Published in final edited form as:

J Am Acad Dermatol. 2009 December ; 61(6): 1033–1043. doi:10.1016/j.jaad.2009.03.048.

Pain Associated with Aminolevulinic Acid-Photodynamic Therapy of Skin Disease

Christine B. Warren, BA^{*}, Laszlo J. Karai, MD PhD[†], Allison Vidimos, MD RPh[†], and Edward V. Maytin, MD PhD^{†,§}

^{*}Cleveland Clinic Lerner College of Medicine of Case Western Reserve University, Cleveland, Ohio, USA

[†]Department of Dermatology, Cleveland Clinic, Cleveland, Ohio, USA

[§]Department of Biomedical Engineering, Cleveland Clinic, Cleveland, Ohio, USA

Abstract

Background—Pain during topical aminolevulinic acid (ALA) mediated photodynamic therapy (PDT) limits the use of this treatment of skin diseases.

Objective—To summarize the effectiveness of interventions to reduce ALA-PDT related pain, and to explore factors contributing to pain induction.

Methods—A PubMed search was performed to identify all clinical PDT trials (2000–2008) that used ALA or methyl-ALA, enrolled at least 10 patients per trial, and used a semiquantitative pain scale.

Results—43 papers were identified for review. Pain intensity is associated with lesion size and location and can be severe for certain diagnoses, such as plaque-type psoriasis. Results are inconsistent for the correlation of pain with light source, wavelength of light, fluence rate, and total light dose. Cooling represents the best topical intervention.

Limitations—Pain perception differs widely between patients and can contribute to variability in the reported results.

Conclusion—GABA receptors, cold/ menthol receptors (TRPM8), and vanilloid/capsaicin receptors (TRPV1) may be involved in pain perception during ALA-PDT and are therefore worthy of further investigation.

I. INTRODUCTION

Photodynamic therapy (PDT) is an increasingly popular treatment modality for both malignant and non-malignant lesions. In topical PDT, aminolevulinic acid (ALA) is applied as a prodrug that is ultimately metabolized to the actual photosensitizer, protoporphyrin IX (PpIX), in lesional cells^{1,2}. When exposed to light, PpIX undergoes photochemical degradation and releases cytotoxic oxygen radicals that result in tumor destruction^{1,2}. During illumination, a sensation of burning, stinging, and prickling commonly occurs that ranges from mild to severe³, varies from patient to patient, and is largely unpredictable⁴. The mechanism of pain is not fully elucidated but likely involves nerve stimulation and/or tissue damage. Common pain interventions include cooling, interrupted illumination, and

Correspondence/Reprints: Address: Edward V. Maytin MD, PhD, Biomedical Engineering/ND-20, Cleveland Clinic, 9500 Euclid Avenue, Cleveland, OH 44195, USA., Office: (216) 445-6676, Fax: (216) 444-9198, maytine@ccf.org.

Conflict of Interest Statement: The authors have no conflict of interest to declare.

topical or injectable anesthetics. The purpose of this review is to summarize the success (or failure) of pain-reducing strategies, and to explore the interrelationship between factors that may contribute to ALA-PDT induced pain, in human clinical studies published since 2000. A PubMed search using the key words "pain AND photodynamic therapy" retrieved 144 articles, of which 88 were dermatology-related. From the 88, we excluded the following: 4 non-English articles, 14 reviews, 12 case reports with fewer than 10 patients, 3 articles not dealing with humans, 10 studies using photosensitizers other than aminolevulinate-based compounds, and 2 studies not providing any scale for pain assessment. This left 43 articles to review. In Tables 1–3, those studies for which parameters can be directly compared are grouped together; all other studies are mentioned in the text.

II. FACTORS CONTRIBUTING TO PAIN ASSOCIATED WITH PDT

Most experience with ALA-PDT related pain has been gained from treatment of precancerous lesions (actinic keratoses, AK) and nonmelanoma skin cancers. Serious attempts have also been made to evaluate pain during ALA-PDT for acne vulgaris, warts, and psoriasis.

i. Preparation of the Skin Surface Prior to ALA Application

The application of ALA has been reported to cause a transient mild stinging sensation immediately after ALA application (before illumination), particularly on ulcerated or abraded skin⁵. Kuijpers et al. attributed this discomfort to the acidity of the cream⁶. Several candidate genes encoding ion channels that are activated by acid have been cloned; these are the capsaicin receptor (TRPV1)^{7,8} and the acid-sensing ion channel (ASIC)⁹ family. Their role here remains purely speculative.

ii. Type of Topical Photosensitizer (5-ALA versus Methyl-ALA)

PDT seems to be less painful with methyl-aminolevulinate (MAL) than with ALA in studies that directly compared the two (see Table I). For example, in a study by Kasche et al. (Table I), 14% of patients with scalp AK discontinued treatment with MAL-PDT before reaching the required light dose of 100 J/cm², whereas 54% of patients stopped treatment with ALA-PDT¹⁰. Moloney et al. also found MAL to be less painful than ALA¹¹. Less pain with MAL-PDT was documented in normal tape stripped skin by Wiegell et al.¹². In a different study, Wiegell et al. found no difference in pain between ALA and MAL for acne vulgaris (Table I)¹³. Disparate results may relate to the fact that in diseased skin, both ALA and MAL can lead to high accumulation of PpIX, but in normal skin PpIX is elevated only after ALA¹⁴. Another study that measured PpIX levels in acne and AK lesions found that pain during MAL-PDT was correlated with the amount of PpIX accumulated prior to illumination¹⁵. A particularly intriguing finding is that after topical ALA application, PpIX accumulates in a homogenous pattern, but after MAL, PpIX accumulation is heterogeneous and localized in discrete spots¹³. This suggests that an appropriate fluorescence detection device (dosimeter) might be helpful for predicting which patients will respond favorably to a given dose of light. Although not yet widely available, such dosimeters are currently used in a research setting^{16,17}.

iii. Location, Size, and Type of Lesion

Several studies noted that PDT is more painful when performed on well-innervated areas of the skin, such as the face, hands and the perineal regions, as well as on larger areas^{4,18,19}. In regards to lesion type, Grapengiesser et al. observed the most pain with AK, and the least with basal cell carcinomas (BCC), although differences in location and size of the treated areas for AK vs. BCC might confound these results⁴. Warts seem to generate considerable pain, significantly more in ALA-PDT treated warts as compared to placebo-PDT alone²⁰;

the pain peaks as late as 24 hr and can persist up to 48 hr²¹. Acne vulgaris can be treated with light alone (without ALA)^{22,23}, due to the fact that *Propionibacterium acnes* produces and accumulates porphyrins within the sebaceous glands^{24,25}. However, if exogenous ALA or MAL are used in the PDT regimen for acne, pain is greater than with light alone, and can be quite severe^{23,25,26}. Psoriasis appears to generate the highest PDT-related pain scores, with many patients stopping treatment due to pain; see Table II^{18,27–29}. Some investigators have concluded that ALA-PDT, at least as currently administered, is not an appropriate option for plaque-type psoriasis^{27,29}.

iv. Fluence Rate and Total Dose of Light

The literature offers conflicting evidence regarding the effect of light dose (in joules/cm²; also called “fluence”) and light intensity (in watts/cm²; also called “dose rate”, “fluence rate”, or “irradiance”) upon ALA-PDT induced pain. Almost all studies in this regard have been conducted with red light. Concerning the total light delivered, Radakovic-Fijan et al.³⁰ (Table II) examined the correlation between light dose (70–140 J/cm²) and pain during the treatment of AK and observed a trend (not statistically significant) toward higher doses causing more pain³⁰. For psoriatic lesions, Radakovic-Fijan et al.¹⁸ (Table II) found that pain was clearly dose dependent, occurring in only 1/21 lesions treated with 5 J/cm²; 5/21 with 10 J/cm²; and 7/21 lesions with 20 J/cm² doses. Other studies also support a general correlation between light dose and pain. Horfelt et al. (Table II) reported that patients undergoing ALA-PDT for acne of the face and back experienced more pain at higher doses³¹.

