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

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British Association of Dermatologists and British Photodermatology Group guidelines for the safe and effective use of PUVA therapy 2015

TC Ling, TH Clayton, J Crawley,* LS Exton,† V Goulden,‡ S Ibbotson,§ K McKenna,¶ MF Mohd Mustapa,† LE Rhodes,ᵀ R Sarkany,* RS Dawe§

Dermatology Centre, Salford Royal NHS Foundation Trust, Salford, Manchester M6 8HD; *Department of Dermatology, University College Hospital, 235 Euston Road, London NW1 2BU; †British Association of Dermatologists, Willan House, 4 Fitzroy Square, London, W1T5HQ, ‡Department of Dermatology, Leeds Teaching Hospitals NHS Trust, Leeds, West Yorkshire LS7 4SA; §Department of Dermatology, Ninewells Hospital & Medical School, University of Dundee, Dundee DD1 9SY; ¶Department of Dermatology, Belfast City Hospital, Belfast BT9 7AB; ᵀDermatology Research Centre, Faculty of Medical and Human Sciences, University of Manchester, Salford Royal Foundation Trust, Manchester M6 8HD

Corresponding author:
Tsui Ling, Tsui.Ling@srft.nhs.uk; guidelines@bad.org.uk

TCL, THC, JC, VG, SI, KMcK, LER, RS and RSD are members of the guideline development group with technical support from LSE and MFMM.

Footnote:
This is an updated set of guidelines prepared for the British Association of Dermatologists' (BAD) Clinical Standards Unit, which includes the Therapy & Guidelines Sub-committee. Members of the Clinical Standards Unit that have been involved are: PM McHenry [Chairman T&G], JR Hughes, M Griffiths, AJ McDonagh, DA Buckley, I Nasr, VJ Swale, CE Duarte Williamson, NJ Levell, T Leslie, E Mallon, S Wakelin, P Hunasehally, MJ 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], AG Brain [BAD Scientific Administrator], LS Exton [BAD Information Scientist], MF Mohd Mustapa [BAD Clinical Standards Manager].

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

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1.0 PURPOSE AND SCOPE

The overall objective of the guidelines is to provide up-to-date, evidence-based recommendations for the use of Psoralen-ultraviolet A photochemotherapy (PUVA) therapy. The document aims to update and expand on the previous guidelines by:

- offering an appraisal of all relevant literature since 1990, focusing on any key developments
- addressing important, practical clinical questions relating to the primary guideline objective
- providing guideline recommendations and, where appropriate, with some health economic implications
- 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 (PIL; available on the BAD website, 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, British Dermatological Nursing Group (BDNG), National Eczema Society (NES), Vitiligo Society, Psoriasis Association, and 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 Sub-committee) prior to publication.

3.0 METHODOLOGY

This set of guidelines has been developed using the British Association of Dermatologists' (BAD) recommended methodology[1] and with reference to the Appraisal of Guidelines Research and Evaluation (AGREE II) instrument.[2] [www.agreetrust.org] Recommendations were developed for implementation in the NHS using a process of considered judgment based on the evidence. PubMed, MEDLINE and EMBASE databases were searched up to December 2014 for meta-analyses, randomised and non-randomised (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 as a web appendix. Additional

relevant references were also isolated from citations in reviewed literature, as well as (independent) targeted searches carried out by co-authors. The authors screened the identified titles and those 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 co-authors were allocated separate sub-sections. Each co-author performed a detailed appraisal of the selected literature with discussions with the entire development group to resolve any issues, e.g. with the quality of evidence and making the appropriate recommendations. When considered helpful to assist with comparing study results and summarize data, forest plots drawn in Microsoft Excel were used,[3] although no formal meta-analyses were performed to prepare these guidelines. All sub-sections were subsequently collated and edited to produce the final guidelines.

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 guidelines and that the results of future studies may require some of the recommendations herein to be changed. Failure to adhere to these guidelines 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 recognise 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 to treat vitiligo.[5,6] It remains an important treatment; being the first-line phototherapy for pityriasis rubra pilaris and plaque stage mycosis fungoides 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 PUVA: THE DIFFERENT FORMS AVAILABLE

There are many different forms of PUVA. Different psoralens are available (8-methoxypsoralen (8-MOP), 5-methoxypsoralen (5-MOP), trimethylpsoralen) and other similar furocoumarin compounds (such as 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 UK, oral PUVA typically involves administration of microcrystalline tablet oral 8-MOP dosed according to estimated body surface area followed 2 hours 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 PUVA: REVIEW OF THE EVIDENCE

8.1 When should patients be treated with PUVA?

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 mycosis fungoides beyond patch stage, pustular psoriasis, pompholyx, hand and foot eczema and, probably, adult generalised pityriasis rubra pilaris.[9]

Commented [LE1]: All subsequent references have been renumbered

8.2 Selection of oral PUVA or topical PUVA (Table 1)

In practice the choice of route of psoralen administration is usually based on patient preference. Many patients prefer oral PUVA as it involves less time in the hospital unit, but some choose topical PUVA, in particular to avoid the inconvenience of eye protection.

9.0 PUVA FOR SPECIFIC DERMATOSES

9.1 Psoriasis

9.1.1 Is oral PUVA therapy more effective than topical PUVA in patients with chronic plaque psoriasis?

Two randomised parallel group studies compared oral 8-MOP PUVA with 8-MOP bath PUVA.[10,11] One prospective contemporaneous controlled (but not reported to be randomised) study compared oral 8-MOP PUVA with trioxsalen (trimethylpsoralen, TMP) bath PUVA[12] and another compared oral 8-MOP PUVA with 8-MOP bath PUVA.[13] None of these studies (**Table 2**) detected a definite difference in efficacy between oral and bath PUVA (**Figure 1**), although one did show 18% more of the small study sample population clearing with bath than with oral PUVA[11] (**Figure 1**). A recently published randomised 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 amongst these patients in which form of PUVA they favoured. A recent questionnaire survey of patients referred to a UK 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 which exists from randomised controlled trials (RCTs) and prospective contemporaneous non-randomised controlled studies showed that 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+)***

- All dermatology phototherapy units should offer bath PUVA as well as oral PUVA to treat psoriasis.

9.1.2 Is PUVA 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 (**Figure 2**)[16] and showed a similar magnitude of benefit as has been shown of various conventional systemic therapies when compared with placebo (**Figure 3**).[17-19] Due 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 systemics. 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 narrowband UVB.

9.1.3 Is PUVA 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 a psoriasis severity score (PASI) by 75% (PASI 75) (**Figure 4**), and even more so in reducing the PASI by 90% (**Figure 5**).[7]

Some national guidelines on use of biological therapy for psoriasis do not clearly indicate if PUVA should be used before biologics. For example, some guidelines stated that one of the criteria 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 randomised comparative study, of adequate duration comparing PUVA with biological therapy would help guidance with prescribing PUVA before biological or not, taking into consideration the relative risks 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 always be considered before biological therapy to treat chronic plaque psoriasis.

