ, Mahnke N, Korpusik D *et al.* Treatment of palmoplantar psoriasis with monochromatic excimer light (308-nm) versus cream PUVA. *Acta Derm Venereol* 2006; **86**:22–4.
169 Sezer E, Erbil AH, Kurumlu Z *et al.* Comparison of the efficacy of local narrowband ultraviolet B (NB-UVB) phototherapy versus psoralen plus ultraviolet A (PUVA) paint for palmoplantar psoriasis. *J Dermatol* 2007; **34**:435–40.
170 Chen X, Yang M, Cheng Y *et al.* Narrow-band ultraviolet B phototherapy versus broad-band ultraviolet B or psoralen-ultraviolet A photochemotherapy for psoriasis. *Cochrane Database Syst Rev* 2013; **10**:CD009481.
171 Murray D, Corbett MF, Warin AP. A controlled trial of photochemotherapy for persistent palmoplantar pustulosis. *Br J Dermatol* 1980; **102**:659–63.
172 Rosén K, Mobacken H, Swanbeck G. PUVA, etretinate, and PUVA-etretinate therapy for pustulosis palmoplantaris. A placebo-controlled comparative trial. *Arch Dermatol* 1987; **123**:885–9.
173 Layton AM, Sheehan-Dare R, Cunliffe WJ. A double-blind, placebo-controlled trial of topical PUVA in persistent palmoplantar pustulosis. *Br J Dermatol* 1991; **124**:581–4.
174 Matsunami E, Takashima A, Mizuno N *et al.* Topical PUVA, etretinate, and combined PUVA and etretinate for palmoplantar pustulosis: comparison of therapeutic efficacy and the influences of tonsillar and dental focal infections. *J Dermatol* 1990; **17**:92–6.
175 Lassus A, Lauharanta J, Eskelinen A. The effect of etretinate compared with different regimens of PUVA in the treatment of persistent palmoplantar pustulosis. *Br J Dermatol* 1985; **112**:455–9.
176 Marsland AM, Chalmers RJ, Hollis S *et al.* Interventions for chronic palmoplantar pustulosis. *Cochrane Database Syst Rev* 2006;**1**: CD001433.
177 van Coevorden AM, Kamphof WG, van Sonderen E *et al.* Comparison of oral psoralen-UV-A with a portable tanning unit at home vs hospital-administered bath psoralen-UV-A in patients with chronic hand eczema: an open-label randomized controlled trial of efficacy. *Arch Dermatol* 2004; **140**:1463–6.
178 Tzaneva S, Kittler H, Thallinger C *et al.* Oral vs. bath PUVA using 8-methoxypsoralen for chronic palmoplantar eczema. *Photodermatol Photoimmunol Photomed* 2009; **25**:101–5.
179 Hawk JL, Grice PL. The efficacy of localized PUVA therapy for chronic hand and foot dermatoses. *Clin Exp Dermatol* 1994; **19**:479–82.
180 Hofer A, Fink-Puches R, Kerl H *et al.* Paired comparison of bath-water versus oral delivery of 8- methoxypsoralen in psoralen plus ultraviolet: a therapy for chronic palmoplantar psoriasis. *Photodermatol Photoimmunol Photomed* 2006; **22**:1–5.
181 Lawrence CM, Marks J, Parker S *et al.* A comparison of PUVA-etretinate and PUVA-placebo for palmoplantar pustular psoriasis. *Br J Dermatol* 1984; **110**:221–6.
182 Norris PG, Hawk JLM, Baker C. British Photodermatology Group guidelines for PUVA. *Br J Dermatol* 1994; **130**:246–55.
183 Martin JA, Laube S, Edwards C *et al.* Rate of acute adverse events for narrow-band UVB and psoralen-UVA phototherapy. *Photodermatol Photoimmunol Photomed* 2007; **23**:68–72.
184 Tilkorn DJ, Schaffran A, Benna SA *et al.* Severe burn injuries induced by PUVA chemotherapy. *J Burn Care Res* 2013; **34**:e195–200.

185 Melski JW, Tanenbaum L, Parrish JA *et al.* Oral methoxsalen photochemotherapy for the treatment of psoriasis: a cooperative clinical trial. *J Invest Dermatol* 1977; **68**:328–35.
186 Henseler T, Wolff K, Hönigsmann H *et al.* Oral 8-methoxypsoralen photochemotherapy of psoriasis. The European PUVA study: a cooperative study among 18 European centres. *Lancet* 1981; **1**:853–7.
187 Wolff K. Side-effects of psoralen photochemotherapy (PUVA). *Br J Dermatol* 1990; **122**:S117–25.
188 Tanew A, Ortel B, Rappersberger K *et al.* 5-Methoxypsoralen (Bergapten) for photochemotherapy. Bioavailability, phototoxicity, and clinical efficacy in psoriasis of a new drug preparation. *J Am Acad Dermatol* 1988; **18**:333–8.
189 Ibbotson SH, Farr PM. The time-course of psoralen ultraviolet A (PUVA) erythema. *J Invest Dermatol* 1999; **113**:346–50.
190 Behrens-Williams S, Gruss C, Grundmann-Kollmann M *et al.* Assessment of minimal phototoxic dose following 8-methoxypsoralen bath: maximal reaction on average after 5 days. *Br J Dermatol* 2000; **142**:112–15.
191 Grundmann-Kollmann M, Leiter U, Behrens S *et al.* The time course of phototoxicity of topical PUVA: 8-methoxypsoralen cream-PUVA vs. 8-methoxypsoralen gel-PUVA. *Br J Dermatol* 1999; **140**:988–90.