Regarding light intensity, Ericson et al. (Table II) found no significant correlation between fluence rate (30–75 mW/cm²) and pain recorded during ALA-PDT of AK³². On the other hand, Clark et al. (Table II) noted less pain with low-intensity lamps than with high-intensity light sources⁵. For MAL-PDT of facial acne using an LED laser, Wiegell et al. (Table II) described less pain when a low fluence rate (34 mW/cm²) was used¹⁵. Ericson et al.³² commented that pain seemed to peak around 20 J/cm² and then leveled off; similar observations of a pain plateau reached early during illumination have been reported in many other studies as well^{5,11,18,25,33,34}. Practitioners often find it useful to coax patients through a PDT treatment session by explaining that pain typically reaches a maximum within five minutes, and then begins to lessen.

In a detailed, mechanistic study to examine the relationship between light intensity and pain during ALA-PDT of BCC, Cottrell et al.³⁵ (Table II) demonstrated that if light is initially delivered at a low fluence rate which generates minimal pain (< 50 mW/cm²), then enough PpIX is destroyed by ~ 3 min (80% reduction by photobleaching) to allow the fluence rate to be subsequently increased to 150 mW/cm² without any further increase in pain. In this way, a large dose of 200 J/cm² can be efficiently delivered while minimizing the discomfort³⁵.

v. Source and Wavelength of Light

An ideal illumination source for PDT should produce light that: (1) is well absorbed by the photosensitizer; (2) achieves a desirable penetration depth; (3) provides an adequate fluence and duration; (4) causes minimal discomfort; (5) produces a good cosmetic outcome³⁶. For most illumination needs, noncoherent sources (lamps) and continuous-mode lasers (defocused to a large spot size) are essentially equivalent. In a study of ALA-PDT for Bowen’s disease (BD), Morton et al. reported a trend towards red light being more painful than green (Table II), although it seemed inconsistent that the only anesthesia required was for two lesions treated by green light³⁷. An earlier study by Fritsch et al. in 1997 (6 patients) had found red light to be more painful than green light¹⁹. For blue light and PDT, published data are limited. Touma et al. conducted a study treating facial AKs with blue light (10 J/

cm²)³⁸; all patients noted mild to moderate discomfort soon after beginning blue light exposure, but no patient asked to discontinue treatment because of pain.

Discontinuous (pulsed) illumination may be beneficial in terms of pain. Babilas et al. 2007 (Table II) reported less pain with a variable pulsed light (VPL) device as compared with a light emitting diode (LED) system in MAL-PDT³⁹. Of interest, the VPL device used a higher light dose (80 J/cm²) than the LED (37 J/cm²), but with a short pulse duration of 5 ms (total pulse time 355 ms) rather than continuous delivery. Other studies, including Wang et al. 2001 for BCC⁴⁰ (Table II), Alexiades-Armenakas et al. 2003 for AK⁴¹ (Table II), and Alexiades-Armenakas et al. 2004 for actinic cheilitis⁴², performed PDT using pulsed lasers at red wavelengths and reported low discomfort levels overall. Comparing continuous laser *versus* incoherent light sources, Babilas et al. 2006 (Table II)^{43, 44} found no significant difference in pain between a LED and an incoherent source, but because the LED delivered only half the irradiance of the halogen source in this study, one could argue that the continuous LED laser was inherently more painful⁴⁴. For psoriasis, pain was very severe regardless of whether a halogen source (Fransson et al. and Schleyer et al.)^{27,28} or laser (Beattie et al.)²⁹ was used (Table II). Finally, a study by Wiegell et al. (Table II) reported that MAL-PDT using daylight, a very low-intensity source, was less painful than a LED and equally effective for the treatment of AK⁴⁵.

Some inconsistencies encountered when trying to interpret studies that compare different light sources may arise because different photosensitizing molecules (other than PpIX) exist in the skin, and these have different absorption spectra. For example, PDT for acne with topically added ALA (or MAL) is very painful when any form of red light is used, whether a long- wavelength laser⁴⁶ or a noncoherent source^{24,25}. This is consistent with the notion that PpIX is the main target responsible for pain. However, for acne treated with blue light, the pain experienced with topical ALA followed by blue light is statistically no different than pain experienced with placebo followed by blue light, suggesting that other endogenous targets (porphyrins made by *P. acnes* in the sebaceous glands, or hemoglobin in microvessels) may be largely responsible for the pain²³.

vi. Temperature

During PDT, light is absorbed not only by PpIX but also by melanin and hemoglobin in the tissue. This leads to a slight temperature increase in the skin, but typically not enough to cause a hyperthermic response⁴⁷. Svaasand et al. showed no hyperthermic effects using fluence rates below 150 mW/cm² at a wavelength of 514 nm⁴⁸. Using fluence rates of 100–150 mW/cm² at 630 nm, Warloe et al. showed that skin surface temperature can rise to 39–40°C⁴⁹. Palsson et al. measured tissue perfusion and the temperature of BCC during ALA-PDT and MAL-PDT and concluded that the increase in tissue temperature was below the limit at which actual tissue damage begins to occur⁴⁷, which is generally 44 °C or higher^{50,51}. However, it should be noted that the capsaicin receptor, also called TRPV1 (also see section III.i.), has an activation threshold of approximately 43°C *in vitro*⁷. An interesting hypothesis is that TRPV1 might be sensitized and activated during ALA-PDT *in vivo* by a combination of inflammation and heat; the TRPV1 activation threshold would be lowered through the action of protein kinase C epsilon (PKC_ε)⁵², inducing heat hyperalgesia through PKC_ε-mediated potentiation of TRPV1^{53,54}. Alternatively, a local drop in pH and the production of endogenous ligands of TRPV1 during the inflammatory process might directly activate the TRPV1 receptor^{55,56}.

III. PAIN MANAGEMENT

Strategies to reduce nerve stimulation and/or tissue damage during PDT have focused upon desensitizing the nerves, blocking nerve depolarization, or trying to minimize PpIX

accumulation in nerve endings. Pain perception is elicited by *nociceptors*, a class of sensory receptors associated with free nerve endings of small myelinated axons (A delta fibers) and unmyelinated axons (C fibers)⁵⁷. During tissue damage, action potentials can be generated at the stump of injured axons. Intact axons can be directly activated by potassium ions or by specific molecules that accumulate during injury such as bradykinin, histamine, serotonin, and prostaglandins (substances contained in mast cells⁵⁸ which can be degranulated directly by photoexcited protoporphyrins)^{59,60}.