9.1.4 Is PUVA therapy more efficacious than NB-UVB in patients with chronic plaque psoriasis?

Ten comparative studies of PUVA with NB-UVB to treat psoriasis have been published (**Figure 6**);[24-33] six of these studies were randomised,[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 was available in the report although it was reported that all (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 (**Figure 6**). A randomised study comparing NB-UVB twice a week with NB-UVB three times a week found 11% more patients in the latter group clearing;[34] possibly those studies comparing twice a week 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 UK, PUVA appears more effective than NB-UVB for psoriasis. It may work better in those with more severe psoriasis, although only one study showed this as 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 to 2009 inclusive), 128 patients had a first course of NB-UVB followed by a first course of PUVA in Tayside. 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 taking tablets, or attending 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 randomised 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 ten irradiations.

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

9.2.1 Is PUVA therapy more efficacious than narrowband UVB in patients with atopic eczema?

We found no prospective trials comparing PUVA and NB-UVB. The efficacy of 8-MOP bath-PUVA versus 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 for atopic eczema as a simpler and safer intervention.

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 PUVA 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 PUVA therapy more efficacious than narrowband UVB in children (younger than 16) with eczema?

Whilst 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 to 19 years, reported that the majority of patients improved with PUVA,[36] although only 31 subjects 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 12 years.[41] This small study of 30 subjects reported patient evaluations with an overall patient satisfaction score of 8.8 on a scale of 0 to 10.

The most convincing evidence for the use of PUVA in children with atopic eczema came from a report by Sheehan *et al*. who described 32 of 39 children 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 commonest form of CTCL, mycosis fungoides (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 PUVA compare to other types of phototherapy in CTCL?

a. **Narrowband UVB (TL-01) compared to PUVA**
   There are no double-blinded, controlled comparison trials of PUVA versus NB-UVB for the treatment of early stage CTCL, and most data is from retrospective studies. These show similar remission rates of 50% to 81% for UVB, and 64% to 71% for PUVA [Refer to online journal for more details].

b. **Other types of phototherapy**

   i. **Broadband UVB (BB-UVB):**
   There are no comparative studies of BB-UVB against PUVA in CTCL. Like NB-UVB, the role of BB-UVB in CTCL appears to be in early stage disease.[49,50]

   ii. **UVA-1**
   There are no comparative studies of UVA1 versus PUVA. There is limited data regarding UVA1 therapy in CTCL, and this suggests that it potentially may be a useful treatment in patch-stage disease[51] and perhaps in more advanced disease as well.[52]

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 PUVA be used in CTCL?

PUVA is very effective in clearing lesions of early-stage CTCL, i.e. patches and thin plaques. Its effect on infiltrative thick lesions and tumours is more controversial.[53] Since patch stage disease is so responsive to NB-UVB, PUVA's role 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.[54] 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.

For more details of PUVA studies in CTCL, please refer to the online journal.

Flexural sites ('sanctuary sites') often fail to respond completely - in both patch and plaque stages - and the duration of response varies.[55]

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.

Treatment schedules vary in studies of PUVA from twice to four times a week with varied increment protocols. In the UK, commonly used schedules are two- to three-times-a-week treatments until disease clearance or best partial response.[55] Unlike in most other conditions treated with phototherapy, maintenance therapy to prevent disease relapse in patients with quickly recurrent disease is still common practice.[56] There is, however, no consensus on this (and a trial comparing maintenance versus no maintenance in PUVA for MF is ongoing [Clinical Trials Registry, NCT01686594]) and the benefits of maintenance therapy are still uncertain. 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) (Whittaker *et al.* BAD skin lymphoma guidelines. In preparation)

Recommendation: ***(Strength of recommendation B; level of evidence 1+)***

- PUVA is the first-line treatment for plaque-stage MF.

Recommendation: ***(Strength of recommendation D(GPP); level of evidence 4)***

- Maintenance therapy may be considered to prevent relapse in quickly-recurrent disease.

9.3.3 When should PUVA be used with other therapies?
In practice, PUVA is often used with other therapies rather than as monotherapy, as follows [Refer to online journal for more details]:

- **PUVA with interferon**
- **PUVA with retinoids and rexinoids**
- **PUVA following Total Skin Electron Beam therapy (TSEB)**

Recommendation: ***(Strength of recommendation B; level of evidence 1+)***

- In the treatment of early-stage CTCL, combination therapy with PUVA and interferon or retinoids/rexinoids should be considered, if the response to monotherapy is slow.

9.4 Vitiligo

9.4.1 Is PUVA therapy more efficacious than narrowband UVB in patients with vitiligo?
No; NB-UVB is at least as effective as PUVA in treating vitiligo (**Figure 7**).[6,57,58] 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 is PUVA.[58,59] 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

Due 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 in 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 PUVA compared to UVB?

a. PLE

In PLE, the reported efficacy of PUVA was 65% to 100% photoprotection rate.[60-71] There were five comparative studies with UVB,[60,61,63,65,66] including two RCTs.[63,65]

The only RCT comparing PUVA with NB-UVB did not detect any significant difference in efficacy. In this trial, 12 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; thrice 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.[63]

There were two studies that compared the efficacy of PUVA with BB-UVB.[65,66] 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).[65] Using self-assessment of treatment efficacy, 92% of patients considered PUVA successful compared with 62% with BB-UVB. These findings were supported by Addo *et al.*, who reported complete remission in 89% of patients treated with PUVA compared with 69% treated with BB-UVB.[66]

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.[60] 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 responded equally well.[60]

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.[61]

The latter two studies were retrospective chart review studies, with smaller numbers of patients receiving PUVA compared to UVB; moreover, patients who had more severe PLE, or who had previously failed UVB tended to receive PUVA.[60,61]

i. **Safety of PUVA compared to UVB 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, though commoner 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 forms of phototherapy. There was no appreciable difference in the efficacy of PUVA and UVB.

b. Photodermatoses other than PLE
No comparative studies with UVB were identified for the other photodermatoses.

9.5.2 When should PUVA 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, beta-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 with ingestion of MOP and

increased convenience as there is no need for taking tablets or using eye protection post-treatment.

a. PLE

There is good evidence of efficacy with UVB as compared with PUVA.[63] There are no other direct comparative studies with other modalities of treatment, which include systemic corticosteroid,[72] azathioprine,[73] ciclosporin,[74] hydroxchloroquine,[75,76] beta-carotene,[77-79] nicotinamide,[80,81] omega-3 fatty acids,[82] antioxidants[83-85] and *E. coli* infiltrate.[86] Systemic corticosteroid has been demonstrated to reduce the severity of PLE when used as a short course on sunny holidays.[87] Systemic immunosuppression is effective in a small number of case reports. Efficacy of treatment with hydroxychloroquine, beta-carotene, nicotinamide, omega-3 fatty acids, antioxidants, and *E. coli* infiltrate has not been well established in RCT.

