Dermatologic Applications of Photodynamic Therapy

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DESCRIPTION

Photodynamic therapy (PDT) refers to light activation of a drug that acts as a photosensitizer to destroy the target tissue. Photosensitizing agents have been used in non-dermatologic applications and are being proposed for use with dermatologic conditions such as actinic keratosis, disseminated superficial actinic porokeratosis (DSAP), non-melanoma skin cancers (basal cell carcinoma or squamous cell carcinoma in situ [Bowen's disease]), acne vulgaris, mycoses, port wine stains and hidradenitis suppurativa.

Photodynamic therapy (PDT) is a two-step process and typically involves two office visits spaced a week apart. More than one treatment series may be required. In step-one the medication is topically applied to the affected tissue and allowed to absorb for a set period of time. The drug accumulates and is retained in dysplastic cells of the skin to a greater degree than normal tissue (i.e., the drug has a greater affinity for dysplastic cells).

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In step two, the affected skin tissue is exposed to the light source (blue or red). The photoactivation (maximum absorption of 404 to 420 nm and 635 nm) of the drug creates a cytotoxic reaction within the cells that destroys the lesion(s). The cytotoxic effect is dependent on light and oxygen. Two common photosensitizing agents are 5-aminolevulinac acid (5-ALA) and methyl aminolevulinate (MAL). PDT can cause erythema, burning, and pain. Healing occurs within 10 to 14 days, with generally acceptable cosmetic results.

Acne
Acne is a common skin condition that occurs when hair follicles become plugged with oil and dead skin cells. It often causes whiteheads, blackheads, or pimples, and usually appears on the face, forehead, chest, upper back and shoulders. Acne is most common among teenagers, though it affects people of all ages, and there is a significant demand for effective acne therapies.

Clinical Context and Therapy Purpose
The purpose of photodynamic therapy (PDT) is to provide a treatment option that is an alternative to or an improvement on existing therapies in patients with acne.

Patients
The relevant population of interest are individuals with acne.

Interventions
The therapy being considered is photodynamic therapy (PDT).

Photodynamic therapy (PDT) has been investigated for a treatment of acne. Photodynamic therapy involves the application of photosensitizing agent such as aminolevulinic acid (ALA) or methyl aminolevulinic acid (MAL) prior to exposure to a blue or red light.

Comparators
The following therapies are currently being used to treat acne: pharmacologic therapy and laser or light therapy.

Outcomes
The general outcomes of interest are symptoms, changes in disease status, quality of life (QOL) and treatment related morbidity.

The duration of follow-up would be based on the extent of acne lesions and 4, 8 and 12 weeks.

Randomized Controlled Trials for Acne
(2021) Wojewoda et al. performed a double-blind RCT comparing MAL-PDT with placebo in patients with facial acne.37, The trial randomized 36 patients to MAL-PDT or placebo, each given in either 2 or 4 treatments. After 20 weeks, the number of

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inflammatory lesions decreased by 74% and 85% with 2 and 4 treatments of MAL-PDT, respectively. However, there were no significant differences in relative change of inflammatory or non-inflammatory lesions in comparisons with the placebo group. No severe adverse effects were reported in either group. Trial limitations included a high rate of attrition and small sample size.

(2018) Nicklas et al. conducted a randomized controlled trial (RCT) comparing the efficacy of aminolaevulinic acid photodynamic therapy (PDT) versus adapalene gel plus oral doxycycline for treatment of moderate acne vulgaris-A. Fourty-six patients with moderate inflammatory facial acne, 23 patients received two sessions of PDT separated by 2 weeks (ALA 20% incubated 1.5 hours before red light irradiation with 37 J/cm^2 fluence) and 23 patients received doxycycline 100 mg/d plus adapalene gel 0.1%. In both groups, from the sixth week, we started adapalene gel 0.1% as maintenance therapy until 12 weeks of follow-up. Primary end point was the reduction of acne lesions at the 6-week follow-up, which was evaluated by 2 investigators blinded to the intervention. The median percent reductions in noninflammatory lesion count (P = 0.013) and total lesions (P = 0.038) at 6 weeks was found to be significantly higher in the group receiving PDT. At 12 weeks there was a greater reduction of inflammatory lesions in PDT group with 84% vs. 74% for group who received doxycycline plus adapalene (P = 0.020) as well as in reducing total lesions with 79% vs. 67% respectively (P = 0.026). No severe side-effects were observed for either therapy. Trial limitations included a small sample size and a short follow-up.

(2017) Xu et al. investigated the effectiveness of photodynamic therapy combined with minocycline in moderate to severe facial acne and influence on quality of life. Ninety-five patients with moderate to severe facial acne (Investigator Global Assessment [IGA] score 3-4) were randomly treated with photodynamic therapy (PDT) and minocycline (n=48) or minocycline alone (n=47). All patients took minocycline hydrochloride 100 mg/d for 4 weeks, whereas patients in the minocycline plus PDT group also received 4 times PDT treatment 1 week apart. IGA score, lesion counts, Dermatology Life Quality Index (DLQI), and safety evaluation were performed before treatment and at 2, 4, 6, and 8 weeks after enrollment. There were no statistically significant differences in characteristics between 2 treatment groups at baseline. Minocycline plus PDT treatment led to a greater mean percentage reduction from baseline in lesion counts versus minocycline alone at 8 weeks for both inflammatory (-74.4% vs -53.3%; P<.001) and non-inflammatory lesions (-61.7% vs -42.4%; P<.001). More patients treated with minocycline plus PDT achieved IGA score <2 at study end (week 8: 30/48 vs 20/47; P<.05). Patients treated with minocycline plus PDT got significant lower DLQI at 8 weeks (4.4 vs 6.3; P<.001). Adverse events were mild and manageable. Trial limitations included a short follow-up and lack of broad consensus on quantitative of acne severity.

(2016) Pariser et al. published a multicenter double-blind placebo-controlled, randomized trial evaluating MAL-PDT for severe facial acne. A total of 153 patients were randomized and included in the intention-to-treat analysis, 100 to MAL-PDT and 53 to a matching vehicle (i.e., placebo) cream. All patients received 4 treatments, 2 weeks apart

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and were evaluated up to 12 weeks after the first treatment. One hundred twenty-nine (84%) patients completed the trial. The primary outcome (change from baseline in facial inflammatory lesion count at 12 weeks) was significantly lower in the MAL-PDT group (mean, -15.6) than the placebo group (mean, -7.8; p=0.006). Change in facial non-inflammatory lesion count at 12 weeks did not differ significantly between groups (-11.8 vs -10.7; p=0.85). The most commonly reported adverse events were pain (n=17 [17%] in the MAL-PDT group vs 0 in the placebo group) and a skin burning cessation (n=15 [15%] in the PDT group vs 5 [9%] in the placebo group). Most adverse events were mild-to-moderate, although 12 patients in the MAL-PDT group dropped out due to treatment-related adverse events. The authors concluded, this large controlled randomized clinical study shows potential of PDT using 80 mg/g MAL cream and red light for treatment of severe acne in patients aged 12 years and older, with all skin types. They noted that more follow-up data is needed on the duration of treatment response and longer-term effect on scarring.

(2010) A randomized, single-blind, split-faced trial was published by Orringer et al. The trial included 44 patients with facial acne. A randomly selected side of the face received ALA-PDT and the other side went untreated and severed as a control. Patients received up to 3 treatments at intervals of approximately 2 weeks. Twenty-nine (66%) patients completed the 16-week study. For most outcomes, there were no statistically significant differences between treated and untreated sides of the face. This included change from baseline to 16 weeks in the mean number of inflammatory papules, pustules, cysts, closed comedones, or open comedones. There was a significantly greater reduction in erythematous macules on the treated (mean reduction, 5.9) than the untreated side of the face (mean reduction, 2.5; p=0.04). In addition, improvement in mean Leed's Acne Severity Grading score was significantly greater on the treated side (-1.07) than on the untreated side of the face (-0.52; p=0.001). There were few adverse events, which tended to be mild. A trial limitation was the high dropout rate. The authors concluded the results suggest that, with a specific treatment protocol employed in this study, results with respect to acne improvement can be expected to be rather modest and inconsistent. However, the fact that some patients did improve with the current regimen allows for the possibility that future work examining dose response curves, optimization of light source, definition of ideal photosensitizer application times and conditions, and number of other variables might one day make PDT for acne an important therapeutic tool.

Systematic Reviews for Acne

(2021) A systematic review by Wu et al. performed a meta-analysis using data from 13 RCTs (N=422) that compared red light PDT with placebo, pharmacotherapy, or other sources of light in the treatment of acne. For the outcome of inflammatory lesions, red light did not differ significantly at any point in time up to 12 weeks compared with other conventional treatment methods (weighted mean difference, 0.701; 95% CI, −0.809 to 2.212). Similar results were reported for the outcome of non-inflammatory lesions (weighted mean difference, -0.527; 95% CI, -3.055 to 2.001). Most domains of study quality were assessed as low or unclear risk of bias. The authors concluded that further study is needed comparing red light PDT with traditional therapies.