GABA receptors in peripheral nerve endings are postulated to transport ALA but not MAL, thereby resulting in more pain with ALA. Rud et al. investigated the mechanisms by which 5-ALA is transported into a human adenocarcinoma cell line (WiDr) and found that 5-ALA, but not the methyl nor hexyl esters of ALA, is transported by beta-amino acid and GABA carriers in this cell line⁶¹. No one has yet tested whether blockers of GABA receptors might be beneficial in reducing pain associated with ALA-PDT.

As of October 2008, a search of 181 trials registered on the website www.clinicaltrials.gov using the keywords "*photodynamic therapy*" and/or "*PDT*" listed only one trial examining PDT-related pain as a primary outcome measure. This was for an agent called IDEA-070 that inhibits cyclooxygenase and lipoxygenase enzymes. Clearly, more research into causation and prevention of PDT-induced pain is needed.

i. Topical Anesthesia

Topical anesthetics target free nerve endings, preventing nerve impulses by limiting sodium ion permeability⁶². To date, most studies have shown no benefit from the use of topical anesthetics for PDT pain. EMLA (Astra Pharmaceuticals, Wayne, Pa) is a eutectic mixture of 2.5% lidocaine and 2.5% prilocaine. A study of 60 patients by Grapengiesser et al.⁴, and a randomized and double blinded trial by Langan et al.⁶³ (Table III) failed to show any benefit for routine use of EMLA in ALA-PDT. In the latter study, cold water spray appeared more effective than any other oral, topical or intradermal anesthetic agent⁶³ (also see item *iii*, below).

Touma et al. used topical 3% lidocaine hydrochloride cream applied 45 minutes prior to light exposure and found that it offered statistically insignificant pain control³⁸. Questions have arisen whether the saturation of the skin with ALA may limit penetration of the topical anesthetic, or whether the pH values of some analgesics may interact with acidic ALA- or MAL-based creams. Holmes et al. (Table III) found no beneficial effect of tetracaine gel applied before ALA-PDT for small lesions of superficial BCC, BD, or AK⁶⁴. Skiveren et al. (Table III) studied topical 0.3% morphine gel during PDT for BCC and AK; the gel was applied following MAL application and removed before illumination, since light absorption of the gel was approximately 50%⁶⁵. Although opioid analgesics are often quite effective under inflammatory conditions, this study showed no benefit of topical morphine for PDT pain⁶⁵.

A particular class of nociceptor, the capsaicin receptor (also known as transient receptor potential cation channel, subfamily V, member 1; vanilloid receptor; TRPV1) may be involved in PDT pain^{7,8}. A pilot study by Sandberg et al. (Table III) investigated the pain relieving effect of capsaicin cream for PDT⁶⁶. A pre-treatment period of one week was used, theoretically allowing enough time for desensitization to substance P and sufficient to demonstrate significant loss of epidermal nerve fibers by immunostaining⁶⁷. However, no statistically significant pain relief was found, and side effects such as burning, stinging, and itching were observed.

In a completely different topical approach, Halldin et al. (Table III) applied electrodes on the shoulders during PDT of the face and scalp to deliver a pulsed current at a frequency of 80 Hz. This transcutaneous nerve stimulation provided a modest but statistically significant reduction in pain scores⁶⁸.

ii. Injected Anesthetics

Anecdotal evidence suggests that anesthetics injected locally can reduce the pain associated with PDT, including 0.5% lignocaine and adrenaline (providing relief for ~1.5 hr), or a longer-acting bupivacaine/adrenaline mixture lasting 2–6 hr³. Berking et al. (Table III) used intraoral mepivacaine injections to help patients tolerate photodynamic ablation of actinic cheilitis⁶⁹. Borelli et al. (Table III) reported that subcutaneous infiltration anesthesia (SIA) is effective for PDT pain, although cheek swelling for 1–3 days may result⁷⁰. Paoli et al. (Table III) performed cranial nerve blocks on one side of the face in patients undergoing MAL-PDT for AK and demonstrated efficient pain reduction on the anesthetized side⁷¹. Thus, SIA or cranial nerve blocks represent potential options for motivated patients who experience intractable PDT-induced discomfort.

iii. Cooling of Treatment Site

Many investigators have now reported that the use of cooling fans or water sprays on the PDT treatment site is very effective at relieving pain. Pagliaro et al. (Table III) investigated cold air anesthesia in ALA-PDT for BCC, finding a lower mean duration of pain compared to the ambient air group⁷². In twenty-one additional studies, some form of local cooling was also offered to the patients^{5111525273038–434663666870717374}. Possible mechanisms for pain reduction include a reduction of tissue metabolism (thus reducing the effects of injury), and vasoconstriction, which would reduce the inflow of inflammatory mediators and thereby decrease edema. It has been shown that topical cold application stimulates myelinated A delta fibers, thus activating inhibitory pain pathways and raising the pain threshold to noxious stimuli⁷⁵. Low temperatures may reduce the optimal activity of TRPV1 (based upon reports of temperature-dependent shifts in voltage-dependent activation curves⁷⁶), thus decreasing its contribution to nociception.

Another strong candidate for involvement in pain-amelioration by cooling is the cold and menthol receptor, also known as TRPM8. Several studies in 2007 identified TRPM8 as a key player in somatosensation and analgesia^{77–79}. Proudfoot et al. used rodent models of neuropathic and inflammatory pain to demonstrate that topical cooling produces a temporary analgesic effect (20–40 minutes) mediated by TRPM8 expressing afferents⁸⁰. Dhaka et al. examined the analgesic effect of cold in TRPM8-null and wild type mice⁷⁹. Whereas wild type mice whose hindpaws had been injected with formalin showed a marked decrease in pain-related behaviors while standing on a cold plate (17 °C), mice lacking the TRPM8 gene maintained their pain-related behaviors (were not able to benefit from cooling). Together, these studies suggest that TRPM8 may be mediating analgesia in the early phases of inflammatory pain.

IV. SUMMARY AND RECOMMENDATIONS

In summary, pain during PDT illumination is a difficult problem. Traditional topical anesthetics simply do not work. Our consensus opinion is that cooling the skin with either ice water or with a high-airflow cooling device (Zimmer MedizinSystems) represents the best topical intervention to control pain during PDT. For rare cases in which cooling simply fails to control the pain, injectable anesthetics (such as a cranial nerve block) can be employed. Improved strategies for relieving pain during ALA-PDT may be discovered through further studies on the mechanisms by which cooling induces analgesia, as well as on

the role of GABA receptors, the cold/ menthol receptor (TRPM8), the capsaicin receptor 1 (TRPV1), and mast cell degranulation products in PDT-induced pain.