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.

b. Chronic actinic dermatitis (CAD)

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.[88-94] These studies include the use of PUVA under cover with topical or oral corticosteroid, and concomitant use of ciclosporin (cyclosporin) and mycophenolate mofetil [Refer to online journal for more details].

One tertiary referral unit in the UK routinely treats CAD patients with PUVA with success (personal communication, Garibaldinos T, Guy's and St Thomas' Hospital, London). Prednisolone (20 to 30 mg) is taken on the day of phototherapy; small-dose increments of 0.05 J/cm^2 is given with each UVA-exposure; the course is given three times a week, then stepped down 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 with 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.

c. Idiopathic solar urticaria (SU)

We found no comparative studies with PUVA in the treatment of SU.

PUVA has been used in small case series as monotherapy (n = 4; n = 6),[66,95] in combination with intravenous immunoglobulins (single case reports)[96] and with plasmapheresis.[97,98] [Refer to online journal for more details]

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.[99-101] High-dose H1 antihistamines are frequently prescribed, in line with published research and recommendations made in general for other chronic urticarias.[102]

NB-UVB has also been reported to be helpful in SU (Calzavara-Pinton *et al.* [n = 39], Wolf *et al.* [n = 1], Collins *et al.* [n = 1]).[103-105] [Refer to online journal for more details] There are no comparative trials between NB-UVB and PUVA.

There was limited evidence from small case series on the use of UVA, either administered on its own,[106-108] or as pre-PUVA de-sensitisation.[109] This has been used in patients who have very low MUD for UVA, where PUVA was thought to be unsafe [Refer to online journal for more details]

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 with managing this disease.

d. EPP

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.[110,111] UVB has been reported in small open studies to be effective in EPP (n = 6; n = 1; n = 12).[105,112,113] [Refer to online journal for more details]

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

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.

e. AP

We did not find any comparative trials of thalidomide or immunosuppressants with PUVA in the treatment of AP.

There was limited evidence of the use of PUVA in AP. UVB has been reported, in a small open study, to be effective in AP (n = 6).[105] [Refer to online journal for more details].

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 PUVA 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. PUVA is usually administered in early spring in temperate countries. The benefit conferred by phototherapy is diminished or lost several weeks post-phototherapy, and post-treatment advice generally includes continued natural sunlight exposure, if tolerable on an individual basis, to keep their resistance to provocation for the rest of summer. As PUVA generally needs to be repeated, the longer-term risk of skin carcinogenesis need to be weighed against the therapeutic benefit and annual desensitization is not usually recommended.

a. PLE

The regimens vary between phototherapy centres; most administer 8-MOP, although 5-MOP, oral and bath TMP, have all been used.[60-71] In most of these studies, 8-MOP PUVA was given three times a week for 12 to 20 treatments. Currently in the UK, a twice-weekly regimen is standard. There are no studies comparing the efficacy and safety of twice- and thrice-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, 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% to 50% of PUVA treatment courses,[60,62-65,68,69,114] which is a little lower than the rates with UVB of 48% to 62%.[60,63] 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.[60,62,63,68,69] To prevent provocation, one group administered oral prednisolone (40 to 50 mg) for the first 2 weeks of phototherapy,[67] whilst another reported routine prophylactic application of a potent topical steroid after each exposure in UVB phototherapy.[60]

Pruritus was also reported in 18% to 33% patients[63,64] with one group managing this with oral corticosteroid.[64]

Post-treatment advice generally includes continued natural sunlight exposure, ranging from 2 hours weekly[65] to 'cautious exposure, with sunscreens for extended outdoor stay',[60] to 'expose freely to sun'.[67,70]

b. CAD

PUVA phototherapy is generally undertaken under close supervision under cover of topical or systemic corticosteroid, as discussed above.[90,91,93,94] 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.

c. SU

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,[106-108] or pre-PUVA UVA has been used.[109] The amount of photoprotection will subside, and maintenance treatment with PUVA or UVA has been reported.

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 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 both oral and topical psoralens, has been widely used to treat hand and foot dermatoses over the past 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 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 minutes between soaking in psoralen solution and maximum UVA sensitivity in the palmar and plantar skin of healthy volunteers.[115] As a result of this, and earlier reports that suggested efficacy in the hand and foot dermatoses of topical psoralens with a 1- to 2-hour delay between psoralen application and UVA exposure but no efficacy in studies with psoralen application immediately before UVA exposure, previous UK guidelines have recommended a delay of at least 30 minutes between immersion and irradiation.[116]

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

9.6.1 What is the efficacy of PUVA therapy in patients with hand and foot dermatoses compared to placebo or other active treatments?

a. Palmoplantar eczema

Oral PUVA vs UVB: A prospective contemporaneous controlled study (n = 35)[117] showed both treatments to be effective but oral PUVA was superior to UVB, although relapse rate was high. A subsequent smaller study (n = 20) carried out by the same group using a similar design showed similar results.[118]

Oral PUVA alone: Uncontrolled studies with oral PUVA have shown significant improvement or clearance in 81% to 86% of patients with hand and foot eczema,[119,120] with similar good results in smaller case series.[121,122]

Topical PUVA alone: Uncontrolled studies of topical PUVA have suggested this might be effective treatment with clearance or considerable improvement reported in 58% to 81% of dyshidrotic eczema and 50% to 67% of hyperkeratotic eczema.[123-134] However, evidence from comparative studies was less convincing. A left-right, within-patient study (n = 15) with 8-MOP paint versus placebo in dyshidrotic eczema found no difference between the two groups, and no patient achieved clearance.[135] The lack of efficacy was supported by a small controlled study (n = 6) with 20% 8-MOP gel in which no patient cleared.[136]

Topical PUVA vs UVB, UVA1, superficial X-ray therapy, and combination therapy of topical PUVA and iontophoresis: [Refer to online journal for more details] Evidence from RCTs and prospective contemporaneous controlled studies has not demonstrated any difference in efficacy .

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.

b. Palmoplantar psoriasis

We found no comparative studies comparing oral PUVA to placebo or other active treatments, though a small retrospective study (n = 12)[137] and case series (n = 5)[121] report improvement or clearance.

Oral PUVA vs NB-UVB: A large retrospective study (n = 92) concluded oral PUVA and NB-UVB were equally effective. However, assessment and outcome measures were unclear and no statistical analysis was carried out.[138]

Topical PUVA alone: Uncontrolled studies have reported clearance or significant improvement occurring in 58% to 87% of patients treated with topical psoralen.[123,126-128,130,131,139-142]

Topical PUVA vs UVA: In a randomised, left-right, within-patient study in patients with hand and foot dermatoses (psoriasis n = 11), topical PUVA (20% 8-MOP gel) was suggested to be more effective overall compared to UVA, but the results were not analyzed separately according to the different dermatoses investigated.[136] No patient was reported as being cleared in either group.