192 Man I, Kwok YK, Dawe RS *et al.* The time course of topical PUVA erythema following 15- and 5-minute methoxsalen immersion. *Arch Dermatol* 2003; **139**:331–4.
193 Berroeta L, Attili S, Wong A *et al.* Time course for development of psoralen plus ultraviolet A erythema following oral administration of 5-methoxypsoralen. *Br J Dermatol* 2009; **160**:717–19.
194 Kerscher M, Gruss C, von Kobyletzki G *et al.* Time course of 8-MOP-induced skin photosensitization in PUVA bath photochemotherapy. *Br J Dermatol* 1997; **136**:473–4.
195 Gruss C, Behrens S, von Kobyletzki G *et al.* Effects of water temperature on photosensitization in bath-PUVA therapy with 8-methoxypsoralen. *Photodermatol Photoimmunol Photomed* 1998; **14**:145–7.
196 George SA, Ferguson J. Liquid formulations of 8-methoxypsoralen (8-MOP) and 5-MOP: a prospective double-blind crossover assessment of acute non-phototoxic adverse effects. *Photodermatol Photoimmunol Photomed* 1992; **9**:33–5.
197 Wainwright NJ, George S, Ferguson J. Phototoxicity at unusual sites during photochemotherapy. *Clin Exp Dermatol* 1993; **18**:292.
198 Suliman MT, Abdolmoneim M. Severe burns following phototherapy with PUVA for vetiligo: a preventable complication that still happening. *Burns* 2005; **31**:1063.
199 Verma SB, Wollina U. Accidental PUVA burns, vitiligo and atopic diathesis resulting in prurigo nodularis: a logical but undocumented rarity. *An Bras Dermatol* 2012; **87**:891–3.
200 Laube S, George SA. Adverse effects with PUVA and UVB phototherapy. *J Dermatolog Treat* 2001; **12**:101–5.
201 Fujii N, Uetsu N, Hamakawa M *et al.* Chronic actinic dermatitis developed during phototherapy for psoriasis. *Photodermatol Photoimmunol Photomed* 2002; **18**:157–9.
202 Dowdy MJ, Nigra TP, Barth WF. Subacute cutaneous lupus erythematosus during PUVA therapy for psoriasis: case report and review of the literature. *Arthritis Rheum* 1989; **32**:343–6.
203 Pirner K, Rubbert A, Salinger R *et al.* [Significance of ultraviolet light in the pathogenesis of systemic lupus erythematosus: case report and discussion of the literature]. *Z Rheumatol* 1992; **51**:20–4. (in German).
204 McFadden N. PUVA-induced lupus erythematosus in a patient with polymorphous light eruption. *Photodermatol* 1984; **1**:148–50.
205 Puig L, de Moragas JM. Enhancement of PUVA phototoxic effects following celery ingestion: cool broth also can burn. *Arch Dermatol* 1994; **130**:809–10.
206 Boffa MJ, Gilmour E, Ead RD. Celery soup causing severe phototoxicity during PUVA therapy. *Br J Dermatol* 1996; **135**:334.
207 Bendriss EK, Bechtel Y, Bendriss A *et al.* Inhibition of caffeine metabolism by 5-methoxypsoralen in patients with psoriasis. *Br J Clin Pharmacol* 1996; **41**:421–4.
208 Mays DC, Camisa C, Cheney P *et al.* Methoxsalen is a potent inhibitor of the metabolism of caffeine in humans. *Clin Pharmacol Ther* 1987; **42**:621–6.
209 Tantcheva Poór I, Servera-Llaneras M, Scharffetter-Kochanek K *et al.* Liver cytochrome P450 CYP1A2 is markedly inhibited by systemic but not by bath PUVA in dermatological patients. *Br J Dermatol* 2001; **144**:1127–32.
210 Stephens RB, Cooper A. Hepatitis from 5-methoxypsoralen occurring in a patient with previous flucloxacillin hepatitis. *Australas J Dermatol* 1999; **40**:217–19.
211 Berg M, Ros AM. Treatment of psoriasis with psoralens and ultraviolet A. A double-blind comparison of 8-methoxypsoralen and 5-methoxypsoralen. *Photodermatol Photoimmunol Photomed* 1994; **10**:217–20.
212 Bjellerup M, Bruze M, Hansson A *et al.* Liver injury following administration of 8-methoxypsoralen during PUVA therapy. *Acta Derm Venereol* 1979; **59**:371–2.
213 Freeman K, Warin AP. Deterioration of liver function during PUVA therapy. *Photodermatol* 1984; **1**:147–8.
214 Markin RS, Donovan JP, Shaw BW *et al.* Fulminant hepatic failure after methotrexate and PUVA therapy for psoriasis. *J Clin Gastroenterol* 1993; **17**:311–13.
215 Pariser DM, Wyles RJ. Toxic hepatitis from oral methoxsalen photochemotherapy (PUVA). *J Am Acad Dermatol* 1980; **3**:248–50.
216 Hann SK, Park YK, Im S *et al.* The effect on liver transaminases of phototoxic drugs used in systemic photochemotherapy. *J Am Acad Dermatol* 1992; **26**:646–8.
217 Park YM, Kim TY, Kim HO *et al.* Reproducible elevation of liver transaminases by topical 8-methoxypsoralen. *Photodermatol Photoimmunol Photomed* 1994; **10**:261–3.