Acknowledgments

Funding sources: NIH/NCI grant CA84203

ABBREVIATIONS AND ACRONYMS

AK	actinic keratosis
ALA	aminolevulinic acid
ASIC	acid-sensing ion channel
BCC	basal cell carcinoma
BD	Bowen's disease
LED	light emitting diode
MAL	methyl aminolevulinate
NMSC	nonmelanoma skin cancer
P. acnes	Propionibacterium acnes
PDT	photodynamic therapy
PKC_ε	Protein kinase C epsilon
PpIX	protoporphyrin IX
SIA	subcutaneous infiltration anesthesia
TRPV1	transient receptor potential cation channel, subfamily V, member 1
TRPM8	transient receptor potential cation channel, subfamily M, member 8
VAS	visual analog scale
VPL	variable pulsed light

REFERENCES

1. Hasan, T.; Ortel, B.; Solban, N.; Pogue, B. Photodynamic therapy of cancer. In: Kufe, DBR.; Hait, W., et al., editors. *Cancer Medicine*. 7th edn. Hamilton, Ontario: BC Decker, Inc.; 2006. p. 537-548.
2. Thunell S, Harper P, Brun A. Porphyrins, porphyrin metabolism and porphyrias. IV. Pathophysiology of erythropoietic protoporphyria--diagnosis, care and monitoring of the patient. *Scand J Clin Lab Invest*. 2000; 60:581-604. [PubMed: 11202051]
3. Wennberg AM. Pain, pain relief and other practical issues in photodynamic therapy. *Australas J Dermatol*. 2005; (46 Suppl):S3-S4. discussion S23-5. [PubMed: 15859299]
4. Grapengiesser S, Ericson M, Gudmundsson F, Larko O, Rosen A, Wennberg AM. Pain caused by photodynamic therapy of skin cancer. *Clin Exp Dermatol*. 2002; 27:493-497. [PubMed: 12372093]
5. Clark C, Bryden A, Dawe R, Moseley H, Ferguson J, Ibbotson SH. Topical 5-aminolaevulinic acid photodynamic therapy for cutaneous lesions: outcome and comparison of light sources. *Photodermatol Photoimmunol Photomed*. 2003; 19:134-141. [PubMed: 12914598]
6. Kuijpers DI, Thissen MR, Thissen CA, Neumann MH. Similar effectiveness of methyl aminolevulinate and 5-aminolevulinate in topical photodynamic therapy for nodular basal cell carcinoma. *J Drugs Dermatol*. 2006; 5:642-645. [PubMed: 16865869]

7. Caterina MJ, Schumacher MA, Tominaga M, Rosen TA, Levine JD, Julius D. The capsaicin receptor: a heat-activated ion channel in the pain pathway. *Nature*. 1997; 389:816–824. [PubMed: 9349813]
8. Tominaga M, Caterina MJ, Malmberg AB, Rosen TA, Gilbert H, Skinner K, et al. The cloned capsaicin receptor integrates multiple pain-producing stimuli. *Neuron*. 1998; 21:531–543. [PubMed: 9768840]
9. Waldmann R, Champigny G, Bassilana F, Heurteaux C, Lazdunski M. A proton-gated cation channel involved in acid-sensing. *Nature*. 1997; 386:173–177. [PubMed: 9062189]
10. Kasche A, Luderschmidt S, Ring J, Hein R. Photodynamic therapy induces less pain in patients treated with methyl aminolevulinate compared to aminolevulinic acid. *J Drugs Dermatol*. 2006; 5:353–356. [PubMed: 16673803]
11. Moloney FJ, Collins P. Randomized, double-blind, prospective study to compare topical 5-aminolaevulinic acid methylester with topical 5-aminolaevulinic acid photodynamic therapy for extensive scalp actinic keratosis. *Br J Dermatol*. 2007; 157:87–91. [PubMed: 17501954]
12. Wiegell SR, Stender IM, Na R, Wulf HC. Pain associated with photodynamic therapy using 5-aminolevulinic acid or 5-aminolevulinic acid methylester on tape-stripped normal skin. *Arch Dermatol*. 2003; 139:1173–1177. [PubMed: 12975159]
13. Wiegell SR, Wulf HC. Photodynamic therapy of acne vulgaris using 5-aminolevulinic acid versus methyl aminolevulinate. *J Am Acad Dermatol*. 2006; 54:647–651. [PubMed: 16546587]
14. Juzeniene A, Juzenas P, Ma LW, Iani V, Moan J. Topical application of 5-aminolaevulinic acid, methyl 5-aminolaevulinate and hexyl 5-aminolaevulinate on normal human skin. *Br J Dermatol*. 2006; 155:791–799. [PubMed: 16965430]
15. Wiegell SR, Skiveren J, Philipsen PA, Wulf HC. Pain during photodynamic therapy is associated with protoporphyrin IX fluorescence and fluence rate. *Br J Dermatol*. 2008; 158:727–733. [PubMed: 18284396]
16. Kleinpenning MM, Smits T, Ewalds E, van Erp PE, van de Kerkhof PC, Gerritsen MJ. Heterogeneity of fluorescence in psoriasis after application of 5-aminolaevulinic acid: an immunohistochemical study. *Br J Dermatol*. 2006; 155:539–545. [PubMed: 16911278]
17. Zhou X, Pogue BW, Chen B, Demidenko E, Joshi R, Hoopes J, et al. Pretreatment photosensitizer dosimetry reduces variation in tumor response. *Int J Radiat Oncol Biol Phys*. 2006; 64:1211–1220. [PubMed: 16504761]
18. Radakovic-Fijan S, Blecha-Thalhammer U, Schleyer V, Szeimies RM, Zwingers T, Honigsmann H, et al. Topical aminolaevulinic acid-based photodynamic therapy as a treatment option for psoriasis? Results of a randomized, observer-blinded study. *Br J Dermatol*. 2005; 152:279–283. [PubMed: 15727639]
19. Fritsch C, Stege H, Saalman G, Goerz G, Ruzicka T, Krutmann J. Green light is effective and less painful than red light in photodynamic therapy of facial solar keratoses. *Photodermatol Photoimmunol Photomed*. 1997; 13:181–185. [PubMed: 9542754]
20. Stender IM, Na R, Fogh H, Gluud C, Wulf HC. Photodynamic therapy with 5-aminolaevulinic acid or placebo for recalcitrant foot and hand warts: randomised double-blind trial. *Lancet*. 2000; 355:963–966. [PubMed: 10768434]
21. Wang YS, Tay YK, Kwok C, Tan E. Photodynamic therapy with 20% aminolevulinic acid for the treatment of recalcitrant viral warts in an Asian population. *Int J Dermatol*. 2007; 46:1180–1184. [PubMed: 17988339]
22. Papageorgiou P, Katsambas A, Chu A. Phototherapy with blue (415 nm) and red (660 nm) light in the treatment of acne vulgaris. *Br J Dermatol*. 2000; 142:973–978. [PubMed: 10809858]
23. Akaraphanth R, Kanjanawanitchkul W, Gritiyarangsarn P. Efficacy of ALA-PDT vs blue light in the treatment of acne. *Photodermatol Photoimmunol Photomed*. 2007; 23:186–190. [PubMed: 17803597]
24. Hongcharu W, Taylor CR, Chang Y, Aghassi D, Suthamjariya K, Anderson RR. Topical ALA-photodynamic therapy for the treatment of acne vulgaris. *J Invest Dermatol*. 2000; 115:183–192. [PubMed: 10951234]
25. Wiegell SR, Wulf HC. Photodynamic therapy of acne vulgaris using methyl aminolaevulinate: a blinded, randomized, controlled trial. *Br J Dermatol*. 2006; 154:969–976. [PubMed: 16634903]

