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British Association of Dermatologists and British Photodermatology Group guidelines for topical photodynamic therapy 2018

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C.A.M. has been an invited speaker for Galderma, Biofrontera/Spirit (specific), Astellas, Almirall and LEO Pharma (nonspecific); on advisory boards for Spirit/Biofrontera (specific), Almirall, Astellas and LEO Pharma (nonspecific); and an investigator participating in a study sponsored by Biofrontera (specific). S.I. has been an invited speaker for Galderma and Spirit Healthcare (specific); and an investigator participating in a Biofrontera-sponsored study (specific). H.M. runs a UKAS laboratory calibrating ultraviolet meters for phototherapy (specific). D.C.S. has received sponsorship to attend a European Academy of Dermatology and Venereology meeting from Galderma (nonspecific) and been on an advisory board for Galderma (nonspecific). L.E.R. has received travel expenses prior to 2013 from Galderma (specific) and nurse support for photodynamic therapy on three occasions prior to 2013 from Galderma (specific). K.A.W. received sponsorship to attend the 2014 Euro PDT meeting from Galderma (specific).

These guidelines were first produced by the British Photodermatology Group in 2002. They were reviewed and updated jointly by the British Association of Dermatologists and the British Photodermatology Group in 2008 and 2018.

This is an updated guideline prepared for the BAD Clinical Standards Unit, which includes the Therapy & Guidelines Subcommittee. Members of the Clinical Standards Unit who have been involved are P.M. McHenry (chairman Therapy & Guidelines), T.A. Leslie, S. Wakelin, R.Y.P. Hunasehally, M. Cork, G.A. Johnston, F.S. Worsnop, P. Rakvit, A. Salim, B. McDonald, S.L. Chua, D. Buckley, G. Petrof, N. Callachand (British National Formulary), T. Flavell (BDNG), A.A. Salad (BAD Scientific Administrator), L.S. Exton (BAD Guideline Research Fellow) and M.F. Mohd Mustapa (BAD Clinical Standards Manager).

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NICE has accredited the process used by the British Association of Dermatologists to produce clinical guidelines. The renewed accreditation is valid until 31 May 2021 and applies to guidance produced using the process described in the updated guidance for writing a British Association of Dermatologists clinical guidance – the adoption of the GRADE methodology 2016. The original accreditation term began on 12 May 2010. More information on accreditation can be viewed at www.nice.org.uk/accreditation.

1.0 Purpose and scope

The overall objective of the guideline is to provide up-to-date, evidence-based recommendations for the use of topical photodynamic therapy (PDT). The document aims to:

- offer an appraisal of all relevant literature up to April 2018, focusing on any key developments
- address important, practical clinical questions relating to the primary guideline objective and
- provide guideline recommendations and if appropriate research recommendations.

The guideline is presented as a detailed review with highlighted recommendations for practical use in primary care and in the clinic, in addition to an updated patient information leaflet [available on the British Association of Dermatologists (BAD) website, www.bad.org.uk/leaflets].

1.1 Exclusions

The guideline does not cover systemically administered PDT or PDT as a treatment option for genital warts and anal intraepithelial neoplasia, as these are out of the remit of dermatology for this guideline

2.0 Methodology

This set of guidelines has been developed using the BAD's recommended methodology[1] (see Appendix K in the Supporting

Information) with reference to the Appraisal of Guidelines Research and Evaluation (AGREE II) instrument (www.agreetrust.org)[2] and the Grading of Recommendations Assessment, Development and Evaluation (GRADE).[3] The recommendations were developed for implementation in the U.K. National Health Service.

The Guideline Development Group (GDG) consisted of consultant dermatologists (later joined by a trainee dermatologist), a consultant physicist, a photobiology technologist, a patient and a technical team (consisting of a guideline research fellow and project manager providing methodological and technical support). The GDG established several clinical questions pertinent to the scope of the guideline and a set of outcome measures of importance to patients, ranked according to the GRADE methodology[4] (see sections 3.1.1 and 3.2).

A systematic literature search of the PubMed, MEDLINE, Embase, Cochrane and AMED databases was conducted to identify key articles for PDT from 1 January 2007 to April 2018; the search terms and strategies are detailed in Appendix L (see Supporting Information). Additional references relevant to the topic were also isolated from citations in the reviewed literature and the previous versions of the guidelines. Evidence from the included studies was graded according to the GRADE system (high, moderate, low or very low quality).