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(2016) A Cochrane review by Barbaric et al. addressed a variety of light therapies for acne, including photodynamic therapy (PDT). For studies on MAL-PDT, only data on investigator-assessed change in lesion counts were suitable for pooling. A meta-analysis of 3 studies on MAL-PDT did not find a significant difference from placebo on investigator-assessed change in inflamed lesion counts (mean difference [MD], -2.85; 95% CI, -7.51 to 1.81) or change in non-inflamed lesion counts (MD = -2.01; 95% CI, -7.07 to 3.05). Reviewers concluded that there is a lack of high-quality evidence on light therapies for treating acne and a low certainty in the usefulness of PDT.

Section Summary: Acne
Several randomized controlled trials (RCTs) and a Cochrane review have evaluated photodynamic therapy (PDT) for treatment of acne. The review did not conduct meta-analyses on most outcomes. For the pooled analysis of studies comparing MAL-PDT and placebo, reviewers did not find a significant difference in investigator assessment of lesion change. The available RCTs have not consistently found significantly better outcomes with PDT than with comparator interventions. Several trials found that PDT was associated with high rates of adverse events leading to the cessation of treatment. Trials tended to have relatively small sample sizes and used a variety of comparison interventions. The 2016 American Academy of Dermatology guideline for the management of acne vulgaris states the following: "Of all laser and light devices, the most evidence exists for PDT in treating acne. With PDT, a photosensitizer, such as aminolevulinic acid, is first applied to the affected skin for a period of time (varying from 15 minutes to 3 hours). The photosensitizer is then absorbed into the pilosebaceous units and is preferentially taken up by sebocytes. A laser or light device is then used to activate the photosensitizer, generating singlet oxygen species, and thereby damaging the sebaceous glands and reducing P acnes. This treatment shows great promise, but additional studies are needed to determine the optimal photosensitizer, incubation time, and light source."

Actinic Keratosis

Clinical Context and Therapy Purpose
The purpose of photodynamic therapy (PDT) is to provide a treatment option that is an alternative to or an improvement on existing therapies in patients with nonhyperkeratotic actinic keratosis (AKs) on the face, scalp, or upper extremities.

Patients
The relevant population of interest are individuals with nonhyperkeratotic actinic keratosis (AKs) on the face, scalp, or upper extremities.

Actinic keratosis are rough, scaly, warty premalignant growths on the sun-exposed skin that are very common in older people with fair complexions, with a prevalence of greater than 80% in fair skinned people older than 60 years of age. In some cases, actinic keratosis may progress to squamous cell carcinoma (SCC).

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Interventions
The therapy being considered is photodynamic therapy.

Comparators
The available treatments for actinic keratosis can generally be divided into surgical and non-surgical methods. Surgical treatments used to treat one or a small number of dispersed individual lesions include excision, curettage (either alone or combined with electrodessication), and laser surgery. Non-surgical treatments include cryotherapy, topical chemotherapy (5-fluorouracil [5-FU] or masoprocol creams), chemexfoliation (also known as chemical peels), dermabrasion and photodynamic therapy (PDT). PDT with topical ALA has been investigated primarily as a treatment of actinic keratosis. Topical treatments are generally used in patients with multiple lesions and the involvement of extensive areas of the skin. Under some circumstances, combinations of different treatment methods may be used.

Outcomes
The general outcomes of interest are symptoms, change in disease status, quality of life (QOL) and treatment related morbidity.

The duration of follow-up is related to the extent of treated disease and is expected to be at least 12 months.

Randomized Controlled Trials Actinic Keratosis on Face and Scalp
(2021) Cortelazzi et al. reported results of an RCT evaluating the effect of imiquimod 3.75% versus MAL-PDT in patients with AK of the scalp. Nine bald male patients were randomized to receive a single session of treatment on either the right or left side of the scalp and were assessed at up to 12 months of follow-up. By degree of AK, rates of clearance for imiquimod versus MAL-PDT were 68.8% and 48.0% for degree I, 64.5% and 69.8% for degree II, and 75% and 66.7% for degree III, respectively.

(2021) Karrer et al. reported findings from an RCT comparing MAL-PDT with cryosurgery in 58 patients with AK of the face. Patients received either 5 full-face treatments with MAL-PDT or a single freeze-thaw cryosurgery cycle, followed by additional intervention in the case of non-cleared or newly developed AK. At 24 months of follow-up, the primary outcome, the cumulative number of new AKs after visit 1, was not significantly different between MAL-PDT and cryosurgery (mean difference, -2.5; 95% CI, -6.2 to 1.2). Overall, complete clearance of AKs was significantly greater with MAL-PDT (mean difference, 43.5%; 95% CI, -12.5 to 39.3); however, no differences were detected in grade I or II lesions.

(Updated 2020: Literature Review 2021) According to an UpToDate review on Photodynamic Therapy by Maytin et al for actinic keratosis – In an earlier phase III trial of 20% aminolevulinic acid (ALA) solution incubated for 14 to 18 hours without occlusion in conjunction with blue light, 73 percent of subjects had 100 percent AK

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clearance at 12 weeks. Shorter incubation times are used in clinical practice, based upon a series of studies showing similar efficacy despite this modification [9,18,19]. In the European phase III trial of 10% ALA nanoemulsion gel incubated for three hours after removal of scales/crusts and occlusion, in conjunction with red light, 91 percent of subjects had 100 percent AK clearance at 12 weeks. The efficacy of PDT for the treatment of AK has been confirmed by multiple randomized trials and two meta-analyses (2017) Yazdanyar et al. published results from a clinical trial on pain during topical PDT, which compared MAL (Metvix) with 5-ALA (Ameluz). Patients with mild-to-moderate actinic keratosis on forehead and scalp were treated with MAL-PDT and ALA-PDT on 2 similar areas of forehead and scalp. Fourteen patients completed the MAL-PDT and ALA-PDT treatments. The pattern of pain intensity was similar for both groups. Both treatments were painful, which gradually intensified during the first minute of treatment, reaching a maximum within the first 5 minutes. The pain eased immediately after the PDT treatment. The authors reported no significant difference in pain intensity between MAL-PDT and ALA- PDT, during the treatment ($p=1.0$) and 30 minutes after the treatment ($p=0.19$). Pain was the only outcome reported in this trial. The authors concluded no significant difference between the pain response during PDT using MAL-PDT and ALA-PDT.

(2016) Reinhold et al. published results from a double-blind RTC comparing BF-200 ALA with placebo for the field-directed treatment of mild-to-moderate actinic keratosis with PDT using the BF-RhodoLED lamp. After a maximum of 2 PDT treatments the results, measured 12 weeks after the last PDT, showed a patient complete clearance rate of 91% using BF-200 ALA vs 22% using placebo ($p<0.001$), and a lesion complete clearance rate of 94.3% using BF-200 ALA vs 32.9% using placebo ($p<0.001$). There were treatment adverse events in 100% of the BF-200 ALA group and in 69% of the placebo group. The adverse events were application-site events and included site pain, erythema, pruritus, scab, exfoliation, edema, and vesicles. Local skin reactions were of a mild-to-moderate intensity. Application-site pain was the most common individual adverse event in both groups (96.4% for BF-200 ALA vs 50.0% for placebo) and was rated as severe by 49% of the BF-200 ALA group and 3% of the patients treated with placebo. One of 32 patients in the placebo group and no patients in the BF-200 ALA group displayed a new lesion after PDT. The authors concluded that field directed therapy with BF-200 ALA and BF-RhodoLED lamp is highly effective and well tolerated for multiple mild-to-moderate AK lesions, providing greatly improved skin quality.

(2014) 3 RCTs compared different light sources for PDT in the treatment of actinic keratosis. One trial used 5-ALA, the second trial used MAL cream, and the third reported on the use of MAL and 5BF-200 ALA using daylight-mediated PDT. There was no clear evidence of the superiority of the differing light sources over another. Some of the alternative approaches (e.g., daylight PDT) have not been cleared by the FDA.

(2014) Zane et al. published results of an RCT on the treatment of multiple actinic keratosis of the face and scalp. The trial compared MAL-PDT with diclofenac 3% plus hyaluronic acid gel (DHA). Two hundred patients were enrolled. At 3 months, the

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complete remission rate was 85.9% for patients using MAL-PDT and 51.8% for patients using with DHA ($p<0.001$). Incomplete responses to MAL-PDT were followed by a second treatment. At 12 months, the complete remission rate was 37% for patients treated with MAL-PDT and 7% for patients treated with DHA. Based on these results, the authors determined MAL-PDT was "superior in comparison with DHA for the treatment of actinic keratosis." Potential weaknesses in the DHA arm were that patients self-administered the DHA gel and had a longer treatment cycle (90 days) than the MAL-PDT arm.