218 Tegner E. Severe skin pain after PUVA treatment. *Acta Derm Venereol* 1979; **59**:467–70.
219 Johansson O. 'PUVA-induced skin pain' – speculations from a neuroscientist. *Exp Dermatol* 1994; **3**:95–6.
220 Norris PG, Maurice PD, Schott GD *et al.* Persistent skin pain after PUVA. *Clin Exp Dermatol* 1987; **12**:403–5.
221 Jordan WP. PUVA, pruritus, and the loss of the axon flare. *Arch Dermatol* 1979; **115**:636.
222 Burrows NP, Norris PG. Treatment of PUVA-induced skin pain with capsaicin. *Br J Dermatol* 1994; **131**:584–5.
223 Zamiri M, Bilsland D. Treatment of bath PUVA-induced skin pain with gabapentin. *Br J Dermatol* 2004; **151**:516–17.
224 Roelandts R, Stevens A. PUVA-induced itching and skin pain. *Photodermatol Photoimmunol Photomed* 1990; **7**:141–2.
225 Takashima A, Yamamoto K, Kimura S *et al.* Allergic contact and photocontact dermatitis due to psoralens in patients with psoriasis treated with topical PUVA. *Br J Dermatol* 1991; **124**:37–42.
226 Legat FJ, Wolf P, Kränke B. Anaphylaxis to 5-methoxypsoralen during photochemotherapy. *Br J Dermatol* 2001; **145**:821–2.
227 Park JY, Rim JH, Choe YB *et al.* Anaphylaxis to 8-methoxypsoralen during photochemotherapy. *Photodermatol Photoimmunol Photomed* 2003; **19**:37–8.
228 Ramsay B, Marks JM. Bronchoconstriction due to 8-methoxypsoralen. *Br J Dermatol* 1988; **119**:83–6.

229 Wennersten G. Exacerbation of bronchial asthma during photochemotherapy with 8-methoxypsoralen and UVA (PUVA). *Photodermatol* 1987; **4**:212–13.
230 Dromgoole SH. Bronchial reactions during psoralens and ultraviolet A (PUVA) therapy. *J Am Acad Dermatol* 1984; **11**:894.
231 Anderson CD, Frodin T, Skogh M. Unusual adverse effects of 8-methoxypsoralen: bronchial reaction during photochemotherapy (PUVA). *J Am Acad Dermatol* 1984; **10**:298.
232 Vázquez-López F, Pérez-Oliva N. Transient hyperpigmentation after calcipotriol ointment and PUVA therapy in psoriatic patients. *Acta Derm Venereol* 1996; **76**:400.
233 Gläser R, Röwert J, Mrowietz U. Hyperpigmentation due to topical calcipotriol and photochemotherapy in two psoriatic patients. *Br J Dermatol* 1998; **139**:148–51.
234 Carlin CS, Florell SR, Krueger GG. Induction of dramatic hyperpigmentation in a patient with generalized lichen planus treated with re-PUVA. *J Cutan Med Surg* 2002; **6**:125–7.
235 Jeanmougin M, Manciet JR, Castelneau JP *et al.* [Systemic photoallergy induced by methoxalen]. *Ann Dermatol Venereol* 1992; **119**:277–80. (in French).
236 Morgan JM, Weller R, Adams SJ. Onycholysis in a case of atopic eczema treated with PUVA photochemotherapy. *Clin Exp Dermatol* 1992; **17**:65–6.
237 McGeorge BC. Lunula change induced by psoralen plus ultraviolet A radiation. *Photodermatol Photoimmunol Photomed* 1992; **9**:15–16.
238 Maravić N, Bogdanić V, Aurer I *et al.* Severe hyperlipidemia following treatment with PUVA for acute skin GVHD. *Bone Marrow Transplant* 1994; **14**:173.
239 Wilczek A, Sticherling M. Concomitant psoriasis and bullous pemphigoid: coincidence or pathogenic relationship? *Int J Dermatol* 2006; **45**:1353–7.
240 Kao CL, Krathen RA, Wolf JE *et al.* Psoralen plus ultraviolet A-induced bullous pemphigoid. *J Drugs Dermatol* 2008; **7**:695–6.
241 Riyaz N, Nasir N, Bindu V *et al.* Bullous pemphigoid induced by topical PUVASOL. *Indian J Dermatol Venereol Leprol* 2014; **80**:363–4.
242 Nanda S, Grover C, Reddy BS. PUVA-induced lichen planus. *J Dermatol* 2003; **30**:151–3.
243 Kuramoto N, Kishimoto S, Shibagaki R *et al.* PUVA-induced lichen planus pemphigoides. *Br J Dermatol* 2000; **142**:509–12.
244 Kivanc MT, Klaus MV, Nashel DJ. Reversible polymyositis occurring during psoralen and ultraviolet A (PUVA) therapy. *J Rheumatol* 2000; **27**:1823–4.
245 van Coevorden AM, Coenraads PJ. Severe influenzalike symptoms associated with methoxsalen photochemotherapy. *Arch Dermatol* 2002; **138**:840–1.
246 Wolf P, Cerroni L, Smolle J *et al.* PUVA-induced lymphomatoid papulosis in a patient with mycosis fungoides. *J Am Acad Dermatol* 1991; **25**:422–6.
247 Vernassière C, Petitpain N, Martin S *et al.* 8-Methoxypsoralen and neurological disorders: from dysosmia to migraine. *Photodermatol Photoimmunol Photomed* 2006; **22**:217–18.
248 Martin S, Petitpain N, Tréchot P *et al.* 8-Methoxypsoralen-induced dysosmia. *Photodermatol Photoimmunol Photomed* 2003; **19**:213–14.
249 Hönigsmann H, Wolff K, Fitzpatrick TB. Oral photochemotherapy with psoralens and UVA (PUVA): principles and practice. In: *Dermatology in General Medicine* (Fitzpatrick TB, Eisen AZ, Wolff K, eds), 3rd edn. New York: McGraw-Hill, 1987; 1533–58.