26. Horfelt C, Funk J, Frohm-Nilsson M, Wiegleb Edstrom D, Wennberg AM. Topical methyl aminolaevulinate photodynamic therapy for treatment of facial acne vulgaris: results of a randomized, controlled study. *Br J Dermatol*. 2006; 155:608–613. [PubMed: 16911289]
27. Schleyer V, Radakovic-Fijan S, Karrer S, Zwingers T, Tanew A, Landthaler M, et al. Disappointing results and low tolerability of photodynamic therapy with topical 5-aminolaevulinic acid in psoriasis. A randomized, double-blind phase I/II study. *J Eur Acad Dermatol Venereol*. 2006; 20:823–828. [PubMed: 16898905]
28. Fransson J, Ros AM. Clinical and immunohistochemical evaluation of psoriatic plaques treated with topical 5-aminolaevulinic acid photodynamic therapy. *Photodermatol Photoimmunol Photomed*. 2005; 21:326–332. [PubMed: 16313245]
29. Beattie PE, Dawe RS, Ferguson J, Ibbotson SH. Lack of efficacy and tolerability of topical PDT for psoriasis in comparison with narrowband UVB phototherapy. *Clin Exp Dermatol*. 2004; 29:560–562. [PubMed: 15347356]
30. Radakovic-Fijan S, Blecha-Thalhammer U, Kittler H, Honigsmann H, Tanew A. Efficacy of 3 different light doses in the treatment of actinic keratosis with 5-aminolevulinic acid photodynamic therapy: a randomized, observer-blinded, inpatient, comparison study. *J Am Acad Dermatol*. 2005; 53:823–827. [PubMed: 16243131]
31. Horfelt C, Stenquist B, Larko O, Faergemann J, Wennberg AM. Photodynamic therapy for acne vulgaris: a pilot study of the dose-response and mechanism of action. *Acta Derm Venereol*. 2007; 87:325–329. [PubMed: 17598035]
32. Ericson MB, Sandberg C, Stenquist B, Gudmundson F, Karlsson M, Ros AM, et al. Photodynamic therapy of actinic keratosis at varying fluence rates: assessment of photobleaching, pain and primary clinical outcome. *Br J Dermatol*. 2004; 151:1204–1212. [PubMed: 15606516]
33. Salim A, Leman JA, McColl JH, Chapman R, Morton CA. Randomized comparison of photodynamic therapy with topical 5-fluorouracil in Bowen's disease. *Br J Dermatol*. 2003; 148:539–543. [PubMed: 12653747]
34. Piacquadio DJ, Chen DM, Farber HF, Fowler JF Jr, Glazer SD, Goodman JJ, et al. Photodynamic therapy with aminolevulinic acid topical solution and visible blue light in the treatment of multiple actinic keratoses of the face and scalp: investigator-blinded, phase 3, multicenter trials. *Arch Dermatol*. 2004; 140:41–46. [PubMed: 14732659]
35. Cottrell WJ, Paquette AD, Keymel KR, Foster TH, Oseroff AR. Irradiance-dependent photobleaching and pain in delta-aminolevulinic acid-photodynamic therapy of superficial basal cell carcinomas. *Clin Cancer Res*. 2008; 14:4475–4483. [PubMed: 18628462]
36. Alexiades-Armenakas M. Laser-mediated photodynamic therapy. *Clin Dermatol*. 2006; 24:16–25. [PubMed: 16427502]
37. Morton CA, Whitehurst C, Moore JV, MacKie RM. Comparison of red and green light in the treatment of Bowen's disease by photodynamic therapy. *Br J Dermatol*. 2000; 143:767–772. [PubMed: 11069454]
38. Touma D, Yaar M, Whitehead S, Konnikov N, Gilchrist BA. A trial of short incubation, broad-area photodynamic therapy for facial actinic keratoses and diffuse photodamage. *Arch Dermatol*. 2004; 140:33–40. [PubMed: 14732657]
39. Babilas P, Knobler R, Hummel S, Gottschaller C, Maisch T, Koller M, et al. Variable pulsed light is less painful than light-emitting diodes for topical photodynamic therapy of actinic keratosis: a prospective randomized controlled trial. *Br J Dermatol*. 2007; 157:111–117. [PubMed: 17542980]
40. Wang I, Bendsoe N, Klinteberg CA, Enejder AM, Andersson-Engels S, Svanberg S, et al. Photodynamic therapy vs. cryosurgery of basal cell carcinomas: results of a phase III clinical trial. *Br J Dermatol*. 2001; 144:832–840. [PubMed: 11298545]
41. Alexiades-Armenakas MR, Geronemus RG. Laser-mediated photodynamic therapy of actinic keratoses. *Arch Dermatol*. 2003; 139:1313–1320. [PubMed: 14568836]
42. Alexiades-Armenakas MR, Geronemus RG. Laser-mediated photodynamic therapy of actinic cheilitis. *J Drugs Dermatol*. 2004; 3:548–551. [PubMed: 15552607]
43. Babilas P, Travník R, Werner A, Landthaler M, Szeimies RM. Split-face-study using two different light sources for topical PDT of actinic keratoses: non-inferiority of the LED system. *J Dtsch Dermatol Ges*. 2008; 6:25–32. [PubMed: 17995967]