(2013) Dirschka et al. reported on the follow-up phase of patients from 2 phase 3 studies that compared BF-200 ALA (n=329) with placebo (n=117) or MAL (n=247) for the treatment of actinic keratosis. No safety concerns were reported. Recurrence rates were similar for BF-200 ALA and MAL. The percentage of patients who achieve complete clearance with PDT and remained completely clear for at least 12 months after PDT were 47% for BF-200 ALA and 36% for MAL treatment. The authors reported that the follow-up phase data confirmed the efficacy and safety of PDT with BF-200 ALA.

(2012) Dirschka et al. reported on an industry sponsored randomized, multicenter, observer-blinded placebo controlled, interindividual trial comparing BF-200 ALA for the treatment of actinic keratosis with MAL cream and placebo. Six hundred patients, each with four to eight mild to moderate actinic keratosis (AK) lesions on the face and/or the bald scalp were enrolled in 26 study centers. Patients received one PDT, if residual lesions remained at 3 months after treatment, PDT was repeated. PDT with BF-200 ALA was superior to placebo PDT with respect to patient complete clearance rate (78.2% vs 17.1%); $P<0.0001$) and lesion complete clearance rate 90.4% vs 37.1%) at 3months after the last PDT. Moreover, superiority was demonstrated over the MAL cream regarding the primary endpoint patient complete clearance (78.2% vs 64.2%; $P<0.05$). Significant differences in the patient and lesion complete clearance rates and severity of treatment-related adverse events were observed for the narrow and broad-spectrum light sources. The authors concluded BF-200 ALA is very effective and well tolerated new formulation for AK treatment with PDT and is superior to a registered MAL medication. Efficacies and adverse events vary greatly with the different light sources used.

(2012) Serra-Guillen et al. in a randomized pilot study compared PDT using MAL alone, imiquimod alone, and the combination of the 2 treatments. Patients with nonhyperkeratonic actinic keratosis on the face and/or scalp were randomized to 1 of 3 groups: (1) 1 session of PDT with MAL (n=40); (2) self-administered imiquimod 5% cream for 4 weeks (n=33); or (3) treatment as with group 1 followed by 4 weeks of imiquimod cream (n=32). Follow-up occurred 1 month after PDT (group 1) or 1 month after the end of treatment with imiquimod (groups 2 and 3). The primary outcome measure (complete clinical response) was defined as the total absence of actinic keratosis by visual evaluation and palpation. Complete clinical response was achieved by 4 (10%) of patients in group 1, 9 (27%) of patients in group 2, and 12 (37.5%) of patients in group 3. There was a statistically significantly higher rate of CR in the PDT plus imiquimod

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group compared with PDT only (p=0.004). A study limitation was that the PDT-only group had shorter follow-up, which could at least partially explain the lower rate of CR.

(2010) Szeimies et al. reported on a phase 3 clinical trial using a stable 5-aminolaevulinic acid nanoemulsion formulation (BF-200 ALA) developed for PDT for actinic keratosis. The multicenter, double-blind, interindividual 2 armed-trial randomized 122 patients to BF-200 ALA or placebo. The patients had 4 to 8 mild-to-moderate actinic keratosis lesions on the face and/or bald scalp. BF-200 ALA was used in combination with 1 of 2 different light sources. The efficacy of BF-200 ALA after the first PDT treatment was evaluated at 12 weeks. For patients who were not completely cleared of actinic keratosis received a second PDT treatment, with the final evaluation 12 weeks later for all participants. The results showed PDT with BF-200 ALA was superior to PDT with placebo in respect to patient complete clearance rate (per-protocol group, 64% vs 11%; p<0.001) and lesion complete clearance rate (per-protocol group, 81% vs 22%) after the last PDT treatment. Statistically significant differences in the patient and lesion complete clearance rates and adverse event profiles were observed for the 2 light sources (Aktilite CL128 and PhotoDyn 750) at both time points of the assessment. The patient and lesion complete clearance rates after illumination with the Aktilite CL128 were 96% and 99%, respectively. No adverse events to include discomfort/pain were mentioned by patients related to application of the gel prior to PDT treatment. Burning and itching were reported during or after the red-light illumination. Moreover, 100% of patients treated using Aktilite CL128 had burning after the second PDT session. Of the patients treated using PhotoDyn 750, 60% reported pain during or after PDT. A limitation of the study was its lack of follow-up for patients beyond study protocols. The authors concluded BF-200 ALA is very effective, well tolerated new formulation for AK treatment with PDT and is superior to registered MAL medication. Efficacies and adverse events vary greatly with the different light sources used.

(2010) Szeimies et al. reported 12-month follow-up data from a study comparing PDT using a self-adhesive patch with cryotherapy. A total of 148 patients were randomized to a 5-ALA patch group, 49 to a placebo group, and 149 to a cryotherapy group. The study used a test of non-inferiority of PDT versus cryosurgery. Fourteen patients who dropped out were excluded from the analysis comparing PDT with cryotherapy. The rate of complete clearance of all lesions was 67% (86/129) in the 5-ALA group, 52% (66/126) in the cryosurgery group, and 12% (5/43) in the placebo group. The clearance rate was significantly higher in the 5-ALA patch group than in either comparator group. Results were similar in the analysis of clearance rates on a per lesion basis. The 360 patients with at least 1 lesion cleared at 12 weeks were followed for an additional 9 months; 316 patients completed the final visit 1 year after treatment. Overall clearance rate on a lesion basis was still statistically higher in the 5-ALA patch group than in the placebo (in both studies) and the cryosurgery (in the second study) groups. Moreover, 32% of patients in the 5-ALA group from the first study, and 50% of patients in the 5-ALA group from the second study, were still completely free from lesions by the end of the trial. The corresponding rate in the cryosurgery group was 37%. In the safety analysis, there were high rates of local reaction to patch application and cryotherapy at the time of treatment;

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however, no serious adverse events due to study intervention were documented. The authors concluded 5-ALA patch PDT proved to be superior to cryosurgery in the non-inferiority study setting.

Randomized Controlled Trails for Actinic Keratosis on the Upper Extremities
(2019) Three placebo controlled RCTs used ALA and PDT with blue light. The largest and most recent of these, Jiang et al. was the basis for the FDA approval of Levulan Kerastick for the treatment of AKs on the upper extremities. Two of these had a similar design: individual patients were randomized to active treatment or placebo, patients were re-treated at 8 weeks if any AKs remained, and outcomes were reported at 8 and 12 weeks. In both, significantly more patients had a complete clearance of all lesions after 12 weeks. The most common adverse events were stinging/burning during light treatment and erythema after light treatment, no subjects withdrew from treatment due to adverse events in Jiang et al. (2019), and 2 requested early withdrawal in Schmieder et al. (2012). Schmieder et al. (2012) additionally randomized patients to occlusion or no occlusion on alternate extremities and found better results with occlusion. Taub et. al. (2011) was a small (n=15), 4-week, intra-individual study in which patients were randomized to receive active treatment or placebo on alternate arms. At four weeks, no patients experienced complete clearance, but the mean lesion count was significantly lower in the treatment group compared to the placebo.

Two other smaller randomized controlled trials (RCTs) compared ALA/PDT using red light to imiquimod or 5-FU and found similar efficacy between the active treatment groups after six months of follow-up.

Systematic Reviews for Actinic Keratoses on the Face and Scalp
(2021) Steeb et al. performed a systematic review and network meta-analysis of RCTs evaluating the long-term efficacy (≥12 months) of interventions for AK of the face and/or scalp. Seventeen trials reporting initial and follow-up results of 15 unique RCTs (N=4252) were included. For the outcome of participant complete clearance, the most favorable RRs were with ALA-PDT (8.06; 95% CI, 2.07 to 31.37; moderate certainty in the evidence) followed by imiquimod 5% (RR, 5.98; 95% CI, 2.26 to 15.84; very low certainty in the evidence), photodynamic therapy with MAL-PDT (RR, 5.95; 95% CI, 1.21 to 29.41; low certainty in the evidence), and cryosurgery (RR, 4.67; 95% CI, 1.36 to 16.66; very low certainty in the evidence). For the outcome of lesion-specific clearance (number of cleared lesions compared with baseline), ALA-PDT had the most favorable RR (5.08; 95% CI, 2.49 to 10.33; moderate certainty in the evidence). For the outcome of participant partial clearance, network meta-analysis was not possible because of poor reporting.

(2020) Ezzedine et al. performed a systematic review and network meta-analysis of RCTs evaluating the efficacy and acceptability of interventions for AK of the face, ears, and/or scalp. For the outcome of complete clearance (number of patients with 100% cleared lesions), 21 RCTs contributed to the network. The most efficacious interventions as measured by surface under the cumulative ranking curve (SUCRA) included 5-FU 5% (85%), 5-FU 4% (78%), ALA-PDT (70%), imiquimod 5% (67%), 5-FU 0.5% (63%), and

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ingenol mebutate (60%). Results were similar in an analysis of partial clearance (number of patients with ≥75% cleared lesions) using data from 10 RCTs. Using data from 9 RCTs, rates of withdrawal due to adverse events were most favorable, as measured by SUCRA, for 5-FU combined with salicylic acid (81%), imiquimod 2.5% (71%), 5-FU 4% (71%), 5-FU 5% (66%), and imiquimod 3.75% (55%). However, rates of withdrawal due to adverse events were not significantly different for any of these agents in comparisons with placebo.