The recommendations are based on evidence drawn from systematic reviews of the literature pertaining to the clinical questions identified. The summary of findings with forest plots (Appendix B), GRADE evidence profiles indicating the quality of evidence (Appendix E), tables Linking the Evidence To the Recommendations (Appendix D), PRISMA flow diagram (Appendix I) and list of excluded studies (Appendix J) are detailed in the Supporting Information and a separate systematic review for basal cell carcinoma (BCC).[5] The strength of recommendation is expressed by the wording and symbols shown in Table 1.

3.0 Introduction

3.1 Topical photodynamic therapy in nonmelanoma skin cancers and precancerous lesions

Topical PDT has been approved in over 18 countries worldwide for use in at least one nonmelanoma skin cancer (NMSC) indication.

Currently, three prodrugs are licensed for use in topical PDT. These include a formulation of 5-aminolaevulinic acid (ALA), Levulan® (DUSA Pharmaceuticals, Wilmington, MA, U.S.A.), for actinic keratosis (AK) and an esterified formulation, methyl aminolaevulinate (MAL), Metvix® (PhotoCure ASA, Oslo, Norway and Galderma, Paris, France) for AK, squamous cell carcinoma (SCC) *in situ* and superficial and nodular BCC. A nanoemulsion (nc-ALA), Ameluz® (Biofrontera AG, Leverkusen, Germany), is licensed for PDT in combination with red light for the treatment of mild and moderate AK. The licensed indications are for the treatment of nonhyperkeratotic AK, SCC *in situ* and superficial BCC (and in certain thin, nodular BCCs) in adults. The nc-ALA was also recently licensed for treatment of superficial and/or nodular BCC unsuitable for surgical treatment due to possible treatment-related morbidity and/or poor cosmetic outcome in adults.

Daylight PDT for AK is a recent indication. Metvix is licensed for PDT in combination with daylight, which is increasingly being used as a light source in the treatment of AK.

3.1.1 Place in the treatment pathway

Topical PDT is used in selected patients after considering the appropriateness, clinical efficacy, other modalities of treatment, patient age, lesion site, histology, cosmesis and patient choice.

To address these issues the GDG has asked the following question in relation to the use of topical PDT in the treatment

Table 1 Strength of recommendation ratings

Strength	Wording	Symbols	Definition
Strong recommendation for the use of an intervention	'Offer' (or similar, e.g. 'use', 'provide', 'take', 'investigate' etc.)	↑↑	Benefits of the intervention outweigh the risks; most patients would choose the intervention while only a small proportion would not; for clinicians, most of their patients would receive the intervention; for policy makers, it would be a useful performance indicator
Weak recommendation for the use of an intervention	'Consider'	↑	Risks and benefits of the intervention are finely balanced; most patients would choose the intervention but many would not; clinicians would need to consider the pros and cons for the patient in the context of the evidence; for policy makers, it would be a poor performance indicator where variability in practice is expected
No recommendation		Θ	Insufficient evidence to support any recommendation
Strong recommendation *against* the use of an intervention	'Do not offer'	↓↓	Risks of the intervention outweigh the benefits; most patients would *not* choose the intervention while only a small proportion would; for clinicians, most of their patients would *not* receive the intervention

of NMSC (see Appendix A in the Supporting Information for the full review protocol).

Review question 1:

In adults with an NMSC and precancerous lesions,[a] what are the clinical effectiveness/efficacy, safety and tolerability of photodynamic therapy (MAL-PDT, ALA-PDT) compared with cryotherapy, curettage, surgical excision, topicals, laser therapy, placebo or no treatment, each alone or in combination?

[a]Including AK, SCC *in situ* (Bowen disease), BCC (superficial, nodular and other), SCC, skin cancer prophylaxis, cutaneous T-cell lymphoma (CTCL), intraepithelial neoplasia of the external genitalia (prostatic, vulval and extragenital), extramammary Paget disease and hyperkeratosis in organ transplant patients.

3.2 Topical photodynamic therapy for infectious and inflammatory dermatoses

Topical PDT has also been used in the treatment of a number of inflammatory conditions on an unlicensed basis.

To address these issues the GDG has asked the following question in relation to the use of topical PDT in the treatment of inflammatory conditions with the following criteria (case series with at least four patients will be included). See Appendix A in the Supporting Information for the full review protocol.

