University of Dundee

Is there an optimal irradiation dose for photodynamic therapy

Todd, B.; Lesar, A.; O'Mahoney, P.; Eadie, Ewan; Ibbotson, Sally

Published in:
British Journal of Dermatology

DOI:
[10.1111/bjd.18644](https://doi.org/10.1111/bjd.18644)

Publication date:
2020

Document Version
Peer reviewed version

[Link to publication in Discovery Research Portal](#)

Citation for published version (APA):

Todd, B., Lesar, A., O'Mahoney, P., Eadie, E., & Ibbotson, S. (2020). Is there an optimal irradiation dose for photodynamic therapy: 37 Jcm⁻² or 75 Jcm⁻²? *British Journal of Dermatology*, 182(5), 1287-1288.
<https://doi.org/10.1111/bjd.18644>

General rights

Copyright and moral rights for the publications made accessible in Discovery Research Portal are retained by the authors and/or other copyright owners and it is a condition of accessing publications that users recognise and abide by the legal requirements associated with these rights.

- Users may download and print one copy of any publication from Discovery Research Portal for the purpose of private study or research.
- You may not further distribute the material or use it for any profit-making activity or commercial gain.
- You may freely distribute the URL identifying the publication in the public portal.

Take down policy

If you believe that this document breaches copyright please contact us providing details, and we will remove access to the work immediately and investigate your claim.

MR BRIAN KENNETH TODD (Orcid ID : 0000-0002-2216-2364)

DR PAUL O'MAHONEY (Orcid ID : 0000-0003-3221-5105)

MR EWAN EADIE (Orcid ID : 0000-0002-7824-5580)

PROFESSOR SALLY H IBBOTSON (Orcid ID : 0000-0001-5685-752X)

Article type : Research Letter

Corresponding Author Email ID: brian.todd@nhs.net

Is there an optimal irradiation dose for PDT: 37 Jcm⁻² or 75 Jcm⁻²?

B. K. Todd¹, A. Lesar¹, P. O'Mahoney^{2,3}, E. Eadie¹ and S. H. Ibbotson^{1,2,3}

1. Photobiology Unit, NHS Tayside, Ninewells Hospital, Dundee, DD1 9SY
2. The Scottish Photodynamic Therapy Centre, Dundee, United Kingdom
3. School of Medicine, University of Dundee, Dundee, United Kingdom

Topical photodynamic therapy (PDT) is widely used for the treatment of Bowen's disease (BD) and superficial basal cell carcinoma (BCC). The process involves oxygen-dependent light activation of the tissue-localised photosensitiser, protoporphyrin IX, three hours after pro-drug application to the lesion. Current approved and licensed regimens involve application of either methylaminolevulinate (MAL, Metvix, Galderma, Switzerland) or 5-aminolaevulinic acid in nanocolloid emulsion (ALA, Ameluz gel, Biofrontera, Germany) and subsequent light activation using narrow spectrum (630-635 nm) red light (typically light emitting diodes (LEDs)), at an unweighted radiant exposure ("dose") of 37 Jcm⁻² (1-3).

This article has been accepted for publication and undergone full peer review but has not been through the copyediting, typesetting, pagination and proofreading process, which may lead to differences between this version and the [Version of Record](#). Please cite this article as [doi: 10.1111/BJD.18644](#). This article may be used for non-commercial purposes in accordance with Wiley Terms and Conditions for Self-Archiving.

This article is protected by copyright. All rights reserved

The original recommended use of topical PDT involved irradiation with a tungsten filament source (Photocure ASA, Norway), wavelength range 570-730 nm, delivering a dose of 75 Jcm⁻² (4). This was our practice until 2004, when we changed to the recommended use of an LED source (Aktelite CL128, Photocure ASA, Norway) delivering a dose of 37 Jcm⁻². (3). However, we observed lower efficacy with this lower PDT irradiation dose, so we reverted to an LED dose of 75 Jcm⁻².

It is not known whether PDT outcomes for BD and BCC are influenced by light dose; specifically by 37 Jcm⁻² or 75 Jcm⁻². It would be more efficient to use a lower light dose if efficacy was similar. Therefore, we compared the outcomes of two clinically utilised PDT regimens in order to ascertain whether total light dose affects treatment efficacy. Patients referred for PDT for BD or BCC were alternately treated with either 37 Jcm⁻² or 75 Jcm⁻² over a one-year period. A total of 62 lesions were treated, with 31 (15 BD and 16 SBCC) irradiated at 37 Jcm⁻² and 31 (10 BD, 20 sBCC and one nodular BCC) irradiated at 75 Jcm⁻². Patients were reviewed three months following the first treatment cycle and a second treatment cycle was administered if partial lesional response was achieved at that time-point. Final review was 12 months following the initial treatment cycle.