(2014) A number of published randomized controlled trials (RCTs) have compared photodynamic therapy (PDT) with other therapies, and a systematic review of these studies has been published. In 2014, Patel et al. reviewed RCTs with at least 10 patients that addressed the efficacy of topical PDT compared with an alternative (i.e., non-PDT) treatment of actinic keratosis. Thirteen studies met the reviewers' inclusion criteria. The meta-analysis consisted of 641 participants, with a total of 2174 AKs treated with cryotherapy and 2170 AKs treated with PDT. Compared with cryotherapy, the pooled relative risk for the meta-analysis for completed response (lesion clearance) was 1.14 (95% Ci, 1.11-1.18) at 3 months after treatment. Visual inspection of a funnel plot revealed no publication bias, which was confirmed by the Begg test (P=.80). The authors concluded photodynamic therapy has a 14% better chance of complete lesion clearance at 3 months after treatment then cryotherapy for thin AKs on the face and scalp.

Systematic Reviews for Actinic Keratoses on the Upper Extremities

(2020) Steeb et al. published a systematic review of RCTs that evaluated cryosurgery, ingenol mebutate, PDT, colchicine, and 5-FU for the treatment of AK in nonscalp and nonface localizations. Thirteen studies (N=1380 participants) met the reviewers' inclusion criteria. Studies evaluating PDT included comparisons to placebo (n=4), cryotherapy (n=3), 5-FU (n=2), colchicine (n=1), and imiquimod (n=1). Direct (pairwise) comparison analyses found that PDT was significantly better than placebo in achieving complete clearance (RR, 3.87; 95% CI, 2.14 to 6.97). Ten of the studies were included in a network analysis. Compared to placebo, cryosurgery showed the highest complete clearance rates (RR, 7.73; 95% CI, 3.21 to 18.61), followed by imiquimod (RR, 7.00; 95% CI, 3.06 to 15.98), and PDT (RR, 3.87; 95% CI, 2.14 to 6.97). Cryosurgery was associated with a higher likelihood of complete clearance than PDT (RR, 2.00; 95% CI, 1.04 to 3.84) with a low certainty of evidence. Authors of the review noted caution in directly comparing topical treatments, which may be more suitable as a field-directed treatment of multiple or clustered lesions, with cryosurgery, which is preferable for single or a limited number of AKs.

Section Summary: Actinic Keratoses on the Face, Scalp and Upper Extremities

Evidence from multiple randomized controlled trials (RCTs) and systematic reviews has suggested that photodynamic therapy (PDT) improves the net health outcome in patients with nonhyperkeratotic actinic keratosis of the face or scalp compared with placebo or other active interventions.

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Regarding the treatment of actinic keratosis (AKs) on the upper extremities, in two placebo controlled RCTs, significantly more patients had a complete clearance of AKs with ALA/PDT with blue light compared to placebo at 12 weeks, and a third found a significantly greater reduction in mean lesion count at 4 weeks. Two small RCTs compared ALA/PDT using red light to imiquimod or 5-FU and found similar efficacy between the active treatment groups after six months of follow-up.

Non-Melanoma Skin Cancers
Non-melanoma skin cancers are the most common malignancies in the Caucasian population. Most often found in light skinned individuals, basal cell carcinoma (BCC) is most common of the cutaneous malignancies. Although BCC tumors rarely metastasize, they can be locally invasive if left untreated, leading to significant local destruction and disfigurement. The most prevalent forms of BCC are nodular BCC and superficial BCC. Bowen's disease is a squamous cell carcinoma (SCC) in situ with the potential for significant lateral spread. Metastases are rare, with less than 5% of cases advancing to invasive SCC. Lesions may appear on sun-exposed or covered skin. Excision surgery is the preferred treatment for smaller non-melanoma skin lesions and those not in problematic areas, such as the face and digits. Other established treatments include topical 5-fuorouracil, topical imiquimod, photodynamic therapy and cryotherapy. Poor cosmesis resulting from surgical procedures can be a significant problem.

Basal Cell Carcinoma

Clinical Context and Therapy Purpose
The purpose of photodynamic therapy (PDT) is to provide a treatment option that is an alternative to or an improvement on existing therapies in patients with low-risk basal cell carcinoma (BCC).

Patients
The relevant population of interest are individuals with low-risk BCC.

Interventions
The therapy being considered is photodynamic therapy (PDT).

Patients with low-risk BCC are actively managed by dermatologists and oncologists in an outpatient setting.

Comparators
The following therapies are currently being used to treat BCC: pharmacologic therapy, cryotherapy, surgery, and radiotherapy. Excision surgery is preferred treatment for smaller nonmelanoma skin lesions and those not in problematic areas, such as the face and digits. Other established treatments include topical 5-FU, imiquimod, and cryotherapy.

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Outcomes
The general outcomes of interest are symptoms, change in disease status, quality of life (QOL), and treatment related morbidity.

Duration of follow-up is dependent on the extent of lesions and evaluation at 1, 3 and 12 months.

(Updated 2020: Literature Review 2021) According to an UpToDate review on Photodynamic Therapy by Maytin et al for basal cell carcinoma – Superficial BCC lesions appear to be most responsive to therapy, with sustained response rates ranging from 72 to 97 percent. Nodular BCCs are less likely than superficial BCCs to respond to treatment with PDT, with sustained response rates of 33 to 76 percent.

Systematic Reviews for Low-Risk Basal Cell Carcinoma
(2020) Mpourazanis et al. compared PDT to cryotherapy for BCC in a systematic review of 19 RCTs and prospective observational trials. Of these studies, only 5 RCTs were included in the quantitative analysis. For rates of complete clearance, there was no significant difference found between PDT and cryotherapy (2 studies; odds ratio [OR], 0.83; 95% CI, 0.47 to 1.49; I2=0%). Similarly, no difference was found between PDT and cryotherapy for the recurrence rate (3 studies; OR, 4.99; 95% CI, 0.40 to 62.40; I2=87.3%). The review did not distinguish among BCC subtypes.

(2016) Zou et al. completed a meta-analysis by identifying 5 RCTs comparing PDT with surgical excision in patients who had nodular BCC and at least 3 months of follow-up. The rate of CR was significantly lower in the PDT group than in the surgical excision group at 1 year (RR=0.89; 95% CI, 0.80 to 0.99) and at 3 years (RR=0.73; 95% CI, 0.63 to 0.85); there were no significant differences in CR at 2, 4, or 5 years. The rate of recurrence was significantly higher in the PDT group than in the surgical excision group at all time points. More large scale RCTs are required to verify these findings.

(2015) Wang et al. published a systematic review of RCTs on photodynamic therapy (PDT) for treating BCC, both superficial and nodular types. To be selected, studies had to include adults with one or more primary BCCs, randomize participants to PDT, placebo, or another treatment, and report the complete clearance rate, recurrence rate, cosmetic outcomes, and/or adverse events rate. Eight RCTs (total N=1583 patients), published between 2001 and 2013, met inclusion criteria. Three trials included patients with superficial BCC: three included patients with nodular BCC, and one included patient with both types of low-risk BCC. Four trials compared PDT with surgery, two compared PDT with cryotherapy, one compared PDT with pharmacologic treatment, and one was placebo-controlled.

In a meta-analysis of 7 studies, the estimated probability of complete clearance after treatment was similar in the PDT and the non-PDT groups (RR=0.97; 95% CI, 0.88 to 1.06). In subgroup analyses by treatment type, PDT was associated with a significantly higher clearance rate only compared with placebo. Surgery was associated with a

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significantly lower rate of recurrence compared with PDT, and there was no significant difference in recurrence rates when PDT was compared with cryotherapy and pharmacologic therapy. In meta-analyses of cosmetic outcomes at 1 year, there was a significantly higher probability of a good-to-excellent outcome with PDT than with surgery (RR=1.87; 95% CI, 1.54 to 2.26) or cryotherapy (RR=1.51; 95% CI, 1.30 to 1.76). The author's concluded PDT is a useful method for the treatment of BCC, more efficient than placebo and with similar efficiency to cryosurgery and pharmacologic treatment. Even though it is less effective than surgical excision, PDT has cosmetic advantages over surgery and cryosurgery.

