Supplementary Material 1 (search terms)

Search Terms

PUBMED STRATEGY

#1 Photochemotherapy[MeSH] 13016
#2 Phototherapy[MeSH] 27958
#4 photochemo*[tiab] 1859
#5 photodynamic[tiab] 14758
#6 PDT[tiab] 8030
#7 phototherapy[tiab] 5344
#8 photosensiti*[tiab] 18756
#9 (#1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8) 48638
#10 Skin Aging[MAJR] 3799
#11 "Keratosis, Actinic"[MeSH] 563
#12 keratosis[tiab] 3905
#13 photodamaged skin[tiab] 364
#14 photodamag*[tiab] 2310
#15 actinic[tiab] 4310
#16 (#10 OR #11 OR #12 OR #13 OR #14 OR #15 OR #16) 30558
#17 (#9 AND #16) 1752
#18 (randomized controlled trial[pt] OR controlled clinical trial[pt] OR randomized[tiab] OR placebo[tiab] OR drug therapy[sh] OR randomly[tiab] OR trial[tiab] OR groups[tiab]) NOT (animals [mh] NOT humans [mh])
#19 (#17 AND #18) 752

EMBASE STRATEGY

('photochemotherapy' or 'phototherapy')
and ('cutaneous parameters' or 'actinic keratosis')
319 results

CLINICAL TRIALS REGISTERS STRATEGY

"Phototherapy" AND "Keratosis, Actinic" **41 results**

Terms and Synonyms

phototherapy: 2378 studies
- photochemotherapy
- actinotherapy
- light
- photoradiation therapy

keratosis, actinic: 212 studies
- keratinocytic intraepidermal neoplasia
- keratoses
- senile hyperkeratosis
- senile keratoma
- solar hyperkeratosis

methylaminolevulinate: 35 studies

methyl 5 aminolevulinate: 33 studies

metvix: 32 studies

metvixia: 4 studies

photodynamic therapy: 317 studies

photochemotherapies
photoradiation therapy
therapy: 69908 studies

disease management
procedure - therapeutic
therapeutic aspects
therapeutic interventions
therapeutic method
therapeutic proced
therapeutic procedures
therapeutic technique
treatment

LILACS STRATEGY
(tw:(photochemotherapy)) OR (mj:(phototherapy))
AND (mj:(Skin Aging)) OR (tw:(Keratosis, Actinic))
116 results

The searches made at other clinical trials registers did not lead to any results, as follows:

ISRCTN registry. The metaregisters of controlled trials
http://www.isrctn.com/
"Phototherapy" - 27
"Keratosis, Actinic" – 1
"Phototherapy" AND "Keratosis, Actinic" – 0 results

Australian New Zealand Clinical Trials Registry (ANZCTR)
http://www.anzctr.org.au/
"Phototherapy" - 31
"Keratosis, Actinic" – 20
"Phototherapy" AND "Keratosis, Actinic" – 0 results

WHO. International Clinical Trials Registry
http://apps.who.int/trialsearch/
"Phototherapy" AND "Keratosis, Actinic" – 0 results

Estrategia desarrollada por el sistema con base en los términos empleados.
Keratosis, Actinic OR "Actinic (Solar) Keratosis" OR "Actinic Keratoses" OR "Actinic keratosis" OR "Keratoses, Actinic" OR "KERATOSIS, ACTINIC" OR "Senile Hyperkeratosis" OR "senile keratosis" OR "solar keratosis"
Phototherapy OR "Light Therapies" OR "light therapy" OR "Mental Health @ None @ Light Therapy @ None @ None @ None @ None" OR "photopheresis" OR "PHOTORAD THER" OR "Photoradiation Therapies" OR "Photoradiation Therapy" OR "PHOTOTHER" OR "Phototherapies" OR "PHOTOTHERAPY" OR "THER PHOTORAD" OR "Therapies, Light" OR "Therapies, Photoradiation" OR "Therapy, Light" OR "Therapy, Photoradiation"

Supplementary Material 2

Trail registries scanned:

Nederlands Trial Register.

http://www.trialregister.nl/trialreg/index.asp
"Phototherapy" - 2
"Keratosis, Actinic" – 0
"Phototherapy" AND "Keratosis, Actinic" – 0 results