Review question 2:

In adults with certain infectious and inflammatory dermatoses,[b] what are the clinical effectiveness/efficacy, safety and tolerability of photodynamic therapy (MAL-PDT, ALA-PDT) compared with standard treatment modalities, including topical therapies, systemic therapies and ultraviolet B phototherapy, control or each other.

[b]Including acne, actinic cheilitis, disseminated superficial actinic porokeratosis, alopecia areata, angiofibroma, cutaneous leishmaniasis, Darier disease, erythrasma, folliculitis, fungal infections, granuloma annulare, hypertrophic scars, keratoacanthoma, lichenoid dermatoses, molluscum contagiosum, morphoea and localized scleroderma, interdigital mycoses, necrobiosis lipoidica, perioral dermatitis, photorejuvenation, porokeratosis, psoriasis, radiodermatitis, rosacea, sebaceous hyperplasia, viral warts, vulval lichen sclerosus, vulvodynia, wound healing and Zoon balanitis.

Outcomes

The GDG also established a set of outcome measures of importance to patients (treatment) for each review question, which were agreed on by the patient representative, ranked according to the GRADE methodology.[4] Data on these outcomes were extracted from the included studies (Table 2) (also see Appendices F, G and H in the Supporting Information). Outcomes ranked 7, 8 or 9 are critical for decision making; those ranked 4, 5 or 6 are important but not critical for decision making.

4.0 Summary of recommendations

The following recommendations and ratings were agreed upon unanimously by the core members of the GDG and patient representative. For further information on the wording used for recommendations and strength of recommendation ratings see Section 2. The evidence for recommendations is based on the studies as listed (for details and discussion of the evidence see Appendices B–F in the Supporting Information). The GDG recommendations relating to referral pathways are based on discussion and clinical experience, as evidence-based details are not available at the time of writing. The GDG is aware of the lack of high-quality evidence for some of these recommendations, therefore strong recommendations with an asterisk (*) are based on the available evidence, as well as consensus and specialist experience. Good practice point (GPP) recommendations are derived from informal consensus. Please note that the recommendations made in this guideline may only partly overlap with formal licensed indications for the use of topical PDT in skin, hair and nail disorders.

The clinical efficacy and appropriateness of other treatment modalities should also be considered, taking into account lesion site, histology, cosmesis, patient age and patient choice.

All of the recommendations listed below apply where service provision makes them practically possible to do so.

Preparation prior to photodynamic therapy

R1 (GPP) Explain the potential benefits and harms of topical PDT to the patient and provide a BAD patient information leaflet (www.bad.org.uk/leaflets) for PDT before choosing the treatment.

R2 (GPP) Refer to the appropriate summaries of product characteristics on the electronic Medicines Compendium when administering PDT, as there are different preparation and administration procedures for each licensed indication.

Basal cell carcinoma

R3 (↑↑) Offer* topical PDT as a treatment option to people with superficial BCC, particularly for poorly healing or cosmetically sensitive skin sites, multiple lesions and large-area lesions.

R4 (↑) Consider topical PDT for people with thin (< 2 mm) nodular BCC in situations where other treatments are not practical or are contraindicated (see R6).

R5 (↑↑) Offer a further cycle of PDT to patients with residual lesions where the BCCs have shown a good response to the preceding treatment.

Table 2 Important outcome measures for photodynamic therapy

Nonmelanoma skin cancer and precancerous lesions		Infectious and inflammatory dermatoses	
Clearance of treated disease[a] (3 months' initial lesion clearance)	9	Improvement of inflammatory and infectious dermatosis[b] (3 months)	9
Sustained clearance of treated disease[a] (1 year)	9	Recurrence rate (only for infectious dermatosis) (6 months)	8
Sustained clearance of treated disease[a] (2 years SCC *in situ*; 5 years BCC)	9	Severe pain (leading to break in treatment or use of local analgesia)	8
Recurrence rate (> 1 year)	8	Cosmetic outcome	6
Severe pain (leading to break in treatment or use of local analgesia)	8	Treatment tolerability – low or manageable pain	5
Cosmetic outcome	6	Other adverse effects – pigmentation etc.	4
Treatment tolerability – low or manageable pain	5	Treatment-associated down time (photorejuvenation)	3
Other adverse effects – pigmentation etc.	4	Quality of life after treatment (acne)	3