Topical PUVA vs 308 UVB excimer laser, and NB-UVB: Refer to online journal for more details. The authors of a Cochrane systematic review of NB-UVB phototherapy versus BB-UVB or PUVA for psoriasis identified only one study for the indication and concluded no significant difference between treatments.[143]

In summary, for palmoplantar psoriasis there is some randomised study evidence for topical PUVA, however, these studies were under-powered. 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.

c. Palmoplantar pustulosis

Oral PUVA vs no treatment: Oral PUVA has been compared with no treatment in a randomised, within-patient study (n = 22).[144] This showed improvement in 100% of PUVA-treated sites compared with 59% of untreated sites, with 55% and 0% clearance, respectively. In a prospective contemporaneous controlled study (n = 14), improvement was recorded in 64% with oral PUVA and 14% with no treatment.[145] The clearance rate was 21% and 0%, respectively.

Topical PUVA vs placebo: In a double-blinded, randomised, left-right, within-patient study (n = 27),[146] there was no difference in improvement with topical PUVA compared to placebo. The lack of efficacy of topical PUVA was further supported by smaller randomised studies (n = 10, n = 5)[136,147] with clearance rate of only 0% to 10%.

PUVA vs oral retinoids: Two RCTs have compared PUVA to oral retinoids. One study (n = 84) compared two forms of topical PUVA, oral PUVA and etretinate.[148] 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 oral PUVA, was much lower than in other published studies. Another study comparing oral PUVA to etretinate showed clearance in 21% (3/12) with PUVA versus 17% (3/18) with etretinate.[145]

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.[149]

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 PUVA compared to topical PUVA therapy in patients with hand and foot dermatoses?

a. Palmoplantar eczema

Two RCTs have compared oral and topical PUVA. Van Coevorden *et al.* performed an open-label RCT (n = 158) comparing oral methoxsalen (as 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.[150] 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 8-week follow-up.

A small RCT compared oral 8-MOP versus 8-MOP soak in dyshidrotic eczema (n =15) and hyperkeratotic eczema (n = 12). This study did not detect a difference in therapeutic efficacy, and that dyshidrotic eczema improved to a greater extent compared to

hyperkeratotic eczema, however, the study was under-powered and does not justify these conclusions.[151]

b. Palmoplantar psoriasis

A retrospective review by Hawk *et al.* of oral and topical 8-MOP PUVA in the treatment of patients with hand and foot dermatoses included 18 patients with psoriasis.[152] Fifty 50% (7/14) of patients who received topical PUVA and 50% (2/4) oral PUVA cleared. A small, within-patient, randomised, right-left comparison study compared PUVA using oral oxsoralen versus 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.[153]

c. Palmoplantar pustulosis

Hawk *et al.*'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.[152]

A small, right-left, within-patient comparative study of oral oxsoralen versus 8-MOP soaks in patients with hand and foot dermatoses included five patients with pustulosis. Oral PUVA was reported to be more effective.[153]

Lassus *et al.*'s RCT of two forms of topical and oral PUVA showed clearance rate of 8% (4/51) with topical PUVA compared with 0% (0/13) oral PUVA.[148] 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 one direct comparison of topical with oral PUVA for this indication.[149]

Recommendation: ***(Strength of recommendation D(GPP); 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 PUVA therapy alone compared to PUVA and adjuvant therapies in the hand and foot dermatoses?

a. Palmoplantar eczema

For foot eczema, topical PUVA has been compared in a randomised 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.[154]

b. Palmoplantar psoriasis

There was only one RCT comparing combination therapy with oral PUVA and etretinate versus PUVA and placebo but this included only three patients with psoriasis.[155] No other relevant studies were identified.

c. Palmoplantar pustulosis

Three RCTs examined combination therapy with oral PUVA and retinoids compared to PUVA alone. Rosen *et al.*'s RCT showed clearance in 61% (14/23) with combination therapy and 21% (3/14) with PUVA alone.[145] A further RCT comparing oral PUVA-etretinate versus oral PUVA alone showed clearance of 100% (8/8) and 44% (4/9), respectively.[155] An RCT using 8-MOP PUVA lotion found 60% (6/10) clearing with topical PUVA-etretinate compared with 10% (1/10) with topical PUVA alone.[147]

A Cochrane review of the interventions for palmoplantar pustulosis concluded there was evidence for an increased efficacy of retinoids combined with PUVA compared to PUVA used alone.[149]

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 PUVA

10.1 Acute

10.1.1 Incidence of acute adverse events [Refer to online journal for full discussion].
Both systemic and topical PUVA are generally well tolerated and the acute adverse effects of PUVA are reasonably well documented. The commonest adverse effects are erythema and pruritus, and nausea associated with oral PUVA.[115,156] In early studies of oral PUVA, reported acute adverse events were uncommon, temporary and generally mild. Melski *et al.* analyzed the adverse events from 41,000 oral PUVA treatments given to 1,308 patients.[157] The incidence of adverse events was: erythema 9.8%, pruritus 14%, nausea 3.2%, headaches 2%, dizziness 1.5%. 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%, Köbner reaction in psoriasis 2%.[158,159] PUVA treatment was interrupted due to erythema in 6.8%, and only uncommonly discontinued. Nausea with 8-MOP is a relatively common occurrence but not with 5-MOP[160] and rarely requires discontinuation of treatment.

a. Erythema

Studies of the time course of PUVA erythema following both oral and topical PUVA indicate erythema peaking at 96 hours or later in the majority of subjects. Oral 5-MOP PUVA has a similar time course to that of 8-MOP.[161] In practice, many centres use an MPD assessment time of 72 hours and no studies have been undertaken to evaluate whether there are differences in efficacy or adverse effects between treatment regimens based on a 72-hour versus 96-hour MPD assessment. Most UK centres use a twice-weekly regimen for both oral and topical PUVA.

The UVA dose should be delivered within 10 minutes after an 8-MOP bath as photosensitivity reduces quickly, although there may be a more prolonged effect over 40 minutes if palmar and plantar skin are being treated.[116,162] The temperature of the bath for PUVA delivery is also important, with photosensitisation being optimal at 37°C and reduced at lower temperatures.[163]

Unusual patterns of erythema and burning have been reported, particularly with TMP bath PUVA due to the powder formulation of TMP and the variable distribution within the bath water as it forms a micro-crystallized suspension.[164] Frank blisters can also occur either due to over-exposure to UVA or psoralen dose, for example, as seen if patients stand in a particular way in the cabinet.[165] Particular care is needed in patients with vitiligo.[166,167,]

Thus, depending on the methods for reporting erythema, incidence of PUVA erythema during treatment is between 10% and 32%, requiring treatment interruption in between 1% to 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.

b. Pruritus

There seems to be a similar incidence of pruritus following oral and bath PUVA occurring in 10% to 40% of patients.[115,157,159] The incidence of pruritus is reported to be lower with 5-MOP (43.6%) compared with 8-MOP (71.8%).[164] There do not appear to be specific predictors for the likelihood of this adverse effect occurring.