44. Babilas P, Kohl E, Maisch T, Backer H, Gross B, Branzan AL, et al. In vitro and in vivo comparison of two different light sources for topical photodynamic therapy. *Br J Dermatol.* 2006; 154:712–718. [PubMed: 16536815]
45. Wiegell SR, Haedersdal M, Philipsen PA, Eriksen P, Enk CD, Wulf HC. Continuous activation of PpIX by daylight is as effective as and less painful than conventional photodynamic therapy for actinic keratoses a randomized, controlled, single-blinded study. *Br J Dermatol.* 2008; 158:740–746. [PubMed: 18294318]
46. Haedersdal M, Togsverd-Bo K, Wiegell SR, Wulf HC. Long-pulsed dye laser versus long-pulsed dye laser-assisted photodynamic therapy for acne vulgaris: A randomized controlled trial. *J Am Acad Dermatol.* 2008; 58:387–394. [PubMed: 18280335]
47. Palsson S, Gustafsson L, Bendsoe N, Soto Thompson M, Andersson-Engels S, Svanberg K. Kinetics of the superficial perfusion and temperature in connection with photodynamic therapy of basal cell carcinomas using esterified and non-esterified 5-aminolevulinic acid. *Br J Dermatol.* 2003; 148:1179–1188. [PubMed: 12828747]
48. Svaasand LO. Photodynamic and photohyperthermic response of malignant tumors. *Med Phys.* 1985; 12:455–461. [PubMed: 4033592]
49. Warloe, T.; Peng, Q.; Moan, J. *Photodynamic Therapy and Biomedical Lasers.* Amsterdam: Elsevier Science Publishers BV; 1992. Photochemotherapy of multiple basal cell carcinoma with endogenous porphyrins induced by topical application of 5-aminolevulinic acid; p. 449-453.
50. Maytin EV, Wimberly JM, Anderson RR. Thermotolerance and the heat shock response in normal human keratinocytes in culture. *J Invest Dermatol.* 1990; 95:635–642. [PubMed: 2250106]
51. Maytin EV, Wimberly JM, Kane KS. Heat shock modulates UVB-induced cell death in human epidermal keratinocytes: evidence for a hyperthermia-inducible protective response. *J Invest Dermatol.* 1994; 103:547–553. [PubMed: 7930680]
52. Mandadi S, Tominaga T, Numazaki M, Murayama N, Saito N, Armati PJ, et al. Increased sensitivity of desensitized TRPV1 by PMA occurs through PKCepsilon-mediated phosphorylation at S800. *Pain.* 2006; 123:106–116. [PubMed: 16564619]
53. Numazaki M, Tominaga M. Nociception and TRP Channels. *Curr Drug Targets CNS Neurol Disord.* 2004; 3:479–485. [PubMed: 15578965]
54. Zhang H, Cang CL, Kawasaki Y, Liang LL, Zhang YQ, Ji RR, et al. Neurokinin-1 receptor enhances TRPV1 activity in primary sensory neurons via PKCepsilon: a novel pathway for heat hyperalgesia. *J Neurosci.* 2007; 27:12067–12077. [PubMed: 17978048]
55. Olah Z, Karai L, Iadarola MJ. Anandamide activates vanilloid receptor 1 (VR1) at acidic pH in dorsal root ganglia neurons and cells ectopically expressing VR1. *J Biol Chem.* 2001; 276:31163–31170. [PubMed: 11333266]
56. Shin J, Cho H, Hwang SW, Jung J, Shin CY, Lee SY, et al. Bradykinin-12-lipoxygenase-VR1 signaling pathway for inflammatory hyperalgesia. *Proc Natl Acad Sci U S A.* 2002; 99:10150–10155. [PubMed: 12097645]
57. Siddall PJ, Cousins MJ. Neurobiology of pain. *Int Anesthesiol Clin.* 1997; 35:1–26. [PubMed: 9246579]
58. Metcalfe DD, Baram D, Mekori YA. Mast cells. *Physiol Rev.* 1997; 77:1033–1079. [PubMed: 9354811]
59. Glover RA, Bailey CS, Barrett KE, Wasserman SI, Gigli I. Histamine release from rodent and human mast cells induced by protoporphyrin and ultraviolet light: studies of the mechanism of mast-cell activation in erythropoietic protoporphyria. *Br J Dermatol.* 1990; 122:501–512. [PubMed: 2337518]
60. Lim HW, Gigli I, Wasserman SI. Differential effects of protoporphyrin and uroporphyrin on murine mast cells. *J Invest Dermatol.* 1987; 88:281–286. [PubMed: 3102621]
61. Rud E, Gederaas O, Hogset A, Berg K. 5-aminolevulinic acid, but not 5-aminolevulinic acid esters, is transported into adenocarcinoma cells by system BETA transporters. *Photochem Photobiol.* 2000; 71:640–647. [PubMed: 10818796]
62. Huang W, Vidimos A. Topical anesthetics in dermatology. *J Am Acad Dermatol.* 2000; 43:286–298. [PubMed: 10906653]

63. Langan SM, Collins P. Randomized, double-blind, placebo-controlled prospective study of the efficacy of topical anaesthesia with a eutetic mixture of lignocaine 2.5% and prilocaine 2.5% for topical 5-aminolaevulinic acid-photodynamic therapy for extensive scalp actinic keratoses. *Br J Dermatol.* 2006; 154:146–149. [PubMed: 16403108]
64. Holmes MV, Dawe RS, Ferguson J, Ibbotson SH. A randomized, double-blind, placebo-controlled study of the efficacy of tetracaine gel (Ametop) for pain relief during topical photodynamic therapy. *Br J Dermatol.* 2004; 150:337–340. [PubMed: 14996106]
65. Skiveren J, Haedersdal M, Philipsen PA, Wiegell SR, Wulf HC. Morphine gel 0.3% does not relieve pain during topical photodynamic therapy: a randomized, double-blind, placebo- controlled study. *Acta Derm Venereol.* 2006; 86:409–411. [PubMed: 16955184]
66. Sandberg C, Stenquist B, Rosdahl I, Ros AM, Synnerstad I, Karlsson M, et al. Important factors for pain during photodynamic therapy for actinic keratosis. *Acta Derm Venereol.* 2006; 86:404–408. [PubMed: 16955183]
67. Nolano M, Simone DA, Wendelschafer-Crabb G, Johnson T, Hazen E, Kennedy WR. Topical capsaicin in humans: parallel loss of epidermal nerve fibers and pain sensation. *Pain.* 1999; 81:135–145. [PubMed: 10353501]
68. Halldin CB, Paoli J, Sandberg C, Ericson MB, Wennberg AM. Transcutaneous electrical nerve stimulation for pain relief during photodynamic therapy of actinic keratoses. *Acta Derm Venereol.* 2008; 88:311–313. [PubMed: 18480950]
69. Berking C, Herzinger T, Flaig MJ, Brenner M, Borelli C, Degitz K. The efficacy of photodynamic therapy in actinic cheilitis of the lower lip: a prospective study of 15 patients. *Dermatol Surg.* 2007; 33:825–830. [PubMed: 17598848]
70. Borelli C, Herzinger T, Merk K, Berking C, Kunte C, Plewig G, et al. Effect of subcutaneous infiltration anesthesia on pain in photodynamic therapy: a controlled open pilot trial. *Dermatol Surg.* 2007; 33:314–318. [PubMed: 17338689]
71. Paoli J, Halldin C, Ericson MB, Wennberg AM. Nerve blocks provide effective pain relief during topical photodynamic therapy for extensive facial actinic keratoses. *Clin Exp Dermatol.* 2008; 33:559–564. [PubMed: 18801096]
72. Pagliaro J, Elliott T, Bulsara M, King C, Vinciullo C. Cold air analgesia in photodynamic therapy of basal cell carcinomas and Bowen's disease: an effective addition to treatment: a pilot study. *Dermatol Surg.* 2004; 30:63–66. [PubMed: 14692930]
73. Stender IM, Borghjerg FM, Villumsen J, Lock-Andersen J, Wulf HC. Pain induced by photodynamic therapy of warts. *Photodermatol Photoimmunol Photomed.* 2006; 22:304–309. [PubMed: 17100738]
74. Goldman MP, Merial-Kieny C, Nocera T, Mery S. Comparative benefit of two thermal spring waters after photodynamic therapy procedure. *J Cosmet Dermatol.* 2007; 6:31–35. [PubMed: 17348993]
75. Leff DR, Nortley M, Dang V, Bhutiani RP. The effect of local cooling on pain perception during infiltration of local anaesthetic agents, a prospective randomised controlled trial. *Anaesthesia.* 2007; 62:677–682. [PubMed: 17567343]
76. Voets T, Droogmans G, Wissenbach U, Janssens A, Flockerzi V, Nilius B. The principle of temperature-dependent gating in cold- and heat-sensitive TRP channels. *Nature.* 2004; 430:748–754. [PubMed: 15306801]
77. Bautista DM, Siemens J, Glazer JM, Tsuruda PR, Basbaum AI, Stucky CL, et al. The menthol receptor TRPM8 is the principal detector of environmental cold. *Nature.* 2007; 448:204–208. [PubMed: 17538622]
78. Colburn RW, Lubin ML, Stone DJ Jr, Wang Y, Lawrence D, D'Andrea MR, et al. Attenuated cold sensitivity in TRPM8 null mice. *Neuron.* 2007; 54:379–386. [PubMed: 17481392]
79. Dhaka A, Murray AN, Mathur J, Earley TJ, Petrus MJ, Patapoutian A. TRPM8 is required for cold sensation in mice. *Neuron.* 2007; 54:371–378. [PubMed: 17481391]
80. Proudfoot CJ, Garry EM, Cottrell DF, Rosie R, Anderson H, Robertson DC, et al. Analgesia mediated by the TRPM8 cold receptor in chronic neuropathic pain. *Curr Biol.* 2006; 16:1591–1605. [PubMed: 16920620]