Outcomes ranked 7, 8 or 9 are critical for decision making, those ranked 4, 5 or 6 are important but not critical for decision making and those ranked 3 are less important. BCC, basal cell carcinoma; SCC, squamous cell carcinoma. [a]Including actinic keratosis, SCC *in situ*, BCC (superficial, nodular and other), SCC, skin cancer prophylaxis, cutaneous T-cell lymphoma, intraepithelial neoplasia of the external genitalia (prostatic, vulval and extragenital), extramammary Paget disease and hyperkeratosis in organ transplant patients. [b]Including acne, actinic cheilitis, disseminated superficial actinic porokeratosis, alopecia areata, angiofibroma, cutaneous leishmaniasis, Darier disease, erythrasma, folliculitis, fungal infections, granuloma annulare, hypertrophic scars, keratoacanthoma, lichenoid dermatoses, molluscum contagiosum, morphoea and localized scleroderma, interdigital mycoses, necrobiosis lipoidica, perioral dermatitis, photorejuvenation, porokeratosis, psoriasis, radiodermatitis, rosacea, sebaceous hyperplasia, viral warts, vulval lichen sclerosus, vulvodynia, wound healing and Zoon balanitis.

R6 (↓↓) Do not offer topical PDT as a standard treatment for nodular BCC at high-risk sites.

R7 (GPP) Use red light and not that of a shorter wavelength (blue or green light, or daylight) for enhanced penetration for BCC.

Squamous cell carcinoma *in situ* (Bowen disease)

R8 (↑↑) Offer PDT as a treatment option to people with SCC *in situ*, particularly for poorly healing or cosmetically sensitive skin sites, multiple lesions and large-area lesions.

Actinic keratosis

R9 (↑↑) Offer topical PDT as a treatment option to people with AK, particularly for cosmetically sensitive skin sites, multiple lesions and large-area lesions.

R10 (↑↑) Offer a further cycle of topical PDT to patients with residual lesions where the AK lesions have shown a good response to the preceding treatment.

R11 (↑) Consider daylight PDT as a treatment option for people with mild (slightly palpable AK, more easily felt than seen; Olsen grade I) or moderate (moderately thick AK, easily felt; Olsen grade II) AK lesions where pain is likely to be an issue, particularly for confluent areas on the face or scalp.

R12 (↑) Consider combining topical PDT with other treatment modalities if feasible (e.g. imiquimod or pretreatment with ablative fractional laser) for people with thick AK lesions (very thick or obvious AK; Olsen grade III).

Squamous cell carcinoma

R13 (↑) Consider PDT as a treatment option for microinvasive SCC if surgery is contraindicated.

R14 (↓↓) Do not offer PDT as a treatment option for invasive SCC.

Skin cancer prophylaxis

R15 (↑) Consider field PDT as prophylaxis to reduce the emergence of new lesions in people with AK or NMSC, including those with organ transplantation.

Vulval intraepithelial neoplasia

R16 (↑) Consider PDT as a treatment option for vulval intraepithelial neoplasia lesions that are:

- unifocal
- nonpigmented
- without associated human papillomavirus infection
- with lower grades of dysplasia.

Erythroplasia of Queyrat

R17 (↑) Consider PDT as a treatment option for erythroplasia of Queyrat, bearing in mind that pain may be a limiting factor.

Cutaneous T-cell lymphoma

R18 (↑) Consider PDT as a treatment option for CTCL, particularly for early-stage disease, few localized lesions and challenging sites such as skinfolds.

Extramammary Paget disease

R19 (↑) Consider PDT as a treatment option for extramammary Paget disease (EMPD) for thin or small lesions:

- where the Paget cell infiltrate is less dense
- when there is limited adnexal involvement.

R20 (↑) Consider PDT as a treatment option for EMPD either before or after surgery.
R21 (↑) Consider CO_2 laser prior to PDT as a treatment option for EMPD.

Acne

R22 (↑) Consider PDT as a treatment option for acne where standard treatments are ineffective or contraindicated.

Antimicrobial: cutaneous leishmaniasis, fungal infections, viral warts

R23 (↑) Consider conventional PDT as a treatment option for cutaneous leishmaniasis, particularly in cosmetically sensitive skin sites.
R24 (↑) Consider daylight PDT as a treatment option for cutaneous leishmaniasis, bearing in mind that many treatments may be required.
R25 (↑) Consider PDT as a treatment option for recalcitrant viral warts.
R26 (↓↓) Do not offer* PDT as a treatment option for fungal infections.