c. Nausea

Nausea is relatively common, occurring in about 3% to 13% of patients.[157,159,168] This can be helped by taking the psoralen with a light meal or using an antiemetic. If nausea is significant then 5-MOP or topical psoralen can be used.[168] The incidence of nausea was reported to be much lower with 5-MOP (7.7%) compared with 8-MOP (51%) in one study.[164]

d. Induction of photodermatoses

Precipitation or aggravation of photodermatoses which are associated with abnormal UVA photosensitivity can occur with PUVA, with reports of CAD and PLE exacerbation having been observed.[63,169] The rate of inducing PLE was estimated to be 50% compared with 62% with NB-UVB in one study.[63] Theoretically, exacerbation or induction of lupus can occur, and there are case reports of the coincidence of PUVA with the development of lupus.[170-172]

e. Drug phototoxicity

Drug phototoxicity in general is not a major problem because of the overwhelming effect of psoralen photosensitisation, and as long as MPD assessment is performed on the patient's drug regimen, this can be largely avoided.[168] However, pseudoporphyria can occur, as with some of the other phototoxic drugs such as the fluoroquinolones, non-steroidals, 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[173] and after taking Rutaceae extracts and celery soup.[174] Reported phototoxicity rates seem to be similar for oral and bath 8-MOP PUVA,[115] although clinical experience suggests that severe

phototoxic reactions are more likely with bath PUVA. In general, avoiding psoralen-containing plants for at least 2 hours 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, NSAID, theophylline, caffeine; more frequent monitoring is advised if a patient is on warfarin. The effects of caffeine are augmented by PUVA,[175-177] 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, 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 underscore 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.

f. Hepatotoxicity

There are case reports of hepatitis following 5-MOP[178,179] and 8-MOP.[180-183] Importantly, two of the four cases arose in patients who had methotrexate-induced liver damage, and the remaining cases resolved once the drug was stopped. In one study of 162 patients receiving PUVA, only three patients had transient elevations of transaminases which all reverted to normal after treatment was stopped.[184] 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.[185]

g. Pain

Severe skin pain with PUVA is uncommon and was seen in 4% (8/210) of patients treated with oral PUVA in one series.[186] It is characterized by persistent severe prickling, burning or dysaesthesia which can last from minutes to hours and can 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.[187-189] Treatment with analgesics, topical anaesthetics and topical or systemic steroids, usually has minimal effect. Capsaicin,[190] gabapentin,[191] phenytoin[188] and low frequency electrotherapy[192] can potentially be of benefit. Once PUVA pain has developed it is then a relative contraindication to further PUVA treatment as it is likely to recur.

h. Miscellaneous

Both allergic and photocontact allergic dermatitis to psoralens have been reported to affect 0.8% (3/371) of patients treated with topical PUVA.[193] Type I anaphylaxis to both 5-MOP[194] and 8-MOP[195] has also been observed in isolated cases and asthma may be aggravated.[196-199]

Hyperpigmentation is usually a result of repeated PUVA treatments but may also occur with the concurrent use of topical vitamin D analogues at treated lesional sites,[200,201] and with concomitant treatment with isotretinoin.[202]

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.[203] Folliculitis can occur and can be managed with applying emollients in a 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.[204] Other associated adverse events include lunular changes,[205] subungual haemorrhage[159] and nail pigmentation.[159]

Clinically significant consistent changes in laboratory parameters are rarely observed. However, severe hyperlipidaemia following PUVA treatment for acute skin GVHD has been reported.[206]

Other rare acute side effects of PUVA include bullous pemphigoid,[207-209] lichen planus,[210] lichen planus pemphigoides,[211] polymyositis,[212] influenza-like symptoms,[213] lymphomatoid papulosis in a patient with mycosis fungoides[214] and neurological disorders such as insomnia, nervousness, headache, migraine, dysomnia, depression and dizziness.[215,216] 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.[159,217] An intertriginous, asymptomatic, self-resolving, maculo-papular rash was reported in 8% of subjects undergoing 5-MOP PUVA and this resolved spontaneously despite continuation of PUVA.[160] In one report three patients with mycosis fungoides developed new lesions at sites previously considered to be clear, early in the PUVA course. This might have been due to unmasking of sub-clinical lesions due to inflammation.[218]

Key points:

Relatively common acute adverse effects of PUVA

- **Erythema**
- **Pruritus**
- **Nausea**
- **Polymorphic light eruption**

Uncommon but important acute adverse effects of PUVA

- **PUVA pain**
- **Idiosyncratic hepatitis**
- **Psoralen allergy**

10.2 Long term [Refer to online journal for full discussion].

10.2.1 PUVA induced skin cancer

PUVA photochemotherapy is mutagenic,[219-221] carcinogenic[222,223] and immunosuppressive.[224-228] 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.[229-234] Additional risk factors include exposure to co-carcinogenic therapeutic agents such as UVB therapy,[235] methotrexate,[236,237] ciclosporin[238] and X-ray radiation/arsenic.[239-242] The human papilloma virus (HPV) has also been suggested as a co-carcinogen and has been detected in PUVA-associated non-melanoma skin cancers (NMSCs), especially types associated with epidermodysplasia verruciformis, particularly types 5, 14 and 20.[243-246] More recently, the USA 16-centre, follow-up study has reported an increased incidence of melanoma in patients treated with PUVA,[247,248] but it remains uncertain that this was a causative association and this association has not been reported by other groups.[233,241,249,250] There is no evidence of either increased incidence of NMSC or melanoma in patients with psoriasis treated by topical PUVA.[251,252] However, the number of patients with high PUVA exposure was low in these studies and many were treated with bath trimethylpsoralen 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.[251] 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.

a. **PUVA and NMSC**

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.[231,232,249] The North American study involved use of maintenance PUVA, and only for one indication (that of 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 demonstrated that patients receiving more than 200 treatments have about 30 times the risk of developing a new NMSC per year than the general population.[231] An almost identical risk was found in the highest risk group (men who had received 200 or more PUVA treatments) in the Swedish study.[232] The relative risk amongst the highest-risk patients in the Swedish study of 30.7 meant 10 of 180 patients.[232] 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.[253] The risk of skin cancer is persistent despite discontinuation of PUVA.[254] Other risk factors for patients developing NMSC include being of lighter skin phototypes,[255] having skin tumours prior to PUVA and age at starting PUVA,[233] the presence of PUVA keratoses[256] and lentigines.[234,257]

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 non-sun-exposed sites.[237] Genital SCC in males treated with PUVA has been reported to be substantially increased (95.7 times that of the general population),[258,259] however, a lower incidence was reported in the Swedish study.[232] A retrospective study from France of a

cancer registry over 20 years identified only one case of genital SCC in someone with a history of intensive PUVA, out of 48 cases of genital SCC. In addition, there were no reported cases of genital SCC from 5,400 patients who had received PUVA, despite lack of genital protection during PUVA exposures.[260] Despite reports that SCC occurring in patients receiving PUVA are usually well differentiated and non-aggressive,[231,233,242,255] these tumours can rarely metastasize.[237]