The data obtained for these treatments are summarised in Table 1. Similar outcomes were achieved at three months after the first PDT cycle, with 64.5% and 67.7% lesion clearance for the 37 Jcm⁻² and 75 Jcm⁻² treatment groups respectively. Similar proportions of each group (35.5%, 32.3%) received a second treatment cycle. The 12-month outcomes showed the most striking difference between the regimens, with clearance in 67.7% of those treated with 37 Jcm⁻² versus 90.3% of lesions treated with 75 Jcm⁻².

These data provide evidence in support of improved outcomes for PDT for BD and BCC lesions when using a higher dose of 75 Jcm⁻² of 630 nm red LED light than when using the lower dose of 37 Jcm⁻² as recommended in the licensed PDT regimen.

It is unclear from the literature as to the reason for the recommended dose of 37 Jcm⁻² when using the narrow spectrum red LED. Mathematical modelling shows that such an LED was more effective than a broadband light source for skin penetration depths greater than 1.5 mm, reaching a maximum ratio between light sources of 1.26 at a depth of 8 mm (4). In mouse skin, the authors also showed that the fluence required by the broadband source was 1.30 times higher than that of the LED source to produce 90% PpIX bleaching. In solution, this value was 2.24, indicating that the LED was proportionately more effective at inducing photobleaching in solution than in mouse skin. Monte Carlo simulations indicate that, at a 2mm depth, the photodynamic dose for the red LED source is more than twice that of a broadband lamp (5). However, these simulations also demonstrate that effective treatment depth is

increased at higher light dose and that singlet oxygen production still occurs at depth even after surface layers have been photobleached (6, 7). To our knowledge, there is no clinical study comparing the efficacy of the two red LED light doses (37 Jcm⁻² and 75 Jcm⁻²) for PDT in BCC or Bowen's disease.

In this study, the use of 75 Jcm⁻² was associated with notably higher clearance rates at 12 month follow up after PDT when compared with the use of 37 Jcm⁻². Optimising PDT regimens in order to ensure improved longer-term outcomes is key to the efficacy and acceptance of PDT for patients with superficial non-melanoma skin cancer and pre-cancerous change. These data indicate that higher irradiation doses may be more effective, although further studies are required to determine the most efficacious quantity of light.

Word count for body text: 735

References:

- (1) Morton CA, Szeimies RM, Sidoroff A, Braathen LR. European guidelines for topical photodynamic therapy part 1: treatment delivery and current indications - actinic keratoses, Bowen's disease, basal cell carcinoma. *J Eur Acad Dermatol Venereol* 2013; 27:536-544.
- (2) Biofrontera Pharma GmbH. Ameluz 78 mg/g gel Summary of Product Characteristics. 2011.
- (3) Galderma (U.K) Ltd. Metvix 160 mg/g cream Summary of Product Characteristics. 2006.
- (4) Juzeniene A, Juzenas P, Ma LW, Iani V, Moan J. Effectiveness of different light sources for 5-aminolevulinic acid photodynamic therapy. *Lasers Med Sci* 2004; 19:139-149.
- (5) Valentine RM, Wood K, Brown CTA, Ibbotson SH, Moseley H. Monte Carlo simulations for optimal light delivery in photodynamic therapy of non-melanoma skin cancer. *Phys Med Biol* 2012; 57:6327-6345.
- (6) Valentine R, Brown CTA, Wood K, Moseley H, Ibbotson S. Monte Carlo modeling of in vivo protoporphyrin IX fluorescence and singlet oxygen production during photodynamic therapy for patients presenting with superficial basal cell carcinomas. *J Biomed Opt* 2011; 16:048002.
- (7) LaRochelle EPM, Marra K, LeBlanc RE, Chapman MS, Maytin EV, Pogue BW. Modeling PpIX effective light fluence at depths into the skin for PDT dose comparison. *Photodiagnosis Photodyn Ther* 2019; 25:425-435.

Conflicts of Interest:

Professor Sally Ibbotson has received honoraria and travel expenses from Galderma, Ambicare, and Spirit Healthcare

Doctor Ewan Eadie has received travel expenses for conference attendance from Galderma

Doctor Paul O'Mahoney has received travel expenses for conference attendance from Galderma

Figures:

Table 1: PDT treatment outcomes at 3 and 12 month follow up following use of an irradiation dose of 37 J/cm² or 75 J/cm²

	37 Jcm ⁻²		75 Jcm ⁻²	
	Number	Percentage	Number	Percentage
Lesions treated	31	100.0	31	100.0
Lesions clear at 3 month review	20	64.5	21	67.7
Lesions clear at 12 Month Review (single treatment)	16	51.6	18	58.1
Lesions requiring repeat PDT at 3 Months	11	35.5	10	32.3
Lesions clear at 3 month review (repeat treatment)	8	72.7	10	100.0
Lesions clear at 12 month review (repeat treatment)	3	27.3	10	100.0
Lesions clear at 12 month review (overall)	21	67.7	28	90.3