Psoriasis

R27 (↓↓) Do not offer* PDT as a treatment option for psoriasis.

Actinic cheilitis

R28 (↑) Consider PDT as a treatment option for actinic cheilitis.

Insufficient evidence to support any recommendation

(Θ) Currently there is insufficient evidence to support any recommendation for the following: alopecia areata, angiofibroma, Darier disease, folliculitis, granuloma annulare, hypertrophic scars, keratoacanthoma, lichenoid dermatoses, necrobiosis lipoidica, morphoea and localized scleroderma, perioral dermatitis, photorejuvenation, porokeratosis, radiodermatitis, rosacea, sebaceous hyperplasia, vulval lichen sclerosus, vulvodynia, wound healing and Zoon balanitis.

List of key future research recommendations (FRRs)

FRR1 Comparison of topical therapies with PDT for superficial or thin nodular BCC:
- where there is residual BCC at 3 months after the first cycle of PDT
- to include detailed assessment of post-treatment events and tolerability assessed both cumulatively over time and in intensity (including pain, irritation), and patient treatment preference.

FRR2 Potential for combination therapy including PDT to optimize sustained response rates in BCC.
FRR3 Comparison of PDT in combination with other therapies for large lesions or lesions unresponsive to monotherapy in BCC.
FRR4 Comparison of conventional vs. fractionated PDT in BCC.
FRR5 Comparison of the efficacy of conventional vs. daylight PDT for AK in a randomized controlled trial:

- stratified by Olsen grade of AK lesion, complete response and recurrence rates
- at sites other than the scalp, with treatment of individual AK lesion(s) vs. treatment of the field area.

FRR6 Comparison of cost-effectiveness of conventional vs. daylight PDT in AK, with consideration of complete response and recurrence rates.
FRR7 What is the efficacy and safety of daylight PDT in SCC *in situ*?
FRR8 Comparison of PDT with curettage and cautery in SCC *in situ*.
FRR9 Comparison of PDT in combination with other therapies for large lesions or lesions unresponsive to monotherapy in SCC *in situ*.
FRR10 Further study of the efficacy and safety of PDT for superficial microinvasive SCC where surgery is contraindicated.
FRR11 Potential for combination therapy including PDT to achieve sustained high response rates in microinvasive SCC when surgery is contraindicated.
FRR12 Need for randomized controlled trial data to assess the efficacy of PDT for vulval intraepithelial neoplasia, erythroplasia of Queyrat, anal intraepithelial neoplasia, CTCL and EMPD.
FRR13 What measures can be used to limit pain in patients with genital lesions treated with PDT?
FRR14 Improved modelling of light transmission, photosensitizer distribution and tumour shape and location to enable more accurate prediction of outcome.
FRR15 Need for larger well-designed randomized, controlled, adequately powered studies of the full face rather than split face for acne, with longer follow-up required to determine the period of remission and whether sustained.
FRR16 Need for well-designed randomized, controlled, adequately powered studies with a longer follow-up and ideally histological confirmation of clinical findings for photorejuvenation.
FRR17 Need for larger well-designed randomized, controlled, adequately powered studies comparing conventional PDT with topical paromomycin, cryotherapy or placebo for cutaneous leishmaniasis.
FRR18 Need for larger well-designed randomized, controlled, adequately powered studies comparing daylight PDT with

topical paromomycin, cryotherapy or placebo for cutaneous leishmaniasis.

FRR19 Need for well-designed randomized, controlled, adequately powered studies comparing PDT with conventional treatments for vitiligo.

5.0 Photosensitizing agents

PDT is commonly performed using the prodrugs ALA and its methyl ester, MAL. MAL is demethylated by intracellular esterases, and ALA is metabolized by the haem biosynthetic pathway, leading to accumulation of the photosensitizer protoporphyrin IX (PpIX). PpIX has several absorption peaks, with the 632-nm (red light) peak being utilized most frequently for irradiation, in treatment of a range of skin lesions including BCC and SCC *in situ*, while the 410-nm (blue light) peak is also utilized for more superficial lesions such as AK.