Lim *et al.* found high levels of UVB exposure (at least 300 treatments) to be associated with a modest but significant increase in SCC (x1.37) and BCC (x1.45) in the USA PUVA cohort.[235] High level of exposure to methotrexate (total of 4 or more years of use) has also been found to be a significant independent risk factor in the latter cohort, with a relative risk of 2.1 for high versus low, or no exposure.[237] Previously, a synergistic carcinogenic potential between methotrexate and PUVA had been suggested.[236] Data also from the USA cohort showed that the risk of SCC in ciclosporin users was about three times higher than in patients who never used ciclosporin.[238] PUVA patients who have previously received arsenic or X-ray therapy have an increased incidence of skin cancer compared with those who have not had such therapy.[239,241,242]

b. Melanoma

Patients who receive high doses of PUVA often develop lentigines which can show cytologically atypical melanocytes.[261] A five-fold increase in annual incidence of malignant melanoma in the 16-centre PUVA cohort study, using PUVA to treat psoriasis, was initially reported in 1997.[247] Further follow-up showed a nine-fold increase.[248] 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,[262-270] but an increased incidence of melanoma has not been observed in European follow-up studies.[233,241,250,271] 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 (psoriasis patients responsive to PUVA seeking sunlight exposure, for example) 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).[272] 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 more than 200 PUVA treatments or those with a personal or family history of melanoma.[271,273]

c. Non-cutaneous cancer risk

As PUVA alters immune function, especially the lymphocyte, 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 psoriasis patients as an association with internal cancer has been found in large cohort studies,[274,275] which includes tumours of oral and pharynx, lung, liver, pancreas, liver, bladder and lymphoma.[276-278] However, previous studies have not demonstrated a consistent increase in cancer risk in the CNS,[279] thyroid,[279] respiratory, pancreas and kidney.[232,249]

Though there are several case reports of leukaemia developing during PUVA therapy.[280-283] Stern *et al.* reported no increase of lymphoma or leukaemia in his PUVA cohort in either 1988 or 1997,[231,247] however, more recent analysis has found the incidence of lymphoma to be increased in this group in those exposed to high levels of methotrexate (RR 4.39), i.e. 36 months of treatment or longer, but not in those exposed to low levels.[284] A study from Finland showed a 2.2-fold increase in non-Hodgkin's lymphoma in patients hospitalized for psoriasis.[277]

d. Non-cancerous chronic cutaneous side effects of PUVA

Keratoses: these are typically localized to non-sun-exposed skin and risk factors for their development include increased age, male sex and high cumulative UVA dose.[256] They are reported to occur in 46% of patients receiving high-dose (more than 2000 J/cm^2) PUVA and show cytological atypia.[234] Disseminated superficial actinic porokeratosis has been reported in association with both oral and topical PUVA.[285-288]

Lentigines: PUVA-induced lentigines are distinct irregular, stellate, darkly pigmented macular lesions and may show cytological atypia.[257,261] Incidence varies from 10% to 53%,[257,289-292] occurring most frequently in those patients exposed to high doses of PUVA[234,257,291] and those of skin type I/II.[289]

Dyspigmentation: PUVA-induced mottling consists of hyper- and hypopigmentation associated with atrophy which is mainly localized to areas of overdose.[159,293] Hyperpigmentation has been reported at the lesional sites of patients where calcipotriol ointment has been applied during bath PUVA.[201] Transient hyperpigmentation has also been reported around psoriatic plaques in patients treated with calcipotriol ointment and PUVA.[200] Acquired dermal melanocytosis typically affecting the back of Japanese patients treated with PUVA has been reported.[294,295]

Photoageing: 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,[296] focal epidermal[297] and elastosis.

Cataracts: Free 8-MOP can be detected in human lenses for at least 12 hours after 8-MOP dosing.[298] Previous guidelines from the British Photodermatology Group recommend that protective eyewear be worn for 12 to 24 hours following PUVA and for 24 hours in high-risk individuals, e.g. patients with atopic eczema, children or those with pre-existing cataracts.[299] Previous clinical studies (involving patients advised on eye protection), including the 16-centre prospective cohort study of USA psoriasis patients,[300-302] 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 to 4 years found no evidence of the development of cataracts.[303]

Key points:

PUVA is associated with:

- **a significant dose-dependent risk of squamous cell carcinoma.**
- **PUVA keratoses, pigmentary changes, and photoageing**

PUVA has not been consistently shown to be associated with:

- **melanoma**
- **internal malignancy**

10.3 How do we identify those who are susceptible to PUVA side effects?

Careful patient selection is essential to prevent side effects, particularly skin cancer (see box below). PUVA should be used with care (generally only if the alteratives are treatments carrying greater risks, such as systemic immunosuppressives) in children due to the risk of causing UV cutaneous damage at a young age.

There is concern that PUVA therapy may lead to worsening of human immunodeficiency virus (HIV) status or may increase risk of skin cancer in people with HIV,[304-306] particularly as SCC and melanoma have been reported to be more aggressive in HIV disease.[307,308] The risk of Merkel cell carcinoma of the skin was increased in the USA PUVA cohort[309] by 100 times, and is also increased in HIV patients.[310] However, studies to date of PUVA use in HIV-infected patients have not demonstrated a deterioration in HIV status or immune function,[311-313] and it has been suggested that in fact, PUVA might be preferable to UVB therapy in those patients infected with HIV.[314]

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

RISK FACTORS ASSOCIATED WITH PUVA-INDUCED SKIN CANCER

History

- 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, excessive sunbed exposure
- History of xeroderma pigmentosum or other genetic disorders associated with skin cancer
- Patients on immunosuppressive drug therapy
- HIV disease

Examination

- Multiple freckles/moles
- Dysplastic naevi/solar keratoses/SCC *in situ (*Bowen's disease)
- Solar elastosis
- Skin cancer

10.4 How can side effects be prevented in patients receiving PUVA 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 pre-malignant or malignant skin lesions. Patients who have received more than 150 to 200 PUVA treatments should be offered an annual skin examination to ensure no pre-malignant or malignant skin lesions have developed,[159,299] 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 hours following PUVA therapy and 24 hours 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[315,316] and these can be tested for suitability.[315,317] 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.[318] 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.[319]

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,[299] i.e. patients with pre-existing cataracts, who have AD 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,[320,321] the avoidance of maintenance treatment, following guidelines on action limit numbers of treatment exposures (e.g. 150 to 200 treatments),[299] consideration of periods of breaks from PUVA with rotational therapy[322] and the use of combination therapy with retinoids[323] or topical vitamin D analogues. Retinoids not only increase the efficacy of PUVA but have a skin cancer prophylactic action.[324,325] Concurrent use of PUVA with ciclosporin should be avoided as it can significantly accelerate skin cancer development in patients receiving such treatment.[238] Topical vitamin D analogues and tazarotene have also been used as dose-sparing agents combined with PUVA.[326,327] There may also be a role of potentially safer photosensitisers such as trimethylangelicin.[328] Photochemotherapy using potentially safer wavelengths of radiation, e.g. NB-UVB requires further research.[329,330] Agents which may protect against PUVA-induced photochemical damage, e.g. green tea or *Polypodium leucotomos* extract may decrease long-term carcinogenesis.[331,332]

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 NMSCs 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 PUVA therapy?