250 Fernandes S, Marques Pinto G, Cardoso J. Development of new lesions: a complication of psoralen plus ultraviolet A light therapy for mycosis fungoides. *Photodermatol Photoimmunol Photomed* 2012; **28**:278–9.
251 Sage E, Bredberg A. Damage distribution and mutation spectrum: the case of 8-methoxypsoralen plus UVA in mammalian cells. *Mutat Res* 1991; **263**:217–22.
252 Peritz AE, Gasparro FP. Psoriasis, PUVA, and skin cancer – molecular epidemiology: the curious question of T–>A transversions. *J Investig Dermatol Symp Proc* 1999; **4**:11–16.
253 Gasparro FP, Liao B, Foley PJ *et al.* Psoralen photochemotherapy, clinical efficacy, and photomutagenicity: the role of molecular epidemiology in minimizing risks. *Environ Mol Mutagen* 1998; **31**:105–12.
254 Roelandts R. Mutagenicity and carcinogenicity of methoxsalen plus UV-A. *Arch Dermatol* 1984; **120**:662–9.
255 Young AR. Photocarcinogenicity of psoralens used in PUVA treatment: present status in mouse and man. *J Photochem Photobiol B* 1990; **6**:237–47.
256 Moscicki RA, Morison WL, Parrish JA *et al.* Reduction of the fraction of circulating helper-inducer T cells identified by monoclonal antibodies in psoriatic patients treated with long-term psoralen/ultraviolet-A radiation (PUVA). *J Invest Dermatol* 1982; **79**:205–8.
257 Friedmann PS. Disappearance of epidermal Langerhans cells during PUVA therapy. *Br J Dermatol* 1981; **105**:219–21.
258 Vella Briffa D, Parker D, Tosca N *et al.* The effect of photochemotherapy (PUVA) on cell mediated immunity in the guinea pig. *J Invest Dermatol* 1981; **77**:377–80.
259 Toyota N, Kitamura Y, Ogawa K. Administration of 8-methoxypsoralen and ultraviolet A irradiation (PUVA) induces turnover of mast cells in the skin of C57BL/6 mice. *J Invest Dermatol* 1990; **95**:353–8.
260 Viander M, Jansén CT, Eskola J. Influence of whole-body PUVA treatments on human peripheral blood NK cell activity. *Photodermatol* 1984; **1**:23–9.
261 Stern RS, Thibodeau LA, Kleinerman RA *et al.* Risk of cutaneous carcinoma in patients treated with oral methoxsalen photochemotherapy for psoriasis. *N Engl J Med* 1979; **300**:809–13.
262 Stern RS, Laird N, Melski J *et al.* Cutaneous squamous-cell carcinoma in patients treated with PUVA. *N Engl J Med* 1984; **310**:1156–61.
263 Stern RS, Lange R. Non-melanoma skin cancer occurring in patients treated with PUVA five to ten years after first treatment. *J Invest Dermatol* 1988; **91**:120–4.
264 Lindelöf B, Sigurgeirsson B, Tegner E *et al.* PUVA and cancer: a large-scale epidemiological study. *Lancet* 1991; **338**:91–3.
265 Bruynzeel I, Bergman W, Hartevelt HM *et al.* 'High single-dose' European PUVA regimen also causes an excess of non-melanoma skin cancer. *Br J Dermatol* 1991; **124**:49–55.
266 Lever LR, Farr PM. Skin cancers or premalignant lesions occur in half of high-dose PUVA patients. *Br J Dermatol* 1994; **131**:215–19.
267 Lim JL, Stern RS. High levels of ultraviolet B exposure increase the risk of non- melanoma skin cancer in psoralen and ultraviolet A-treated patients. *J Invest Dermatol* 2005; **124**:505–13.
268 Fitzsimons CP, Long J, MacKie RM. Synergistic carcinogenic potential of methotrexate and PUVA in psoriasis. *Lancet* 1983; **1**:235–6.
269 Stern RS, Laird N. The carcinogenic risk of treatments for severe psoriasis. Photochemotherapy Follow-up Study. *Cancer* 1994; **73**:2759–64.
270 Marcil I, Stern RS. Squamous-cell cancer of the skin in patients given PUVA and ciclosporin: nested cohort crossover study. *Lancet* 2001; **358**:1042–5.
271 Hönigsmann H, Wolff K, Gschnait F *et al.* Keratoses and nonmelanoma skin tumors in long-term photochemotherapy (PUVA). *J Am Acad Dermatol* 1980; **3**:406–14.
272 Lassus A, Reunala T, Idänpää-Heikkilä J *et al.* PUVA treatment and skin cancer: a follow-up study. *Acta Derm Venereol* 1981; **61**:141–5.
273 Henseler T, Christophers E, Hönigsmann H *et al.* Skin tumors in the European PUVA Study. Eight-year follow-up of 1643 patients treated with PUVA for psoriasis. *J Am Acad Dermatol* 1987; **16**:108–16.

274 Mali-Gerrits MG, Gaasbeek D, Boezeman J *et al.* Psoriasis therapy and the risk of skin cancers. *Clin Exp Dermatol* 1991; **16**:85–9.
275 Harwood CA, Spink PJ, Surentheran T *et al.* Detection of human papillomavirus DNA in PUVA-associated non-melanoma skin cancers. *J Invest Dermatol* 1998; **111**:123–7.
276 Rübben A, Baron JM, Grussendorf-Conen EI. Demonstration of human papillomavirus type 16-related DNA and absence of detectable p53 gene mutations in widespread cutaneous squamous cell carcinomas after oral psoralen with UV-A treatment. *Arch Dermatol* 1996; **132**:1257–9.