The prodrugs are relatively selectively concentrated in the target lesion. ALA is hydrophilic and addition of the methyl group produces the more lipophilic MAL, with the aim to enhance tissue penetration.[6] Studies comparing ALA and MAL in AK and inflammatory acne report higher PpIX levels but less selectivity for the target tissue with ALA, and less pain with MAL, although similar treatment efficacy of ALA- and MAL-PDT is seen.[6] Both ALA- and MAL-PDT are effective in SCC *in situ* and BCC, with less pain reported with MAL-PDT.[7]

PDT with MAL is performed according to its licence, a treatment cycle comprising one PDT treatment in AK and two PDT treatments with a 1-week interval in SCC *in situ* and nodular and superficial BCC, with light exposure 3 h after prodrug application. A second PDT cycle is usually performed at 3 months in incompletely responding lesions. In contrast, a range of different ALA formulations and ALA–light exposure intervals have been used. A self-adhesive ALA patch has been licensed for use in mild AK.[8] A gel formulation of ALA with nanoemulsion, nc-ALA (BF-200 ALA, Ameluz), which enhances ALA stability and skin penetration, has shown higher complete lesion clearance than MAL-PDT in thin-to-moderate-thickness AK.[9] The nc-ALA formulation has also recently been licensed for the treatment of superficial and nodular BCC.

Further approaches to enhance skin-target-cell delivery of prodrugs and photosensitizers include the use of liposomal delivery.[10,11] With liposomal ALA, a low (0·5%) ALA concentration reduces phototoxic effects in acne.[12] Levels of PpIX have been potentiated by adjuvant treatment with ferrochelatase inhibitors,[13] differentiating agents, including low-dose methotrexate and vitamin D,[14] and heat.[15] Higher PpIX levels are also seen with ALA after skin-surface disruption, for example in pretreatment with fractional laser.[16]

Attempts have also been made to perform topical PDT using exogenous photosensitizers, particularly to pursue the advantage of using chemicals with longer activation wavelength, and hence potentially PDT with deeper tissue effect. This includes exploratory studies of the use of silicon phthalocyanine (Pc4), peak absorption 675 nm, which was safe and tolerable in a dose-escalation study in NMSC and CTCL,[17] and meso-tetra (hydroxyphenyl)chlorin, peak absorption 652 nm.[10] A phase IIa randomized controlled trial of PDT with topical application of the cationic photosensitizer PPA904 [3,7-bis(*N*,*N*-dibutylamino)phenothiazin-5-ium bromide] vs. placebo in chronic leg ulcers demonstrated significant reduction in bacterial load with a trend towards wound healing.[18]

6.0 Photodynamic diagnosis

Photodynamic diagnosis (PDD) employs noninvasive detection with or without quantification of photosensitizer fluorescence; when performed, this is usually prior to treatment with PDT or another modality. The topical prodrugs ALA and MAL have been utilized, with PpIX fluorescence used in both therapy and diagnosis.[19]

The simplest method involves the illumination of a porphyrin-enriched tumour by Wood's lamp (long-wavelength ultraviolet A), revealing a brick-red fluorescence. However, this is a crude technique and its relevance to clinical practice is undefined. The fluorescence can also be quantitatively measured through use of charge-coupled-device camera systems with digital imaging.[20]

In addition to wide-field optical imaging, technological approaches include surface point measurements (e.g. fluorescence spectroscopy), which allow assessment of superficial tissues. Multimodal techniques are in development, combining fluorescence with technologies such as ultrasound, optical coherence tomography or confocal microscopy, allowing greater depth assessment.[19]

There is particular interest in applying PDD to delineate lesional margins,[21] with human studies indicating high predictive value, for example in MAL-PDD of BCC.[22,23] Assessment of PpIX levels and kinetics can also be applied in a range of situations including evaluation of prodrugs, impact of adjunctive agents and prediction of clinical clearance.[24] In future, PDD could enable tailoring of treatment regimens to optimize patient outcomes.

7.0 Light sources and dosimetry

A light source is required that will deliver the necessary irradiance within the absorption band of the photosensitizer at sufficient depth to destroy the target tissue, while causing minimal damage to surrounding healthy tissue.[25,26] The most common light sources used for PDT of skin lesions are laser diodes, filtered lamps or light-emitting diodes (LEDs). LEDs have the advantage of a narrow spectral emission with minimal cost and are virtually maintenance free. These all emit light centred around 630 nm. Fluorescent lamps with an emission spectrum between 400 and 450 nm are also used for PDT of AK. There are numerous publications describing the use of other light sources including dye lasers and intense pulsed light.[27–32] In the case of MAL-PDT, standard procedures involve the use of LEDs.[6,33] Further details and spectra are provided in Appendix M (see Supporting Information).