CAPSULE SUMMARY

- Pain experienced during photodynamic therapy (PDT) with aminolevulinic acid can be very unpleasant for patients.
- This review summarizes current knowledge about this problem, discussing pain intensity as a function of light source, wavelength, fluence rate, and type of lesion.
- In general, topical anesthetics are ineffective. Cooling represents the best option.
- Pain receptors, including TRPV1 and the cold/menthol receptor TRPM8, may be involved in the mechanism behind pain relief with cooling techniques.

TABLE I

Effect of photosensitizing agent (ALA vs. MAL) upon pain

Ref	Dx (No. of patients) ^a	PS ^b	Dur ^c (hr)	Location	Light source ^e	Dose rate, mW/cm ²	Dose, J/cm ²	Differences in pain between the agents
Kasche 2006 ¹⁰	AK (69)	ALA; MAL	6 (3) ^d	Scalp	Red	160	100	More patients with ALA stopped treatment.
Moloney 2007 ¹¹	AK (16)	ALA; MAL	5 (3) ^d	Scalp	Red	50	50	Greater with ALA than with MAL.
Kuijpers 2006 ⁶	nBCC (39)	ALA; MAL	3 3	Various locations	Red	100	75	No difference.
Wiegell 2003 ¹²	NL-Sun (20)	ALA; MAL	3 3	Forearm	Red	90	70	Greater with ALA than with MAL.
Wiegell & Wulf 2006 ¹³	Acne (15)	ALA; MAL	3 3	Face	Red	34	37	Similar for ALA and MAL. More side effects with ALA.

^aDiagnoses, (number of patients in study). AK, Actinic keratosis; nBCC, nodular basal cell carcinoma; sBCC, superficial basal cell carcinoma; NL-sun; normal sun-damaged skin, tape-stripped; Acne, acne vulgaris.

^bPS, photosensitizer; (20% ALA, or 16% MAL).

^cDur, duration of topical application.

^dIn Kasche 2006¹⁰ and Moloney 2007¹¹ duration of application for ALA was 5 hr or 6 hr, and for MAL was 3 hr.

^eAll of these studies used incoherent red light sources, wavelength approximately 580–740 nm. Most used the broadband Waldmann PDT 1200 halogen source, except Wiegell & Wulf 2006¹³ which used a narrowband LED source (Aklite CL128, Photocure).

TABLE II

Effects of light dose (fluence), dose rate (fluence rate), and wavelength upon pain

Ref	Dx (No. of patients)	PS	Dur, (hr)	Location	Light source <i>a-m</i>	Dose rate, mW/cm ²	Dose, J/cm ²	Differences in pain between the conditions
VARIED DOSE, CONSTANT DOSE RATE								
Radakovic-Fijan 2005 ³⁰	AK (27)	ALA	4	Scalp, Face	Red, halogen-1 ^a	100 100 100	70 100 140	Trend toward positive correlation between pain and light dose.
Radakovic-Fijan 2005 ¹⁸	Psoriasis (29)	ALA	4-6	Trunk, Arms, Legs	Red, halogen-1 ^a	60 60 60	5 10 20	Pain was dose dependent. 1 patient stopped treatment. 8 patients interrupted treatment.
Horfelt 2007 ³¹	Acne (15)	ALA	3	Face, Back	Red, halogen-1 ^a	50 50 50	30 50 70	Greater with higher doses.
CONSTANT DOSE, VARIED DOSE RATE								
Ericson 2004 ³²	AK (37)	ALA	3	Head, Neck, Chest	Red, sodium, narrowband filter ^g Red, sodium, broadband filter ^g	30 45 50 75	100 100 100 100	No correlation with fluence rate. However, pain was most intense during illumination, up to a cumulative dose of 20 J/cm ² , then it leveled off.
Clark 2003 ⁵	Bowens; sBCC; AK; warts (207)	ALA	4-6	Various locations	Red, xenon ^f Red, halogen-1 ^a Red, halogen-2 ^b Red, laser ^e	20-25 80-90 70-150 120-150	150 125 125 125	Stinging quality, worse if ulcerated. Maximal during first few min of treatment. Less with low-irradiance xenon arc. Severe with halogen and diode laser.
Wiegell 2008 ¹⁵	Acne (34) AK (26)	MAL	3	Face; Various locations	Red, LED-2 ^d	34 68	37 37	Pain scores during illumination correlated with PpIX concentration in skin. Pain was less with lower fluence rate, even after correction for the amount of PpIX.
Cottrell 2008 ³⁵	BCC (26)	ALA	4	Various locations	Red, laser ^j	10-50 for ~ 3 min, then 150	200	Intensity was increased stepwise, to find the dose rate at which pain exceeded a preset threshold (see text).
WAVELENGTH EFFECTS (LASER AND NONCOHERENT LIGHT):								
Morton 2000 ³⁷	Bowen's (16)	ALA	4	Legs	540 nm (green) ^h 630 nm (red) ^h	86 86	62.5 125	Red slightly more painful than green (trend only).
Babilas 2007 ³⁹	AK (25)	MAL	3	Split-face comparison	Red laser, LED ^d Red, VPL ^k	50 50	37 80 ^j	Pain lower with VPL (pulsed light). Patients needed cooling with LED, but not with VPL.
Wang 2001 ⁴⁰	BCC (88)	ALA	6	Various locations	Red, laser (pulsed) ^L	80	60	Pain tolerated without anesthesia, not noticeably different than with cryotherapy