277 Weissenborn SJ, Höpfl R, Weber F *et al.* High prevalence of a variety of epidermodysplasia verruciformis-associated human papillomaviruses in psoriatic skin of patients treated or not treated with PUVA. *J Invest Dermatol* 1999; **113**:122–6.
278 Zumtobel U, Schwarze HP, Favre M *et al.* Widespread cutaneous carcinomas associated with human papillomaviruses 5, 14 and 20 after introduction of methotrexate in two long-term PUVA-treated patients. *Dermatology* 2001; **202**:127–30.
279 Stern RS, Nichols KT, Väkevä LH. Malignant melanoma in patients treated for psoriasis with methoxsalen (psoralen) and ultraviolet A radiation (PUVA). The PUVA Follow-Up Study. *N Engl J Med* 1997; **336**:1041–5.
280 Stern RS. The risk of melanoma in association with long-term exposure to PUVA. *J Am Acad Dermatol* 2001; **44**:755–61.
281 Lindelöf B, Sigurgeirsson B, Tegner E *et al.* PUVA and cancer risk: the Swedish follow-up study. *Br J Dermatol* 1999; **141**:108–12.
282 McKenna KE, Patterson CC, Handley J *et al.* Cutaneous neoplasia following PUVA therapy for psoriasis. *Br J Dermatol* 1996; **134**:639–42.
283 Lindelöf B, Sigurgeirsson B, Tegner E *et al.* Comparison of the carcinogenic potential of trioxsalen bath PUVA and oral methoxsalen PUVA: a preliminary report. *Arch Dermatol* 1992; **128**:1341–4.
284 Hannuksela-Svahn A, Sigurgeirsson B, Pukkala E *et al.* Trioxsalen bath PUVA did not increase the risk of squamous cell skin carcinoma and cutaneous malignant melanoma in a joint analysis of 944 Swedish and Finnish patients with psoriasis. *Br J Dermatol* 1999; **141**:497–501.
285 Stern RS, Lunder EJ. Risk of squamous cell carcinoma and methoxsalen (psoralen) and UV-A radiation (PUVA). A meta-analysis. *Arch Dermatol* 1998; **134**:1582–5.
286 Nijsten TE, Stern RS. The increased risk of skin cancer is persistent after discontinuation of psoralen+ultraviolet A: a cohort study. *J Invest Dermatol* 2003; **121**:252–8.
287 Forman AB, Roenigk HH, Caro WA *et al.* Long-term follow-up of skin cancer in the PUVA-48 cooperative study. *Arch Dermatol* 1989; **125**:515–19.
288 van Praag MC, Bavinck JN, Bergman W *et al.* PUVA keratosis. A clinical and histopathologic entity associated with an increased risk of nonmelanoma skin cancer. *J Am Acad Dermatol* 1993; **28**:412–17.
289 Rhodes AR, Stern RS, Melski JW. The PUVA lentigo: an analysis of predisposing factors. *J Invest Dermatol* 1983; **81**:459–63.
290 Stern RS. Genital tumors among men with psoriasis exposed to psoralens and ultraviolet A radiation (PUVA) and ultraviolet B radiation. The Photochemotherapy Follow-up Study. *N Engl J Med* 1990; **322**:1093–7.
291 Perkins W, Lamont D, MacKie RM. Cutaneous malignancy in males treated with photochemotherapy. *Lancet* 1990; **336**:1248.
292 Aubin F, Puzenat E, Arveux P *et al.* Genital squamous cell carcinoma in men treated by photochemotherapy. A cancer registry-based study from 1978 to 1998. *Br J Dermatol* 2001; **144**:1204–6.
293 Rhodes AR, Harrist TJ, Momtaz-T K. The PUVA-induced pigmented macule: a lentiginous proliferation of large, sometimes cytologically atypical, melanocytes. *J Am Acad Dermatol* 1983; **9**:47–58.
294 Frenk E. Malignant melanoma in a patient with severe psoriasis treated by oral methoxsalen photochemotherapy. *Dermatologica* 1983; **167**:152–4.
295 Marx JL, Auerbach R, Possick P *et al.* Malignant melanoma *in situ* in two patients treated with psoralens and ultraviolet A. *J Am Acad Dermatol* 1983; **9**:904–11.
296 Kemmett D, Reshad H, Baker H. Nodular malignant melanoma and multiple squamous cell carcinomas in a patient treated by photochemotherapy for psoriasis. *Br Med J (Clin Res Ed)* 1984; **289**:1498.
297 Johnson J. Melanoma and psoralens and ultraviolet A. *J Am Acad Dermatol* 1984; **11**:143.
298 Gupta AK, Stern RS, Swanson NA *et al.* Cutaneous melanomas in patients treated with psoralens plus ultraviolet A. A case report and the experience of the PUVA Follow-up Study. *J Am Acad Dermatol* 1988; **19**:67–76.
299 Bergner T, Przybilla B. Malignant melanoma in association with phototherapy. *Dermatology* 1992; **184**:59–61.
300 Haciyakupoğlu G, Varinli I, Memişoğlu HR *et al.* PUVA treatment and choroidal malignant melanoma. *Acta Ophthalmol* 1993; **71**:846–9.
301 Reseghetti A, Tribbia G, Locati F *et al.* Cutaneous malignant melanoma appearing during photochemotherapy of mycosis fungoides. *Dermatology* 1994; **189**:75–7.
302 Wolf P, Schöllnast R, Hofer A *et al.* Malignant melanoma after psoralen and ultraviolet A (PUVA) therapy. *Br J Dermatol* 1998; **138**:1100–1.
303 Lindelöf B. Risk of melanoma with psoralen/ultraviolet A therapy for psoriasis. Do the known risks now outweigh the benefits? *Drug Saf* 1999; **20**:289–97.