Randomized controlled Trials for Low-Risk Basal Cell Carcinoma

(2016) a non-inferiority RCT by Roozeboom et al. compared MAL-PDT with imiquimod cream and with fluorouracil cream in patients with superficial BCC. A total of 601 patients were randomized, 202 to MAL-PDT, 198 to imiquimod, and 201 to fluorouracil. A total of 490 (82%) patients completed the 1-year follow-up and 417 (69%) completed the 3-year follow-up. Median follow-up was 35 months. The estimated tumor-free survival rates at 3 years were 58% (95% CI, 47.8% to 66.9%) in the PDT group, 79.7% (95% CI, 71.6% to 85.7%) in the imiquimod group, and 68.2% (95% CI, 58.1% to 76.3%) in the fluorouracil group. Results of the noninferiority analysis suggested that imiquimod was superior to MAL-PDT and imiquimod was non-inferior to MAL-PDT.

(2008) An industry sponsored multicenter RCT was published in 2008 by Szeimies et. al. This trial compared MAL-PDT with surgery for small (8-20 mm) superficial BCC in 196 patients. At 3 months post-treatment, 92% of lesions treated with MAL-PDT showed clinical response, compared with 99% of lesions treated with surgery (per-protocol analysis). At 12-month follow-up, no lesion recurrence was reported in the surgery group, while the recurrence rate was 9% in the MAL-PDT group. Approximately 10% of patients discontinued MAL-PDT due to an incomplete response or adverse event compared with 5% of patients in the surgery group. Cosmetic outcomes were rated by the investigators as good-to-excellent in 94% of lesions treated with MAL-PDT and 60% after surgery.

(2007) Rhodes et al. published 5-year follow-up to an industry-sponsored multicenter randomized trial comparing MAL-PDT with surgery for nodular BCC. A total of 101 adults with previously untreated nodular BCC were randomized to MAL therapy or surgery. At 3 months, CR rates did not differ between groups; however, at 12 months, the CR rate had fallen from 91% to 83% in the MAL-PDT group, and from 98% to 96% in the surgery group. Of 97 patients in the per-protocol population, 66 (68%) were available for 5-year follow-up; 16 (32%) discontinued in the MAL-PDT group due to treatment failure or adverse events vs 6 (13%) in the surgery group. A time-to-event analysis of lesion response estimated a sustained lesion response rate of 76% for MAL-PDT and 96% for excision surgery. Cosmetic outcomes were rated as good-to-excellent in 87% of the MAL-PDT patients and in 54% of the surgery patients.

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Section Summary: Low – Risk Basal Cell Carcinoma
Systematic reviews of randomized controlled trials (RCTs) have found that photodynamic therapy (PDT) may not be as effective as surgery for superficial and nodular BCC. In the small number of trials available, PDT was more effective than placebo. The available evidence from RCTs has suggested that PDT has better cosmetic outcomes than surgery.

Disseminated Superficial Actinic Porokeratosis (DSAP)
Disseminated superficial actinic porokeratosis (DSAP) is an uncommon skin condition that leads to reddish brown scaly spots. The spots are mostly seen on the arms and legs, but sometimes will show up on other sun-damaged skin. It is due to an abnormal sun sensitivity leading to pre-cancerous skin cells. This is typically seen in fair skinned people mid-life and beyond. For some reason, most women are affected. Once a spot of DSAP forms, it may slowly enlarge to form a ring or circle. While DSAP is pre-cancerous, it is uncommon for it to develop into a true skin cancer. Sometimes the spots develop worrisome changes, such as redness, crusting or scaling and need to be biopsied.

Treatment of DSAP includes creams such as topical retinoids, 5-fluorouracil and imiquimod. Cyosurgery may be used but can lead to areas of hypopigmentation. Photodynamic therapy (PDT) has been used with mixed results.

Based on review of the peer reviewed medical literature regarding photodynamic therapy (PDT) for the treatment of disseminated superficial actinic porokeratosis (DSAP), only case series reports were found. Controlled studies with greater number of patients and long-term follow-up are needed to evaluate the efficacy and safety of PDT for the treatment of DSAP. The evidence is insufficient to determine the effects of the technology on net health outcomes

Other Noncancerous Dermatologic Conditions

Clinical Context and Therapy Purpose
The purpose of photodynamic therapy (PDT) is to provide a treatment option that is an alternative to or an improvement on existing therapies in patients with noncancerous dermatologic skin conditions (e.g., hidradenitis suppurative, mycoses, port-wine stain).

Patients
The relevant population of interest are individuals with noncancerous dermatologic skin conditions, including hidradenitis suppurative, mycoses, port-wine stain.

Interventions
The therapy being considered is photodynamic therapy (PDT)

Comparators
The following therapies are currently being used to treat noncancerous dermatologic skin conditions: pharmacologic therapy, cryotherapy, and laser therapy.

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Outcomes
The general outcomes of interest are symptoms, change in disease status, quality of life (QOL) and treatment related morbidity.

Duration of follow-up would be based on the type and extent of lesions and would typically occur in weeks to months after treatment.

Case Series: Other Noncancerous Dermatologic Conditions
No controlled studies using FDA-approved photosensitizing agents for PDT in other dermatologic conditions were identified for conditions other than a port-wine stain and onychomycosis. Only case series were identified, including series on PDT for hidradenitis suppurativa and PDT for interdigital mycoses. Most series were small (e.g., <25 patients). There are a few systematic reviews. For example, a systematic review by Mostafa and Tarakji (2015) evaluated PDT for oral lichen planus identified 5 case reports, and a systematic review by Yazdani Abyaneh et al. (2015) identified 15 case series (N=223 patients) on PDT for actinic cheilitis. Xiao et al (2011) in China published a large retrospective case series. A total of 642 patients with port-wine stains were treated with PDT; 507 were included in analyses, and the rest were excluded because they had previous lesion treatments or were lost to follow-up. After treatment, 26 (5.1%) patients were considered to have complete clearing, 48 (9.5%) had significant (<75% to <100%) clearing, and 77 (15.2%) had moderate (<50% to <75%) clearing. Similarly, Chun-Hua et al (2021) reported a retrospective review of 439 children with port-wine stains treated with PDT. An effective response (>20% fading) occurred in 95.2% of patients, and 74.3% experienced almost complete resolution and great improvement (≥60% fading). Zhang et al. (2021) also evaluated a series of 107 children who received PDT for port-wine stains that were resistant to pulsed dye laser. Good-to-excellent improvement was achieved in 32.7% of 107 patients who received a single session of treatment and in 50.8% of patients who received 2 sessions of treatment. These uncontrolled studies are insufficient to draw conclusions about the effect of PDT on health outcomes in patients with port-wine stains.

Randomized Controlled Trials: Other Noncancerous Dermatologic Conditions
(2018) Wu et al. conducted a prospective, multicenter RCT involving 100 patients (age range, 16-50 years) to measure the efficacy of different dose levels of hemoporfin with PDT in treating a port-wine stain. In the trial, 40 patients received hemoporfin 2.5 mg/kg intravenously, 40 received hemoporfin 5 mg/kg intravenously, and 20 received a saline placebo. Ten minutes after infusion, all patients received PDT. After an evaluation at week 8, 75% of the high-dose group reported improvements in skin lesions compared with 40% of the low-dose group and 15% of the placebo group. Adverse events were mild and resolved within a week. Limitations included a short follow-up and small sample size.

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Systematic Reviews: Other Noncancerous Dermatologic Conditions
(2020) Shen et al. published a systematic review of clinical trials and case series evaluating PDT, with a focus on the photosensitizers used, for superficial fungal infections. Thirty-four studies were identified for inclusion, including 13 clinical trials and 20 cases (N=440 [n=336 for PDT participants only]). None of the clinical trials were blinded. The follow-up times of the studies varied from no follow-up to 2 years. Quantitative analyses were not performed. The majority of the included studies (n=18) evaluated PDT for onychomycosis. Seven different photosensitizers were evaluated for onychomycosis, ALA (3 studies), MAL (6 studies), porphyrin (1 study), methylene blue (5 studies), rose Bengal (1 study), curcumin (1 study), and aluminum phthalocyanine chloride nanoemulsions (1 study). Treatment with methylene blue had complete cure rates ranging from 70% to 80% (2 trials); whereas mycological cure rates for ALA and MAL ranged from 17% to 57% (2 trials) and 32% (1 trial), respectively. The most common adverse events reported in the included studies were pain/burning/stinging sensation (n=147/323 [45.5%]), erythema (n=66/177 [37.3%]), blistering (n=14/150 [9.3%]), edema (n=48/170 [28.2%]), and hyper-/hypopigmentation (n=10/140 [7.1%]).

Section Summary: Other Noncancerous Dermatologic Conditions
There is insufficient evidence that photodynamic therapy (PDT) improves the net health outcome in patients with these other dermatologic conditions e.g., hidradenitis suppurativa, mycoses, port wine stains.

Squamous Cell Carcinoma In-Situ (Bowen's Disease)

Clinical Context and Therapy Purpose
The purpose of photodynamic therapy (PDT) is to provide a treatment option that is an alternative to or an improvement on existing therapies in patients with squamous cell carcinoma in situ (Bowen disease).