Only a few clinical comparative studies have been carried out using different light sources. Narrowband LEDs appeared

more efficacious than broadband LEDs in one study,[34] but other studies failed to find a significant difference when different light sources were used.[35–37] There is evidence to support a fractionated treatment regimen in which a dark interval is introduced between two light fractions.[38,39] Also, pretreatment using a fractional laser may enhance penetration of the prodrug.[16,40,41]

Traditionally, PDT has been a hospital-based treatment using relatively bulky light sources. Developments are underway to facilitate easier delivery of the treatment. These include so-called ambulatory PDT using a lightweight portable LED device,[42,43] and light-diffusing textiles.[44] Another novel way to deliver PDT outside the hospital is to use daylight as the light source.[45–47]

Commercial PDT light sources are supplied with no evidence of traceability to national measurement standards to validate the indicated delivered dose.[48] In one case, the dose fell to just over one-third at a distance of only 2 cm from the central area.

It is important to know the effective dose being delivered to the target cells.[49,50] Factors such as photobleaching can increase the treatment depth, and use of Monte Carlo (MC) models provides an insight into generation of singlet oxygen within the tumour.[26,51–55] MC simulations predict a 72% increase in depth of tumour necrosis for a wavelength of 630 nm compared with 405 nm.[55] MC modelling also showed that the effective treatment depth increased from 2·0 to 2·7 mm for light doses of 37·5 and 75 J cm^{-2}, respectively, and increased further to 3·3 mm for 150 J cm^{-2}, largely due to photobleaching.[53]

8.0 Protocols for delivery of photodynamic therapy

A successful PDT outcome requires the optimization of applying the appropriate prodrug, drug or photosensitizer, light parameters and oxygen, thereby achieving the mechanism of action intended. The resultant photodynamic reaction at the target cell produces the therapeutic result. PDT utilizes the higher selectivity of the photosensitizer for the target tissue compared with healthy tissue. The topically applied photosensitizer prodrugs are converted intracellularly to active photosensitizers, principally PpIX. Reactive oxygen species, namely singlet oxygen produced by the photodynamic reaction, cause programmed cell death (apoptosis) and necrosis of target cells, and can also modify cellular processes via molecular events. In addition to the direct effects of PDT on lesional tissue, indirect effects can occur both through dermal vascular events and via the host inflammatory and immune responses.[56]

The various regimens of PDT delivery with multiple different combinations are aimed to optimize the therapeutic response.

The following recommended protocols refer to the two prodrugs that are currently licensed for use in the U.K.: MAL (Metvix) for nonhyperkeratotic AKs, SCC *in situ* and superficial BCCs, and BF-200 ALA (Ameluz) nc-ALA, which is the only ALA source approved in the U.K. that is licensed for AKs on face and scalp, recently also licensed for BCC.

Variation of administration of PDT protocols between studies may contribute to limitations in the ability to compare studies.

Lesion preparation is a routinely performed aspect of delivering topical PDT regardless of which product is being used. The gentle removal of crusts and scale with a scalpel or curette is commonly performed without causing pain and does not require local anaesthesia. The treatment area can be degreased with 70% isopropyl alcohol (especially for Ameluz). Other additional preparation techniques or combination treatment approaches reported include microneedling, skin vaporization with CO_2 laser or ablative fractional resurfacing.[57–61] A layer of prodrug cream approximately 1 mm thick is applied via spatula to the lesion and the surrounding 5–10 mm of skin.

Treatment sites are covered with light-occlusive dressings, as full exposure to ambient light during the incubation period potentially increases activation of PpIX superficially (bleaching), thereby reducing deeper prodrug or photosensitizer penetration before photoactivation. Occlusion is standard practice for conventional PDT using MAL and nc-ALA.

After the incubation time of 3 h the dressing is removed, with the remnant cream or gel wiped off with saline 0·9% solution. This is followed by illumination using red light of 570–670 nm, achieving a dose of 75 J cm^{-2}, or a narrow-spectrum 635-nm LED lamp with a distance from skin to lamp of 5–8 cm, achieving a dose of 37 J cm^{-2} with an intensity of approximately 50–80 mW cm^{-2}.

The regimen for AK is one treatment, whereas for BCC and SCC *in situ* it is two treatments 7 days apart. Protocols used in other indications are discussed with each indication.