Pre-malignant and malignant skin lesions are treated in the same way as patients not receiving PUVA. PUVA requires to be discontinued if neoplastic lesions develop and alternative therapy should be considered but ciclosporin should be avoided.[238] Introduction of acitretin can be helpful in management of patients with multiple keratoses and skin cancer following PUVA.[324,325,333] These individuals will require careful follow-up as they are at increased risk of further skin cancers developing with time.

10.6 PUVA 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,[334-336] but this is not found in humans.[337-339] One study observed a marked increase in infants with low birth weights when pregnancy occurred after treatment.[338] It was thought 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.[340] 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.[341] It was recommended that PUVA therapy should be avoided during pregnancy whenever possible as it is mutagenic.[337,342]

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 female patients should avoid conception during PUVA therapy and that, if despite this advice pregnancy does occur, PUVA should then be discontinued.

11.0 PROTOCOLS AND PRACTICAL CONSIDERATIONS

11.1 What is the optimum protocol for the delivery of PUVA therapy to optimize outcome in patients with psoriasis, eczema and PLE?

Examples of treatment schedules commonly used in the UK can be accessed at:

http://www.bad.org.uk/healthcare-professionals/clinical-services/service-standards/phototherapy

http://www.photonet.scot.nhs.uk [the Scottish national managed clinical network for phototherapyphotonet 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 PUVA therapy clinic be set up, taking account of:

- equipment
- staffing/training
- support (e.g. medical physics, servicing)

- dosimetry/QA
- 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.
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 ultraviolet radiation therapy.[343] A joint BAD and BPG update of these guidelines is currently in press with the BJD.[344]
http://www.bpg.org.uk/index.asp?SID=7&PID=13
http://www.bad.org.uk/healthcare-professionals/clinical-standards/clinical-guidelines

12.0 PRE-TREATMENT 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 more than 150 to 200 exposures of PUVA should be offered annual assessment for any pre-malignant or malignant skin lesions.
- Advice should be given on eye protection for 12 to 24 hours following oral PUVA, and considered for bath PUVA for widespread dermatoses, and for 24 hours in high-risk individuals, e.g. patients with atopic eczema, children or those with pre-existing cataracts or 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 ultraviolet A (including 'energy saving' compact fluorescent lamps).
- Advice should be given on photoprotection following each PUVA session, especially over the 12 hours after each treatment.
- Informed consent should be taken and appropriate patient information leaflet provided.
- Some examples of patient information leaflets can be viewed on:
  http://www.bad.org.uk/shared/get-file.ashx?itemtype=document&id=1644 [page 35-38]
  http://www.phototherapysupport.net/view-document.asp?FileID=40 [appendix 2, page 44-49]
  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 (ANA) 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.[345]

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:

- A randomised comparative study, comparing PUVA with biological therapy for chronic plaque psoriasis; this would help guidance on whether to prescribe PUVA before biological therapies, taking into consideration the relative risks and efficacy.

- A study to investigate whether or not there is an effect of MPD measurement at 72 and 96 hours on erythemal episodes during PUVA and efficacy outcome measures.

14.0 RECOMMENDED AUDIT POINTS

(A) Is there a system in place to record and recall episodes of 'burning' which clearly:
   a. grades each episode
   b. reviews all episodes at 6-monthly intervals
   c. interprets the result in the context of the total number of treatments and total number of patients treated?

(B) Over the past 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:
      a. the last 20 consecutive patients receiving topical PUVA therapy?
      b. 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:
      a. the last 20 consecutive patients receiving topical PUVA therapy?
      b. 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 allow 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

(See full manuscript for details of evidence)

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

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 always 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)***
Cutaneous T cell lymphoma of the mycosis fungoides (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 interferon 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)***
Polymorphic light eruption	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)***
Chronic actinic dermatitis (CAD)	In the treatment of CAD, PUVA therapy should be considered in a specialist unit experienced with managing this disease, with full knowledge of the individual patient's action spectrum. Special

	precautions including inpatient supervision, topical/oral corticosteroid cover may be required. (***Strength of recommendation D)***
Idiopathic solar urticaria (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 with managing this disease. (***Strength of recommendation D)***
Erythropoietic protoporphyria (EPP)	PUVA is rarely appropriate in EPP, NB-UVB is the phototherapy of first choice. (***Strength of recommendation D)***
Actinic prurigo (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)***

Table 4. Recommendations in particular clinical situations

SUPPORTING INFORMATION

Additional supporting information including the search strategy may be found in the online version of this article.

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Commented [AE2]: As now changed and this was not like a study in which all authors and contributers are cited with place of work at time of the study.

APPENDIX 1

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*
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*
3	Non-analytical studies (for example, case reports, case series)
4	Expert opinion, formal consensus

*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, **or** • 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, **or** • 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, **or** • Extrapolated evidence from studies rated as 2++
D	• Evidence level 3 or 4, or • Extrapolated evidence from studies rated as 2+, **or** • 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: randomised controlled trial; NICE: National Institute for Health and Clinical Excellence.

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

1st author	Publication year	Bath psoralen	Oral psoralen	UVA regimen	Randomised ?	Blinded?	Proportion (percentage) cleared with oral PUVA	Proportion (percentage) cleared with bath PUVA	Difference (% more clearing with oral PUVA); 95% CI for difference
Turjanmaa[12]	1985	TMP 3 mg/l	8-MOP 0.6 mg/Kg	arbitrary starting doses; 3 times a week; incremental regimen not reported	No	No	37/43 (86%)	42/50 (84%)	2%; -12% to 17%
Lowe[13]	1986	3.75 mg/l	8-MOP 0.6 mg/Kg	Skin phototype based starting dose and incremental regimen	No	No	8/20 (40%)	8/20 (40%)	0%; -30% to 30%
Collins[10]	1992	8-MOP 3.78 mg/l	8-MOP 0.6 mg/Kg	skin phototype based starting doses; 3 times a week; no > 20 treatments	Yes (but allocation not concealed)	No	14/22 (64%)	14/22 (64%)	0%; -28% to 28%
Cooper[11]	2000	8-MOP 2.6 mg/l	8-MOP 0.6 mg/Kg	70% MPD starting dose; 2 times a week; percentage based incremental regimen	Yes (but allocation not concealed)	No	14/17 (82%)	17/17 (100%)	-18%; -36% to 0.5%

Table 2. Controlled studies comparing whole-body topical PUVA ('bath PUVA') with oral PUVA