304 Whitmore SE, Morison WL. Melanoma after PUVA therapy for psoriasis. *N Engl J Med* 1997; **337**:502–3.
305 Wolff K. Should PUVA be abandoned? *N Engl J Med* 1997; **336**:1090–1.
306 Olsen JH, Møller H, Frentz G. Malignant tumors in patients with psoriasis. *J Am Acad Dermatol* 1992; **27**:716–22.
307 Boffetta P, Gridley G, Lindelöf B. Cancer risk in a population-based cohort of patients hospitalized for psoriasis in Sweden. *J Invest Dermatol* 2001; **117**:1531–7.
308 Gelfand JM, Berlin J, Van Voorhees A *et al.* Lymphoma rates are low but increased in patients with psoriasis: results from a population-based cohort study in the United Kingdom. *Arch Dermatol* 2003; **139**:1425–9.
309 Hannuksela-Svahn A, Pukkala E, Läärä E *et al.* Psoriasis, its treatment, and cancer in a cohort of Finnish patients. *J Invest Dermatol* 2000; **114**:587–90.
310 Margolis D, Bilker W, Hennessy S *et al.* The risk of malignancy associated with psoriasis. *Arch Dermatol* 2001; **137**:778–83.
311 Stern RS, Väkevä LH. Noncutaneous malignant tumors in the PUVA follow-up study: 1975–1996. *J Invest Dermatol* 1997; **108**:897–900.
312 Hansen NE. Development of acute myeloid leukaemia in a patient with psoriasis treated with oral 8-methoxypsoralen and longwave ultraviolet light. *Scand J Haematol* 1979; **22**:57–60.
313 Freeman K, Warin AP. Acute myelomonocytic leukaemia developing in a patient with psoriasis treated with oral 8-methoxypsoralen and longwave ultraviolet light. *Clin Exp Dermatol* 1985; **10**:144–6.
314 Sheehan-Dare RA, Cotterill JA, Barnard DL. Transformation of myelodysplasia to acute myeloid leukaemia during psoralen photochemotherapy (PUVA) treatment of psoriasis. *Acta Derm Venereol* 1989; **69**:262–4.

315 Kwong YL, Au WY, Ng MH *et al.* Acute myeloid leukemia following psoralen with ultraviolet A therapy: a fluorescence *in situ* hybridization study. *Cancer Genet Cytogenet* 1997; **99**:11–13.
316 Stern RS. Lymphoma risk in psoriasis: results of the PUVA follow-up study. *Arch Dermatol* 2006; **142**:1132–5.
317 Neumann RA, Knobler RM, Jurecka W *et al.* Disseminated superficial actinic porokeratosis: experimental induction and exacerbation of skin lesions. *J Am Acad Dermatol* 1989; **21**:1182–8.
318 Reymond JL, Beani JC, Amblard P. Superficial actinic porokeratosis in a patient undergoing long-term PUVA therapy. *Acta Derm Venereol* 1980; **60**:539–40.
319 Hazen PG, Carney JF, Walker AE *et al.* Disseminated superficial actinic porokeratosis: appearance associated with photochemotherapy for psoriasis. *J Am Acad Dermatol* 1985; **12**:1077–8.
320 Allen AL, Glaser DA. Disseminated superficial actinic porokeratosis associated with topical PUVA. *J Am Acad Dermatol* 2000; **43**:720–2.
321 Ros AM, Wennersten G, Lagerholm B. Long-term photochemotherapy for psoriasis: a histopathological and clinical follow-up study with special emphasis on tumour incidence and behavior of pigmented lesions. *Acta Derm Venereol* 1983; **63**:215–21.
322 Swart R, Kenter I, Suurmond D. The incidence of PUVA-induced freckles. *Dermatologica* 1984; **168**:304–5.
323 Cox NH, Jones SK, Downey DJ *et al.* Cutaneous and ocular side-effects of oral photochemotherapy: results of an 8-year follow-up study. *Br J Dermatol* 1987; **116**:145–52.
324 Takashima A, Matsunami E, Yamamoto K *et al.* Cutaneous carcinoma and 8-methoxypsoralen and ultraviolet A (PUVA) lentigines in Japanese patients with psoriasis treated with topical PUVA: a follow-up study of 214 patients. *Photodermatol Photoimmunol Photomed* 1990; **7**:218–21.
325 Gschnait F, Wolff K, Hönigsmann H *et al.* Long-term photochemotherapy: histopathological and immunofluorescence observations in 243 patients. *Br J Dermatol* 1980; **103**:11–22.
326 Nagase K, Hirashima N, Koba S *et al.* Acquired dermal melanocytosis induced by psoralen plus ultraviolet A therapy. *Acta Derm Venereol* 2012; **92**:691–2.
327 Ono T, Egawa K, Kayashima K *et al.* Late onset dermal melanocytosis: an upper back variant. *J Dermatol* 1991; **18**:97–103.
328 Sator PG, Schmidt JB, Hönigsmann H. Objective assessment of photoageing effects using high-frequency ultrasound in PUVA-treated psoriasis patients. *Br J Dermatol* 2002; **147**:291–8.
329 Cox AJ, Abel EA. Epidermal dystrophy. Occurrence after psoriasis therapy with psoralen and long-wave ultraviolet light. *Arch Dermatol* 1979; **115**:567–70.
330 Lerman S, Megaw J, Willis I. Potential ocular complications from PUVA therapy and their prevention. *J Invest Dermatol* 1980; **74**:197–9.
331 British Photodermatology Group. British Photodermatology Group guidelines for PUVA. *Br J Dermatol* 1994; **130**:246–55.