Patients
The relevant population of interest are individuals with squamous cell carcinoma in situ. Bowen disease is a squamous cell carcinoma in situ with the potential for significant lateral spread. Metastases are rare, with less than 5% of cases advancing to invasive squamous cell carcinoma. Lesions may appear on sun exposed or covered skin.

Interventions
The therapy being considered is photodynamic therapy (PDT).

Patients with squamous cell carcinoma in situ are actively managed by dermatologists and oncologists in an outpatient setting.

Comparators
The following therapies are currently being used to treat squamous cell carcinoma in situ: pharmacologic therapy, cryotherapy, surgery and radiotherapy.

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Outcomes
The general outcomes of interest are symptoms, change in disease status, quality of life (QOL), and treatment related morbidity.

Duration of follow-up is dependent on the extent of lesions and evaluation at 1, 3 and 12 months.

(Updated 2020: Literature Review 2021) According to an UpToDate review on Photodynamic Therapy by Maytin et al for squamous cell carcinoma in-situ (Bowen disease) – In patients with SCC in situ, studies have demonstrated initial clearance rates of 88 to 100 percent at three months and sustained clearance of 68 to 89 percent at one and a half to four years after one to two cycles of methyl aminolevulinate (MAL)-PDT. A randomized study comparing MAL-PDT with placebo-PDT, cryotherapy, or topical 5-fluoruracil (5-FU) for the treatment of SCC in situ found that MAL-PDT was superior in efficacy to 5-FU and placebo-PDT and was less painful than cryotherapy. After a single session of ALA-PDT, only 53 percent of patients were reported to still be clear at five years. Therefore, repeated sessions and monitoring should be considered as part of the treatment plan. PDT is not recommended for invasive SCCs due to poor clearance rates and metastatic potential.

Randomized Controlled Trials for Squamous Cell Carcinoma In-Situ (Bowen's Disease)
(2013) Bath-Hextall et al. published a Cochrane review to assess the effects of therapeutic interventions for cutaneous Bowen's disease. Reviewers identified 7 RCTs evaluating PDT: 4 compared 2 PDT protocols, 1 compared PDT with cryotherapy, 1 compared PDT with topical 5-FU, and 1 compared PDT with both PDT and 5-FU. Reviewers did not pool study results.

(2006) The largest study (N=225 patients) was a 3-arm trial published by Morton et al. This multicenter trial was conducted in 11 European countries. A total of 225 patients were randomized to MAL-PDT, cryotherapy, or 5-FU for treatment of Bowen disease. Unblinded assessment of lesion clearance found PDT to be noninferior to cryotherapy and 5-FU (93% vs 86% vs 83%, respectively) at 3 months and superior to cryotherapy and 5-FU (80% vs 67% vs 69%, respectively) at 12 months. Cosmetic outcomes at 3 months were rated higher for PDT than for standard nonsurgical treatments by both investigators and blinded evaluators, with investigators rating cosmetic outcomes as good or excellent in 94% of patients treated with MAL-PDT, 66% of patients treated with cryotherapy, and 76% of those treated with 5-FU.

The primary outcome measures were complete clearance of lesions after the first treatment cycle and recurrence rate at 12 months. The secondary outcomes included the number of lesions that cleared after each treatment cycle, the number of treatment cycles needed to achieve clearance, the recurrence rates at > 12 months, cosmetic outcome, quality of life assessment, and adverse outcomes as reported by both participant and clinician. They included 9 studies, with a total of 363 participants. One study

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demonstrated statistically significantly greater clearance of lesions of Bowen's disease with MAL-PDT (methyl aminolevulinate with photodynamic therapy) when compared with placebo-PDT (RR (risk ratio) 1.68, 95% CI (confidence interval) 1.12 to 2.52; n = 148) or cryotherapy (RR 1.17, 95% CI 1.01 to 1.37; n = 215), but there was no significant difference when MAL-PDT was compared to 5-FU (5-fluorouracil). One study demonstrated statistically significantly greater clearance of lesions with ALA-PDT (5-aminolevulinic acid with photodynamic therapy) versus 5-FU (RR 1.83, 95% CI 1.10 to 3.06; n = 66), but no statistically significant difference in recurrence rates at 12 months (RR 0.33, 95% CI 0.07 to 1.53).Cryotherapy showed no statistically significant difference in clearance rates (RR 0.99, 95% CI 0.78 to 1.26) or recurrences at 1 year (RR 1.48, 95% CI 0.53 to 4.17) when compared to 5-FU in 1 study of 127 participants. One study compared imiquimod to placebo and demonstrated statistically significantly greater clearance rates in the imiquimod group (9/15 lesions) compared to placebo (0/16) (Fisher's Exact P value < 0.001). The imiquimod group did not report any recurrences at 12 months, but at 18 months, 2/16 participants in the placebo group had developed early invasive squamous cell carcinoma.

The authors concluded, overall, there has been very little good-quality research on treatments for Bowen's disease. There is limited evidence from single studies to suggest MAL-PDT is an effective treatment. Although cosmetic outcomes appear favorable with PDT, five-year follow-up data are needed. Significantly more lesions cleared with MAL-PDT compared to cryotherapy. No significant difference in clearance was seen when MAL-PDT was compared with 5-FU, but one study found a significant difference in clearance in favor of ALA-PDT when compared to 5-FU. There was no significant difference in clearance when cryotherapy was compared to 5-FU. The lack of quality data for surgery and topical cream therapies has limited the scope of this review to one largely about PDT studies. The age group, number, and size of lesions and site(s) affected may all influence therapeutic choice; however, there was not enough evidence available to provide guidance on this. More studies are required in the immunosuppressed populations as different therapeutic options may be preferable. Specific recommendations cannot be made from the data in this review, so we cannot give firm conclusions about the comparative effectiveness of treatments.

Systematic Reviews for Squamous Cell Carcinoma In-Situ (Bowen’s Disease)
(2020) Zhong et al. performed meta-analyses using data from 12 RCTs (n=446) comparing PDT with other treatments in patients with Bowen disease. For the outcome of lesion reduction reported between 1 and 12 months, PDT was associated with a significantly higher lesion reduction rate compared with control groups (OR, 2.86; 95% CI, 1.89 to 4.33). In comparisons with specific control groups, PDT was associated with significant improvements in lesion reduction compared with 5-FU (OR, 3.70; 95% CI, 2.07 to 6.62) and compared with cryotherapy (OR, 2.24; 95% CI, 1.24 to 4.04). No significant differences were observed in recurrence rates between PDT and control groups. Most domains of study quality were assessed as low or unclear risk of bias. The authors reported the potential for publication bias and concluded PDT to be a safe and effective therapy for Bowen disease.

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Section Summary; Squamous Cell Carcinoma In-Situ (Bowen's Disease)
Randomized controlled trials (RCTs) have found that photodynamic therapy (PDT) has similar or greater efficacy than cryotherapy and 5-FU for patients with Bowen disease. Additionally, adverse effects and cosmetic outcomes appeared to be better after PDT.

Summary of Evidence
For individuals who have nonhyperkeratotic actinic keratosis on the face, scalp who receive photodynamic therapy (PDT), the evidence includes randomized controlled trials (RCTs) and systematic reviews. The evidence has found that PDT improves the net health outcome in patients with nonhyperkeratotic actinic keratosis on the face or scalp compared with placebo or other active interventions. The evidence is sufficient to determine that the technology results in a meaningful improvement in the net health outcomes.

For individuals who have nonhyperkeratotic AKs on the upper extremities who receive photodynamic therapy (PDT), the evidence includes randomized controlled trials (RCTs). In two placebo controlled RCTs, significantly more patients had a complete clearance of AKs with ALA/PDT with blue light compared to placebo at 12 weeks, and a third found a significantly greater reduction in mean lesion count at 4 weeks. Two small RCTs compared ALA/PDT using red light to imiquimod or 5-fluorouracil and found similar efficacy between the active treatment groups after six months of follow-up. The evidence is sufficient to determine that the technology results in a meaningful improvement in the net health outcome.

For individuals who have disseminated superficial actinic porokeratosis (DSAP) who receive photodynamic therapy (PDT), the evidence includes case series. Controlled studies with greater number of patients and long-term follow-up are needed to evaluate the efficacy and safety of PDT for the treatment of DSAP. The evidence is insufficient to determine the effects of the technology on net health outcomes.

For individuals who have low-risk basal cell carcinoma who receive photodynamic therapy (PDT), the evidence includes randomized controlled trials (RCTs) and systematic reviews of RCTs. Systematic reviews of RCTs have found that PDT may not be as effective as surgery for superficial and nodular basal cell carcinoma. In the small number of trials available, PDT was more effective than placebo. The available evidence from RCTs has suggested that PDT has better cosmetic outcomes than surgery. The evidence is sufficient to determine that the technology results in a meaningful improvement in the net health outcomes.