Ref	Dx (No. of patients)	PS	Dur, (hr)	Location	Light source ^{a-m}	Dose rate, mW/cm ²	Dose, J/cm ²	Differences in pain between the conditions
Alexiades-Armenakas 2003 ⁴¹	AK (41)	ALA	3; 14	Various locations	Red, laser (pulsed) ^m	---	4-7.5	Pain during laser treatment scored as none (50% of patients), slight (36%), mild (8%), moderate (3%), severe (3%).
Babilas 2006 ⁴⁴ 2008 ⁴³	AK (40)	ALA	4	Not given	Red, LED-1 ^c Red, halogen-1 ^a	80 160	40 100	No difference between laser and incoherent light sources or between light doses.
Fransson 2005 ²⁸	Psoriasis (12)	ALA	4-5	Back, Arms, Legs	Red, halogen-1 ^a	20-315	10-30	4 patients stopped treatment. 30 J/cm ² very painful.
Schleyer 2006 ²⁷	Psoriasis (12)	ALA	4-6	Trunk, Arms, Legs	Red, halogen-1 ^a	60	20	Very painful. No difference between the concentrations of ALA (0.1, 1, 5%).
Beattie 2004 ²⁹	Psoriasis (10; only 4 completed)	ALA	4	Trunk, Arms, Legs	Red, laser ^e	120	10	Pain significant. Trial stopped early.
Wiegell 2008 ⁴⁵	AK (29)	MAL	0.5 ^g 3	Face, Scalp	Daylight, 2-5 hr Red, LED-2-1 ^d	6 50	43 37	Greater with LED. Two patients discontinued treatment in LED group.

The light sources (wavelength ranges) used in these studies were as follows:

^aRed, halogen-1; broadband metal halide lamp, PDT 1200, Waldmann, Medizintechnik, Germany (~600–740 nm)

^bRed, halogen-2; broadband metal halide lamp, Curelight 150, Photocure (570–680 nm)

^cRed, LED-1; light-emitting diode, Omnilux, Waldmann (633 ± 20 nm)

^dRed, LED-2; light-emitting diode, Akti-lite CL128, Photocure (630 ± 5 nm)

^eRed, laser; diode laser, Diomed Inc. (630 ± 3 nm)

^fRed, xenon; broadband xenon arc lamp, noncommercial

^gRed, sodium; broadband sodium lamp, PhotoDemarcation System 1, Prototype 5, Meditek, Gothenberg, Sweden

^hGreen or Red, xenon arc lamp, Phototherapeutics, Ltd, U.K. with appropriate filters

ⁱRed, laser; Argon-pumped dye laser filtered to provide 633 nm

^kRed, variable pulsed light (VPL); Energist Ltd., Swansea, U.K. (610–950 nm). Pulse train of 15 impulses, 5 ms duration each. Fluence: 40 J/cm² (double-pulsed); therefore, total dose delivered was 80 J/cm².

^LRed, pulsed laser; A frequency doubled Nd:YAG laser pumping a dye laser (Multilase Dye, Technomed International, France); laser tuned to a wavelength of 635 nm and operated in a quasicontinuous mode with a repetition rate of 5 kHz and a pulse width of 100 ns.

\$watermark-text

\$watermark-text

\$watermark-text

^mRed, pulsed laser; V-beam 595 nm (Candela Laser Corporation, Wayland, Mass, USA) at 4–7.5 J/cm² fluence, pulse duration 10 ms, 10 mm spot size, with a 30 msec cryogen spray followed by 30 ms delay prior to each laser pulse; 1 to 4 pulses.

* In Wiegeil 2008 ⁴⁵, the MAL was applied for 0.5 hr for the daylight patients and 3 hr for the LED patients.

TABLE III

Effectiveness of different methods for analgesia during PDT

Ref	Method to alleviate pain	Dx (No. of patients)	PS	Dur (hr)	Location	Light source ^{a-e}	Pain reported
Grapengiesser 2002 ⁴	EMLA 1 hr	BCC, AK, Bowens (60)	ALA	4	Various locations	Red, halogen ^b	No benefit with EMLA.
Langan 2006 ⁶³	EMLA 2 hr	AK (14)	AK (14)	4	Scalp	Red, halogen ^b	No difference with EMLA. No difference in oral analgesia needed. No patients stopped treatment.
Touma 2004 ³⁸	Lidocaine 3% cream	AK (19)	AK (19)	1–3	Face	Blue, fluore ^e	No benefit with lidocaine.
Holmes 2004 ⁶⁴	Tetracaine 4% gel 1 hr after ALA	sBCC, AK (42)	ALA	3–5	Legs	Red, halogen ^b Red, laser ^c	No decrease with tetracaine. No difference with lesion type.
Skiveren 2006 ⁶⁵	Morphine 0.3% gel after MAL, 15 min before light	AK, BCC (28)	MAL	3	Not provided	Red, LED ^a	No difference with morphine. 4 patients interrupted treatment.
Sandberg 2006 ⁶⁶	Capsaicin 0.075%, applied 3–5 times daily for 1 week pre-PDT	AK (91)	ALA	3	Head, Chest	Red, sodium ^d	No relief. Worse with larger lesions. Adverse events: erythema and burning.
Halldin, 2008 ⁶⁸	Transcutaneous electrical nerve stimulation (TENS)	AK (14)	MAL	3	Face, scalp	Red, LED ^a	Mean pain score (scale of 0–10) was 8.1 ± 0.3 without TENS; reduced to 6.2 ± 0.4 with TENS.
Berking 2007 ⁶⁹	Intraoral injections at site: 1% mepivacaine (5–15 mL)	Actinic cheilitis (15)	MAL	3	Lower lip	Red, LED ^a	With anesthesia, mean pain score was ~4 (on scale of 0–10); clinical response reportedly good.
Borelli 2007 ⁷⁰	Subcutaneous infiltration anesthesia (SIA) with a cocktail of ropivacaine, prilocaine, and epinephrine.	AK (16)	ALA	5	Face	Red, halogen ^b	Pain reduced with SIA, compared to oral analgesics alone. Acute side effect: cheek swelling that resolved in 3 days.
Paoli 2008 ⁷¹	Subcutaneous cranial nerve block with mepivacaine-adrenaline; half-face study	AK (16)	MAL	3	Face	Red, LED ^a	Significantly reduced on the side of the nerve block; authors claim good patient satisfaction.
Pagliari 2004 ⁷²	Cold air analgesia (CAG) [*]	sBCC, Bowen's (26)	ALA	4	Various locations	Red, LED ^a	Pain during treatment, and pain duration after treatment, were less with CAG.

The light sources (wavelength ranges) used in these studies were as follows:

^aRed, LED; light-emitting diode, Aktelite CL128, Photocure (630 ± 5 nm)

\$watermark-text

\$watermark-text

\$watermark-text

- ^bRed, halogen; broadband metal halide lamp, PDT 1200, Waldmann, Medizintechnik, Germany (~600–740 nm)
- ^cRed, laser; diode laser, Diomed Inc. (630 ± 3 nm)
- ^dRed, sodium; broadband sodium lamp, PhotoDemarcation System 1, Prototype 5, Medelkonos, Gothenberg, Sweden
- ^eBlue, Blu-U fluorescent lamp, DUSA Pharmaceuticals, USA (417 ± 5 nm)
- * **CAG (cold air or cooling water)** was also used in 21 additional studies (see text).