332 Stern RS, Parrish JA, Fitzpatrick TB. Ocular findings in patients treated with PUVA. *J Invest Dermatol* 1985; **85**:269–73.
333 Stern RS. Ocular lens findings in patients treated with PUVA. Photochemotherapy Follow-Up-Study. *J Invest Dermatol* 1994; **103**:534–8.
334 Malanos D, Stern RS. Psoralen plus ultraviolet A does not increase the risk of cataracts: a 25-year prospective study. *J Am Acad Dermatol* 2007; **57**:231–7.
335 Calzavara-Pinton PG, Carlino A, Manfredi E *et al.* Ocular side effects of PUVA-treated patients refusing eye sun protection. *Acta Derm Venereol Suppl* 1994; **186**:164–5.
336 Ullrich SE. Does exposure to UV radiation induce a shift to a Th-2-like immune reaction? *Photochem Photobiol* 1996; **64**:254–8.
337 Wang CY, Brodland DG, Su WP. Skin cancers associated with acquired immunodeficiency syndrome. *Mayo Clin Proc* 1995; **70**:766–72.
338 Matz H. Phototherapy for psoriasis: what to choose and how to use: facts and controversies. *Clin Dermatol* 2010; **28**:73–80.
339 Rodrigues LK, Klencke BJ, Vin-Christian K *et al.* Altered clinical course of malignant melanoma in HIV-positive patients. *Arch Dermatol* 2002; **138**:765–70.
340 Wilkins K, Turner R, Dolev JC *et al.* Cutaneous malignancy and human immunodeficiency virus disease. *J Am Acad Dermatol* 2006; **54**:189–206.
341 Lunder EJ, Stern RS. Merkel-cell carcinomas in patients treated with methoxsalen and ultraviolet A radiation. *N Engl J Med* 1998; **339**:1247–8.
342 Izikson L, Nornhold E, Iyer JG *et al.* Merkel cell carcinoma associated with HIV: review of 14 patients. *AIDS* 2011; **25**:119–21.
343 Ranki A, Puska P, Mattinen S *et al.* Effect of PUVA on immunologic and virologic findings in HIV-infected patients. *J Am Acad Dermatol* 1991; **24**:404–10.
344 Horn TD, Morison WL, Farzadegan H *et al.* Effects of psoralen plus UVA radiation (PUVA) on HIV-1 in human beings: a pilot study. *J Am Acad Dermatol* 1994; **31**:735–40.
345 Pechère M, Yerly S, Lemonnier E *et al.* Impact of PUVA therapy on HIV viremia: a pilot study. *Dermatology* 1997; **195**:84–5.
346 Morison WL. PUVA therapy is preferable to UVB phototherapy in the management of HIV-associated dermatoses. *Photochem Photobiol* 1996; **64**:267–8.
347 Moseley H, Cox NH, Mackie RM. The suitability of sunglasses used by patients following ingestion of psoralen. *Br J Dermatol* 1988; **118**:247–53.
348 Moseley H, Jones SK. Clear ultraviolet blocking lenses for use by PUVA patients. *Br J Dermatol* 1990; **123**:775–81.
349 Diffey BL, Miller JA. A comment on the routine testing of sunglasses in photochemotherapy. *Br J Dermatol* 1980; **102**:665–8.
350 Deleu H, Roelandts R. Protecting the eye from ultraviolet A radiation during photochemotherapy. *Photodermatol Photoimmunol Photomed* 1990; **7**:233–6.
351 Otman SG, El-Dars LD, Edwards C *et al.* Eye protection for ultraviolet B phototherapy and psoralen ultraviolet A patients. *Photodermatol Photoimmunol Photomed* 2010; **26**:143–50.
352 Tanew A, Ortel B, Hönigsmann H. Half-side comparison of erythemogenic versus suberythemogenic UVA doses in oral photochemotherapy of psoriasis. *J Am Acad Dermatol* 1999; **41**:408–13.
353 Legat FJ, Hofer A, Quehenberger F *et al.* Reduction of treatment frequency and UVA dose does not substantially compromise the antipsoriatic effect of oral psoralen-UVA. *J Am Acad Dermatol* 2004; **51**:746–54.
354 Weinstein GD, White GM. An approach to the treatment of moderate to severe psoriasis with rotational therapy. *J Am Acad Dermatol* 1993; **28**:454–9.
355 Morison WL. PUVA combination therapy. *Photodermatol* 1985; **2**:229–36.
356 van de Kerkhof PC, de Rooij MJ. Multiple squamous cell carcinomas in a psoriatic patient following high-dose photochemotherapy and cyclosporin treatment: response to long-term acitretin maintenance. *Br J Dermatol* 1997; **136**:275–8.
357 Agnew KL, Bunker CB. Multiple cutaneous squamous carcinoma in a psoriatic associated with ciclosporin, alcohol abuse and ultraviolet radiation exposure which were suppressed by acitretin. *J Eur Acad Dermatol Venereol* 2003; **17**:113–14.

358 Speight EL, Farr PM. Calcipotriol improves the response of psoriasis to PUVA. *Br J Dermatol* 1994; **130**:79–82.
359 Tzaneva S, Hönigsmann H, Tanew A *et al.* A comparison of psoralen plus ultraviolet A (PUVA) monotherapy, tacalcitol plus PUVA and tazarotene plus PUVA in patients with chronic plaque-type psoriasis. *Br J Dermatol* 2002; **147**:748–53.
360 Cristofolini M, Recchia G, Boi S *et al.* 6-Methylangelicins: new monofunctional photochemotherapeutic agents for psoriasis. *Br J Dermatol* 1990; **122**:513–24.