Daylight PDT is performed by the application of an organic sunscreen initially,[62] followed by lesion preparation 15 min later, then MAL to the treatment area without occlusion. After a 30-min application, patients are exposed to daylight for 1·5–2 h for treatment of AK.[46,63] Location, weather and the availability of daylight could be limitations.

9.0 Adverse effects

The most apparent acute adverse effect of topical PDT is pain. Historically, with high-irradiance regimens, this was a limiting factor for the effective delivery of PDT in some instances. PDT-induced pain appears to have neurogenic and inflammatory components. Predictive factors for PDT-induced pain have been investigated, but many studies have multiple confounding influences. Overall, it appears that treatment of larger lesions or areas, particularly if there is field-change photodamage, and those on the head and neck, are associated with the likelihood of higher levels of pain than smaller lesions or fields on nonhead and neck sites. Methods of pain relief such as topical analgesics and anaesthetics, cold air and pausing irradiation have little or limited impact on minimizing the pain experienced, although nerve blockade may be more effective. The introduction of PDT with lower-

irradiance regimens (e.g. daylight PDT) has markedly improved both the ability to deliver to a large area and the tolerability of the treatment. Indeed, with current usage and appropriate selection of PDT treatment regimens, pain appears no longer to be a major limiting factor for most patients receiving PDT.

The inflammation induced during topical PDT is an expected effect rather than an adverse effect, manifesting as erythema, oedema and even frank urticaria in some patients. Hyper- and hypopigmentation are also uncommon occurrences, which may last for weeks to months after treatment. Scarring is a rare event, and excellent cosmetic outcome is a considerable advantage of PDT in comparison with other treatments such as cryotherapy.

Rarely, contact sensitization to the prodrugs used in topical PDT may occur, and this should be considered particularly for patients who have received treatment to large areas and in multiple sessions, such as those with extensive field change and AKs, including patients receiving daylight PDT. Vigilance is required with respect to patients developing unusually severe reactions or dermatitic responses after PDT; patch testing should be carried out if indicated. Other medium-term to chronic adverse effects of PDT are rare. While there are isolated reports of invasive SCC and melanoma developing at sites treated by PDT, these are in patients with otherwise premalignant skin changes, and any causal association with PDT is unproven.[64] Although there is no convincing evidence of a carcinogenic risk of PDT, vigilance is recommended. Details and references of the adverse effects of topical PDT are included in a separate review.[65]

10.0 Recommended audit points

In the last 20 consecutive patients treated with PDT is there evidence of:

1 Clearance rates of ≥ 75% of AK, SCC *in situ* and superficial BCC lesions (including daylight PDT for individual AK lesions or field areas)
   a at 3 months after the last treatment
   b at 12 months after the last treatment (SCC *in situ* and superficial BCC only).
2 An effective pain management protocol for patients treated for individual AK, SCC *in situ* or BCC lesions who experience severe pain requiring interruption of treatment or local anaesthesia.
3 Patient feedback on their
   a satisfaction with cosmetic outcome at 1 year (poor, moderate, good or excellent)
   b satisfaction with PDT therapy in general (very satisfied, satisfied, dissatisfied or very dissatisfied)
   c preferred therapy, if they had received alternative therapies for the same or similar lesion previously.
4 Initial clearance rates (3 months) in indications for which PDT is not licensed.

The audit recommendation of 20 cases per department is to reduce variation in the results and to allow benchmarking between different units. However, departments unable to achieve this recommendation may choose to audit all cases seen in the preceding 12 months (see Appendix N in the Supporting Information).

11.0 Stakeholder involvement and peer review

The draft document and supporting information were made available to the BAD membership, the British Photodermatology Group (BPG), the British Dermatological Nursing Group (BDNG), the Primary Care Dermatological Society (PCDS) and the Gorlin Syndrome Group for comments, which were actively considered by the GDG. Following further review, the finalized version was sent for peer review by the Clinical Standards Unit of the BAD (made up of the Therapy & Guidelines Subcommittee) prior to submission for publication.

12.0 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. Additionally, it is acknowledged that limited cost-effectiveness data in the context of the U.K. healthcare setting may impact on the availability of a given therapy within the National Health Service, despite evidence of efficacy. 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.

13.0 Plans for guideline revision

The proposed revision date for this set of recommendations is scheduled for 2023; where necessary, important interim changes will be updated on the BAD website.

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Supporting Information

Additional Supporting Information may be found in the online version of this article at the publisher's website:

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