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%

Table 3. Incidence of side effects with different phototherapy

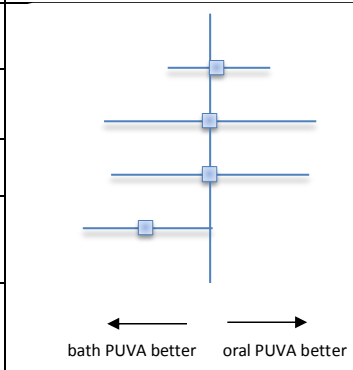
1st Author	Year	n=	% more cleared with oral PUVA (95% CI)	
Turjanmaa[12]	1985	93	2% (-12% to 17%)	
Lowe[13]	1986	40	0% (-30% to 30%)	
Collins[10]	1992	44	0% (-28% to 28%)	
Cooper[11]	2000	34	-18% (-36% to 0.5%)	

Figure 1. Controlled study (including RCTs by Collins *et al.* and Cooper *et al.*) comparisons of oral PUVA with bath PUVA for psoriasis

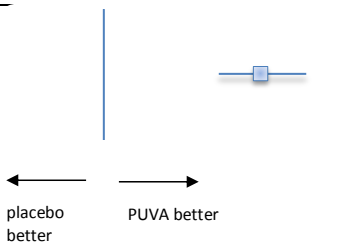
1st Author	Year	n=	% more cleared with oral PUVA (95% CI)	
Sivanesan[16]	2009	40	2% (-12% to 17%)	

Figure 2. RCT comparing PUVA with placebo for psoriasis

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%

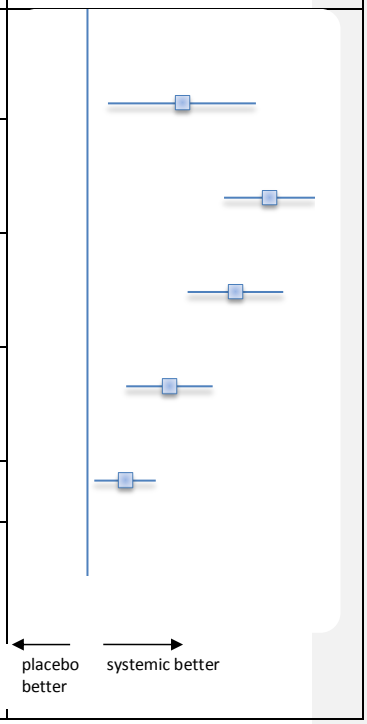


Figure 3. RCTs comparing conventional systemic therapies with placebo for psoriasis

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%)	

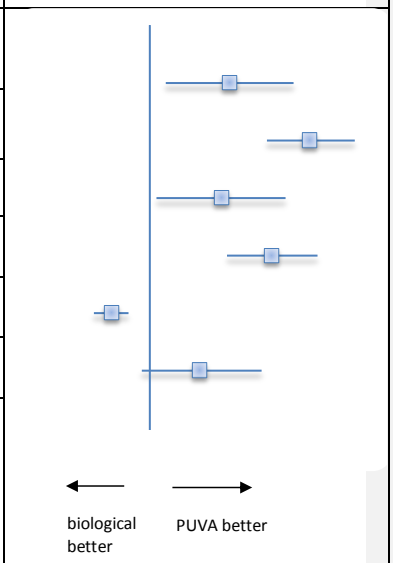


Figure 4. Retrospective comparison of PUVA (n = 118 patients) with biologicals, Inzinger *et al.*[7] Baseline mean PASI for PUVA was 15 and for biologicals was 16.9. Outcome **of PASI 75%** reduction.

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%)	

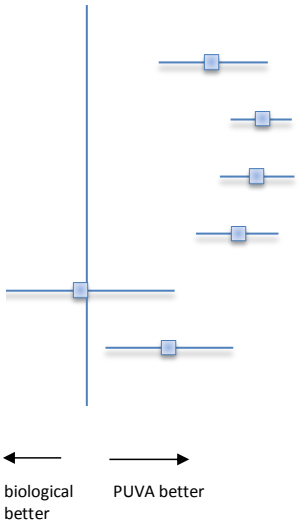


Figure 5. Retrospective comparison of PUVA (n = 118 patients) with biologicals, Inzinger *et al.*[7] Baseline mean PASI for PUVA was 15 and for biologicals was 16.9. Outcome of **PASI 90%** reduction (similar outcome measure to 'clearance' or 'minimal residual activity').

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	randomised, 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	randomised, 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	randomised, 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	randomised, 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	randomised, 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	randomised, paired	3 times a week	3 times a week	excellent clinical response	18	-33% (-6% to -61%)
Yones[30]	2006	randomised, 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	randomised, parallel group	3 times a week	3 times a week, oral 8-MOP	marked improvement	51	1% (-22% to 24%)

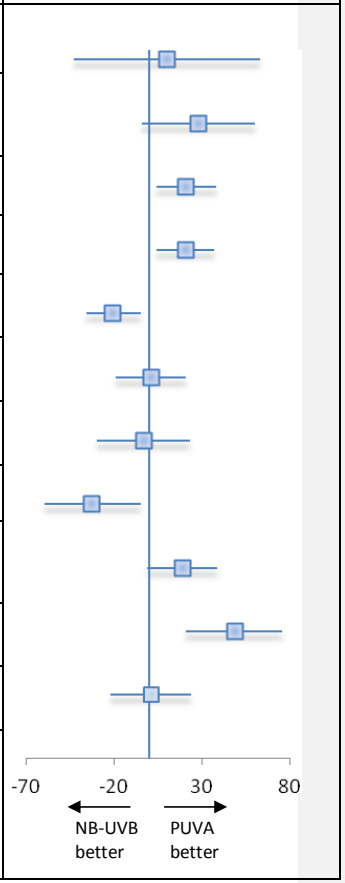


Figure 6. Controlled studies comparing PUVA with narrowband UVB for psoriasis

1st Author	Year	Design	NB-UVB	PUVA	Outcome	Total n=	% more cleared with PUVA (95% CI)	
Westerhof[57]	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[58]	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	randomised, 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	randomised, 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	randomised, 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 to before course on follow-up 12 months after end course	50	-12% (-37% to 13%)	

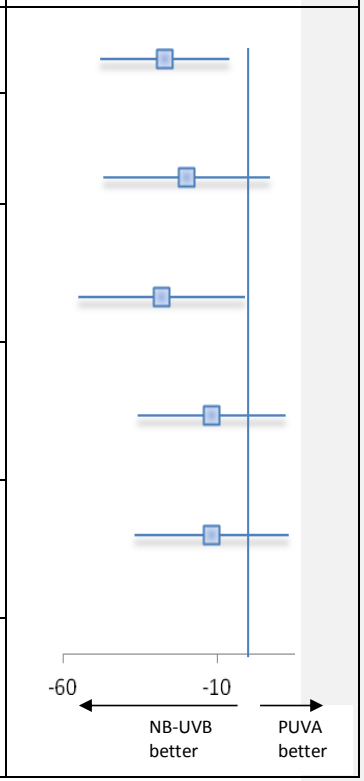


Figure 7 Controlled studies comparing PUVA with narrowband UVB for vitiligo

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