For individuals who have squamous cell carcinoma in situ (Bowen disease) who receive photodynamic therapy (PDT), the evidence includes randomized controlled trials (RCTs) and systematic review. RCTs have found that PDT has similar or greater efficacy compared with cryotherapy and 5-fluorouracil. Additionally, adverse events and cosmetic outcomes appear to be better after PDT. Few RCTs have compared PDT with surgery or radiotherapy; as a result, conclusions cannot be drawn about PDT compared with these

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other standard treatments. The evidence is sufficient to determine that the technology results in a meaningful improvement in the net health outcome.

For individuals who have acne who receive photodynamic therapy (PDT), the evidence includes randomized controlled trials (RCTs) and a systematic review. The available RCTs have not consistently found significantly better outcomes with PDT compared with other interventions, and a meta-analysis did not find significantly better results with PDT versus placebo. Several trials have found that PDT is associated with high rates of adverse events leading to the cessation of treatment. Trials have tended to have relatively small sample sizes and used a variety of comparison interventions. The 2016 American Academy of Dermatology guideline for the management of acne vulgaris states the following: "Of all laser and light devices, the most evidence exists for PDT in treating acne. This treatment shows great promise, but additional studies are needed to determine the optimal photosensitizer, incubation time, and light source." The evidence is insufficient to determine the effects of the technology on health outcomes.

For individuals who have noncancerous dermatologic skin conditions (e.g., hidradenitis suppurativa, mycoses, port wine stains) who receive photodynamic therapy (PDT), the evidence includes case series and systematic reviews of uncontrolled series and a randomized controlled trial (RCT) for port wine stains. Further randomized controlled trials (RCTs) are needed to determine the safety and efficacy of PDT for these conditions. The evidence is insufficient to determine the effects of the technology on health outcomes.

Practice Guidelines and Position Statements
American Academy of Dermatology (AAD)

- **Acne Vulgaris**
    - (2016) The American Academy of Dermatology issued a guideline of care for the management of acne vulgaris which states the following: "Of all laser and light devices, the most evidence exists for PDT in treating acne. With PDT, a photosensitizer, such as aminolevulinic acid, is first applied to the affected skin for a period of time (varying from 15 minutes to 3 hours). The photosensitizer is then absorbed into the pilosebaceous units and is preferentially taken up by sebocytes. A laser or light device is then used to activate the photosensitizer, generating singlet oxygen species, and thereby damaging the sebaceous glands and reducing P acnes. This treatment shows great promise, but additional studies are needed to determine the optimal photosensitizer, incubation time, and light source." (*Accessed January 2022*)

- **Actinic Keratosis**:
    - (2021): PDT is included in the following recommendations for individuals with AK:
        - ALA-red light PDT is conditionally recommended (low quality of evidence)

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        - ALA-daylight PDT is conditionally recommended as less painful than but equally effective as ALA-red light PDT (moderate quality of evidence)
        - ALA-blue light PDT is conditionally recommended (moderate quality of evidence)
        - ALA-red light PDT is conditionally recommended over cryosurgery alone (low quality of evidence)

    (*Accessed January 2022*)

- **Basal Cell Carcinoma**
    - (2018) The American Academy of Dermatology issued an updated guideline for the management of basal cell carcinoma (BCC) which includes the following recommendation regarding nonsurgical therapy of BCC:
        - If surgical therapy is not feasible or preferred, topical therapy (e.g., imiquimod or 5-FU), MAL or ALA PDT, and radiation therapy (e.g., superficial radiation therapy, brachytherapy, external electron beam, and other traditional radiotherapy forms for BCC) can be considered when tumors are low risk, with the understanding that the cure rate may be lower. (*Accessed January 2022*)

- **Cutaneous Squamous Cell Carcinoma (cSCC)**
    - (2018) The American Academy of Dermatology issued an updated guideline for the management of cutaneous squamous cell carcinoma (cSCC) which includes the following recommendation regarding nonsurgical therapy of cSCC:
    - Topical therapies (imiquimod or 5-FU) and PDT are not recommended for the treatment of cSCC on the basis of available data. (*Accessed January 2022*)

International Society for Photodynamic Therapy in Dermatology (ISPDT)

- (2012) The International Society of Photodynamic Therapy in Dermatology (ISPDT) published consensus-based guideline for photodynamic therapy (PDT) for skin field cancerization. Field cancerization is a term that describes the presence of genetic abnormalities in a tissue chronically exposed to a carcinogen. With respect to the skin, this term is used to define the presence of multiple non-melanoma skin cancer, its precursors, actinic keratosis and dysplastic keratinocytes in sun exposed areas. The multiplicity of the lesions and the extent of the area influence the treatment decision. ISPDT recommendations includes the following:
    - "PDT is a suitable therapeutic option for patients with multiple AKs and a diagnosis of field cancerization. It may be one of the best options due to the combination of high and sustained response rate, limited downtime for patients and an excellent aesthetic outcome."

  (*Accessed January 2022*)

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- (2005) The International Society for Photodynamic Therapy in Dermatology (ISPDT) published consensus-based guidelines on the use of photodynamic therapy (PDT) for non-melanoma skin cancer with the following information:
    - **Actinic Keratoses (AK):** As PDT with either ALA or MAL is highly effective and offers excellent cosmetic outcome, it should be considered as a first-line therapy for AK (Rating: AI); MAL-PDT has a superior cosmetic outcome compared to cryotherapy (Rating: AI)
    - **Bowen's Disease (BD)**: Topical PDT is effective in BD, achieving good cosmesis, and is at least as effective as cryotherapy or 5-fluorouacil, but with fewer adverse events; topical PDT should be considered as a first-line therapy for BD (Rating AI).
    - **Squamous Cell Carcinoma (SCC):** There is insufficient evidence to support the routine use of topical PDT for SCC (Rating: CIIiii).
    - **Superficial Basal Cell Carcinoma (sBBC):** PDT is an effective and reliable treatment option for SBCC that offers excellent cosmetic outcomes (Rating: AI); PDT offers an advantage in treatment of large, extensive and multiple lesions (Rating AI); MAL-PDT has demonstrated long-term efficacy, with 5 year follow up data (Rating: AI).
    - **Nodular Basal Cell Carcinoma (nBBC):** MAL-PDT is an effective and reliable treatment option for nBBC less than 2 mm in depth with the advantage of good cosmetic outcome (Rating: AI); MAL-PDT has demonstrated long-term efficacy with 5 year follow up data. (Rating: AI).

  (*Accessed January 2022*)

National Comprehensive Cancer Network (NCCN)

- **Basel Cell Skin Cancer Version 1.2022**
    - Principles of Treatment for Basal Cell Skin Cancers: The principles of treatment for basal cell skin cancers includes the following:
        - In patients with low risk, superficial basal cell skin cancer, where surgery or radiation is contraindicated or impractical, therapies such as topical 5-fluorouracil, topical imiquimod, photodynamic therapy (e.g., aminolevulinic acid (ALA), porfimer sodium) or vigorous cryotherapy may be considered, even though the cure rates may be lower than with surgical treatment modalities. (*Accessed January 2022*)

    - Superficial Therapies
        - Since cure rates may be lower, superficial therapies should be reserved for those patients where surgery or radiation is contraindicated or impractical. Superficial therapies include topical treatment with 5-fluororacil (5-FU) or imiquimod, photodynamic therapy (PDT) and cryotherapy. (*Accessed January 2022*)

    - Photodynamic Therapy
        - PDT involves the application of a photosensitizing agent on the skin followed by irradiation with a light source. Photosensitizing agents often

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used include methyl aminolevulinate (MAL) and 5-aminolevulinic acid (ALA). These two agents have similar efficacy outcomes and pain scores when used to treat patients with nodular BCC. Multiple randomized trials and a meta-analysis including 4 of these trials have shown that rates of excellent or good cosmetic outcomes were higher with PDT versus surgery, even though surgery was superior to PDT in terms of efficacy (complete clearance, 1 year and 5-year recurrence rates).

- Reviews of clinical trials reported cure rates from 70% to 90% by PDT for patients with BCC. Most of the studies of PDT for BCC have focused on the superficial and nodular histologic subtypes, and several have found higher cure rates for superficial versus nodular subtypes. Ulceration and thickness are associated with lower response to therapy, and within the nodular subtype, cure rates are better with thinner lesions. Clinical studies have demonstrated PDT activity against "difficult-to-treat" lesion within 24-month complete response rate of 78%. Currently PDT is being utilized at some NCCN Member Institutions for premalignant or superficial low risk lesions on any location on the body although response rates may be higher on the face and scalp.

- Although MAL is an approved photosensitizer for PDT, it is no longer produced in the United States.