361 Ortel B, Perl S, Kinaciyan T *et al.* Comparison of narrow-band (311 nm) UVB and broad-band UVA after oral or bath-water 8-methoxypsoralen in the treatment of psoriasis. *J Am Acad Dermatol* 1993; **29**:736–40.
362 Sakuntabhai A, Diffey BL, Farr PM. Response of psoriasis to psoralen-UVB photochemotherapy. *Br J Dermatol* 1993; **128**:296–300.
363 Zhao JF, Zhang YJ, Jin XH *et al.* Green tea protects against psoralen plus ultraviolet A-induced photochemical damage to skin. *J Invest Dermatol* 1999; **113**:1070–5.
364 Middelkamp-Hup MA, Pathak MA, Parrado C *et al.* Orally administered *Polypodium leucotomos* extract decreases psoralen-UVA-induced phototoxicity, pigmentation, and damage of human skin. *J Am Acad Dermatol* 2004; **50**:41–9.
365 Hudson-Peacock MJ, Angus B, Farr PM. Response of PUVA-induced keratoses to etretinate. *J Am Acad Dermatol* 1996; **35**:120–3.
366 Diawara MM, Allison T, Kulkosky P *et al.* Psoralen-induced growth inhibition in Wistar rats. *Cancer Lett* 1997; **114**:159–60.
367 Diawara MM, Chavez KJ, Hoyer PB *et al.* A novel group of ovarian toxicants: the psoralens. *J Biochem Mol Toxicol* 1999; **13**:195–203.
368 Lam J, Polifka JE, Dohil MA. Safety of dermatologic drugs used in pregnant patients with psoriasis and other inflammatory skin diseases. *J Am Acad Dermatol* 2008; **59**:295–315.
369 Stern RS, Lange R. Outcomes of pregnancies among women and partners of men with a history of exposure to methoxsalen photochemotherapy (PUVA) for the treatment of psoriasis. *Arch Dermatol* 1991; **127**:347–50.
370 Gunnarskog JG, Källén AJ, Lindelöf BG *et al.* Psoralen photochemotherapy (PUVA) and pregnancy. *Arch Dermatol* 1993; **129**:320–3.
371 Garbis H, Eléfant E, Bertolotti E *et al.* Pregnancy outcome after periconceptional and first-trimester exposure to methoxsalen photochemotherapy. *Arch Dermatol* 1995; **131**:492–3.
372 Yang YW, Chen CS, Chen YH *et al.* Psoriasis and pregnancy outcomes: a nationwide population-based study. *J Am Acad Dermatol* 2011; **64**:71–7.
373 Pham CT, Koo JY. Plasma levels of 8-methoxypsoralen after topical paint PUVA. *J Am Acad Dermatol* 1993; **28**:460–6.
374 Weatherhead S, Robson SC, Reynolds NJ. Management of psoriasis in pregnancy. *BMJ* 2007; **334**:1218–20.
375 Taylor DK, Anstey AV, Coleman AJ *et al.* Guidelines for dosimetry and calibration in ultraviolet radiation therapy: a report of a British Photodermatology Group workshop. *Br J Dermatol* 2002; **146**:755–63.
376 Moseley H, Allan D, Amatiello H *et al.* Guidelines on the measurement of ultraviolet radiation levels in ultraviolet phototherapy: report issued by the British Association of Dermatologists and British Photodermatology Group 2015. *Br J Dermatol* 2015; **173**:333–50.
377 Macfarlane L, Bhoyrul B, Ibbotson SH *et al.* Practice when minimal phototoxic and minimal erythema doses are not determinable. *Photodermatol Photoimmunol Photomed* 2015; **31**:224–6.

Appendix

Levels of evidence

Level of evidence	Type of evidence
1++	High-quality meta-analyses, systematic reviews of RCTs or RCTs with a very low risk of bias
1+	Well-conducted meta-analyses, systematic reviews of RCTs or RCTs with a low risk of bias
1−	Meta-analyses, systematic reviews of RCTs or RCTs with a high risk of bias[a]
2++	High-quality systematic reviews of case–control or cohort studies High-quality case–control or cohort studies with a very low risk of confounding, bias or chance, and a high probability that the relationship is causal
2+	Well-conducted case–control or cohort studies with a low risk of confounding, bias or chance, and a moderate probability that the relationship is causal
2−	Case–control or cohort studies with a high risk of confounding, bias or chance, and a significant risk that the relationship is not causal[a]
3	Nonanalytical studies (e.g. case reports, case series)
4	Expert opinion, formal consensus

RCT, randomized controlled study. [a]Studies with a level of evidence '−' should not be used as a basis for making a recommendation.

Strength of recommendation

Class	Evidence
A	At least one meta-analysis, systematic review or RCT rated as 1++, and directly applicable to the target population A systematic review of RCTs or a body of evidence consisting principally of studies rated as 1+, directly applicable to the target population and demonstrating overall consistency of results Evidence drawn from a NICE technology appraisal
B	A body of evidence including studies rated as 2++, directly applicable to the target population and demonstrating overall consistency of results Extrapolated evidence from studies rated as 1++ or 1+
C	A body of evidence including studies rated as 2+, directly applicable to the target population and demonstrating overall consistency of results Extrapolated evidence from studies rated as 2++
D	Evidence level 3 or 4 Extrapolated evidence from studies rated as 2+ Formal consensus
D(GPP)	A good practice point (GPP) is a recommendation for best practice based on the experience of the guideline development group

RCT, randomized controlled trial; NICE, National Institute for Health and Care Excellence.

Supporting Information

Additional Supporting Information may be found in the online version of this article at the publisher's website:
Data S1. Literature search strategies.