(*Accessed January 2022*)

- **NCCN Recommendations Low-Risk BCC**
  - The NCCN Panel discussed the use of alternative therapies as first-line treatment in patients with low risk, superficial BCC where surgery or radiation is contraindicated for impractical. These include 5-FU, imiquimod, PDT with porfimer sodium or ALA, or vigorous cryotherapy. Data suggest that the cure rate of these approaches may be lower compared with surgery. On the other hand, panelist experience indicated that they may be effective for anatomically challenging locations, and recurrence are often small and manageable. Panelists agreed that these therapies may be considered for superficial BCCs based on patient preference. (*Accessed January 2022*)

- **Squamous Cell Skin Cancer Version 2.2022**
  - Principles of Treatment for Squamous Cell Skin Cancer The principles of treatment for squamous cell skin cancer includes the following:
    - In patients with squamous cell carcinoma in situ (Bowen's disease) that is low risk, alternative therapies such as topical 5-flurouracil, topical imiquimod, photodynamic therapy (e.g., aminolevulinic acid (ALA), profimer sodium) or vigorous cryotherapy may be considered,

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even though cure rates may be lower than the surgical treatment modalities. (*Accessed January 2022*)

- **Superficial Therapies**
  - Given the limited penetration beyond epidermis and lower cure rates than with surgical techniques, superficial therapies should be reserved for those patients with SCC in situ. Recommended superficial therapies include topical fluorouracil (5-FU), topical imiquimod, photodynamic therapy (PDT), and cryotherapy.
    (*Accessed January 2022*)

- **Photodynamic Therapy**
  - PDT involves the application of a photosensitizing agent on the skin followed by irradiation with a light source. Photosensitizing agents often used include methyl aminolevulinate (MAL) and 5-aminolevulinic acid (ALA). For SCC in situ rates of initial complete clearance following PDT with ALA or MAL range between 52% and 98% according to prospective studies (n=23-96 lesions). Most of these studies reported recurrences, such that durable complete response rates range from 48% to 89%. Small, randomized trials have shown that differences in PDT techniques can cause significant differences in clearance rate for SCC in situ, which likely contributes to the broad range of rates reported in the literature. One small, randomized trial showed that fewer treatments were required for complete clearance with PDT versus cryotherapy, and two randomized trials shows that durable complete response rates were high with PDT. Another small, randomized trial in patients with SCC in situ showed that PDT was associated with higher rates of initial complete clearance compared with 5-FU, and two randomized trials showed that durable complete response were higher with PDT. (*Accessed January 2022*)

  - Results from randomized trials in patients with SCC in situ suggest that 5-FU may be associated with lower risk of adverse events compared with PDT or cryotherapy, but due to inconsistent results across trials it is unclear whether risk of toxicity differs between cryotherapy and PDT. All three treatment modalities are associated with risk of including erythema, burning, crusting, stinging, itching, edema/blistering, and ulceration/erosions. All three also occasionally lead to pigmentary changes or scarring. (*Accessed January 2022*)

  - Currently PDT is being utilized at some NCCN Member Institutions for SCC in situ lesions. Although MAL is an approved photosensitizer for PDT, it is no longer produced in the United States. (*Accessed January 2022*)

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- **Treatment of Precancers (Diffuse Actinic Keratoses, Field Cancerization, and CSCC Prophylaxis**
  - The following recommendations were made: "Accepted treatment modalities include cryotherapy, topical 5-fluorouracil (5-FU) with or without calcipotriol (calcipotriene), topical imiquimod, topical ingenol mebutate, photodynamic therapy (e.g., aminolevulinic acid, porfimer sodium), and curettage and electrodesiccation. For hyperkeratotic actinic keratoses, pretreatment with topical tazarotene, curettage, or topical keratolytics (topical urea, lactic acid, and salicylic acid) prior to above therapies may be considered." (*Accessed January 2022*)

- **NCCN Recommendations for Treating Low Risk Local SCC**
  - The NCCN Panel discussed the use of alternative therapies for first-line treatment in patients with SCC in situ (Bowen's disease). Although cure rates may be lower than with surgical treatment modalities, alternative therapies the panel recommends considering 5-FU, imiquimod, PDT with porfimer sodium or ALA, or vigorous cryotherapy. Data suggest that the cure rates of these approaches may be lower compared with involvement. Due to the potential for skull involvement the intracranial extension, an MRI with contrast of the area of interest should be considered if large-nerve invasion is suspected for tumors on the head and neck. (*Accessed January 2022)*

Regulatory Status

In 1999 Levulan® Kerastick™ is a topical preparation of ALA used in conjunction with illumination with the BLU-U™ Blue Light Photodynamic Therapy Illuminator, a blue light source. It is approved by the U.S. Food and Drug Administration (FDA) for the treatment of non-hyperkeratotic actinic keratoses of the face and scalp. The product is applied in the physician's office.

Another variant of PDT for skin lesions is Metvixia® and the Aktilite CL 128 lamp, each of which received FDA approval in 2004. Metvixia consists of the topical application of methyl aminolevulinate (MAL) followed by exposure with the Altilite CL 128 lamp, a red-light source. Metvixia is indicated for the treatment of non-hyperkeratotic actinic keratosis of the face and scalp in immunoincompetent patients when used in conjunction with lesion preparation (debridement using a sharp dermal curette) in the physician's office when other therapies are unacceptable or considered medically less appropriate.

A 5-aminoleveulinic acid patch technology (5-ALA Patch) is available outside of the U.S. through an agreement between Intendis (part of Bayer HealthCare) and Photonamic GmbH and Co. KG. The 5-ALA patch is not approved by the FDA.

In 2016, the FDA approved Ameluz® (aminolevulinic acid hydrochloride) gel, 10% (BF-200 ALA; Biofrontera AG) in combination with PDT using BF-RhodoLED lamp, to be used for the lesion-directed and field-directed treatment of actinic keratoses of mild-to-

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moderate severity on the face and scalp. The treatment is to be administered by a health care provider.

Note: PDT using Metvixia with the Aktilite Lamp is no longer manufactured and has been withdrawn from market.

PRIOR APPROVAL

Not applicable.

POLICY

Photodynamic therapy (PDT) may be considered **medically necessary** for the treatment of **one of the following** conditions:

- Non-hyperkeratotic actinic keratosis of the face, scalp, and upper extremities.
- Low-risk superficial or nodular basal cell carcinoma (BCC) *only* when surgery and radiation are contraindicated.
- Bowen's disease (squamous cell carcinoma in situ) *only* when surgery and radiation are contraindicated.

Photodynamic therapy is considered **investigational** when the criteria above is not met and for all other dermatologic applications, including, but not limited to one of the following conditions as there is insufficient evidence to support a conclusion concerning net health outcomes or benefits associated with this procedure:

- Acne vulgaris
- Disseminated superficial actinic porokeratosis (DSAP)
- High-risk basal cell carcinomas
- Hidradenitis suppurativa
- Mycoses
- Port wine stains

Policy Guidelines

Surgery and radiation are the preferred treatments for low-risk basal cell cancer and Bowen disease. If photodynamic therapy is selected for these indications because of contraindications to surgery or radiation, patients and physicians need to be aware that it may have a lower cure rate than surgery or radiation.

PROCEDURE CODES AND BILLING GUIDELINES

To report provider services, use appropriate CPT* codes, Alpha Numeric (HCPCS level 2) codes, Revenue codes, and/or ICD diagnosis codes.

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- 96567 Photodynamic therapy by external application of light to destroy premalignant lesions of the skin and adjacent mucosa with application and illumination/activation of photosensitive drug(s), per day.
- 96573 Photodynamic therapy by external application of light to destroy premalignant lesions of the skin and adjacent mucosa with application and illumination/activation of photosensitive drug(s) provided by a physician or other health care professional, per day
- 96574 Debridement of premalignant hyperkeratotic lesion(s) (i.e. targeted curettage, abrasion) following by photodynamic therapy by external application of light to destroy premalignant lesions of the skin and adjacent mucosa with application and illumination/activation of photosensitizing drug(s) provided by a physician or other qualified health care professional, per day
- J7308 Aminolevulinic hydrochloric acid for topical administration, 20%, single unit dosage form (354 mg)
- J7309 Methyl aminolevulinate (MAL) for topical administration, 16.8%, 1 gram (no longer manufactured and has been withdrawn from the market)
- J7345 Aminolevulinic acid HCl for topical administration, 10% gel, 10 mg

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POLICY HISTORY

Date	Reason	Action
February 2022	Annual Review	Policy Revised
February 2021	Annual Review	Policy Renewed
February 2020	Annual Review	Policy Revised
February 2019	Annual Review	Policy Revised
February 2018	Annual Review	Policy Revised
February 2017	Annual Review	Policy Renewed
February 2016	Annual Review	Policy Renewed
March 2015	Annual Review	Policy Revised
April 2014	Annual Review	Policy Renewed
May 2013	Annual Review	Policy Renewed
June 2012	Annual Review	Policy Renewed
August 2011	Annual Review	Policy Renewed

New information or technology that would be relevant for Wellmark to consider when this policy is next reviewed may be submitted to:

Wellmark Blue Cross and Blue Shield
Medical Policy Analyst
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