National Institutes of Health. Clinical Studies
clinicalstudies.info.nih.gov
"Phototherapy" – 6
"Keratosis, Actinic" – 0
"Phototherapy" AND "Keratosis, Actinic" – 0 results

Chinese Clinical Trial Registry
http://www.chictr.org/en/
"Phototherapy" – 0
"Keratosis, Actinic" – 0
"Phototherapy" AND "Keratosis, Actinic" – 0 results

Supplementary Material 3. Excluded studies and reason for exclusion

Study Reference	Reason for exclusion in the analysis
1. Ruiz-Rodríguez , Sanz-Sánchez T, Córdoba S.. Photodynamic Photorejuvenation. Dermatol Surg 28:8:August 2002	It was a case-series not a RCT.

2. Hall JA, Keller PJ, Keller GS. Dose Response of Combination Photorejuvenation Using Intense Pulsed Light–Activated Photodynamic Therapy and Radiofrequency Energy. Arch Facial Plast Surg. 2004;6:374-378.	It was not a RCT
3. Gold MH, Bradshaw VL, Boring MM. Split-Face Comparison of Photodynamic Therapy with 5-Aminolevulinic Acid and Intense Pulsed Light Versus Intense Pulsed Light Alone for Photodamage. Dermatol Surg. 2006 Jun;32(6):795-801	It was not a RCT
4. Bruscino N, Rossi R, Dindelli M. Facial skin rejuvenation in a patient treated with photodynamic therapy for actinic keratosis. Dermatologic Therapy, Vol. 23, 2010, 86–89.	It was a case-report not a RCT
5. Park MY, Sohn S, Lee ES, Kim YC. Photorejuvenation induced by 5-aminolevulinic acid photodynamic therapy in patients with actinic keratosis: A histologic analysis. J Am Acad Dermatol 2010;62:85-95	It was not a RCT
6. Issa MC, Piñeiro-Maceira J, Vieira MT, Olej B. Photorejuvenation with Topical Methyl Aminolevulinate and Red Light: A Randomized, Prospective, Clinical, Histopathologic, and Morphometric Study. Dermatol Surg 2010;36:39–48	It was not a RCT
7. Szeimies RM, Torezan L, Niwa A, Valente N. Clinical, histopathological and immunohistochemical assessment of human skin field cancerization before and after photodynamic therapy. British Association of Dermatologists 2012 167, pp150–159	It was not a RCT
8. Morton CA. Can photodynamic therapy reverse the signs of photoageing and field cancerization? British Association of Dermatologists 2012 167, pp2–5	It was not a RCT
9. Zane C, Capezzera R, Sala R. Clinical and Echographic Analysis of Photodynamic Therapy Using Methylaminolevulinate as Sensitizer in the Treatment of Photodamaged Facial Skin. Lasers in Surgery and Medicine 39:203–209 (2007)	It was not a RCT
10. Tierney E, Barker A, Ahdout J. Photodynamic Therapy for the Treatment of Cutaneous Neoplasia, Inflammatory Disorders, and Photoaging. Dermatol Surg 2009;35:725–746	It was not a RCT
11. Wiegell, M. Hædersdal, P.A. Philipsen. 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. British Journal of Dermatology 2008 158, pp740–746	It was a RCT but related to AK´s not to facial photodamage
12. Wiegell, J. Skiveren, P.A. Philipsen. Pain during photodynamic therapy is associated with protoporphyrin IX fluorescence and fluence rate. British Journal of Dermatology 2008 158, pp727–733.	It was a RCT but with pain as main outcome
13. Kaae J, Philipsen PA, Haedersdal M. Immediate Whealing Urticaria in Red Light Exposed Areas During Photodynamic Therapy. Acta Derm Venereol. 2008;88(5):480-3.	It was not a RCT
14. Wiegell SR, Haedersdal M, Wulf HC. Cold Water and Pauses in Illumination Reduces Pain During	

Photodynamic Therapy: A Randomized Clinical Study. Acta Derm Venereol.2009;89(2):145-9	It was a RCT but with pain as main outcome
15. Gholam P, Denk K, Sehr T, Enk A, Hartmann M. Factors influencing pain intensity during topical photodynamic therapy of complete cosmetic units for actinic keratoses. J Am Acad Dermatol. 2010 Aug;63(2):213-8	It was not a RCT
16. Nobbe S, Trüeb RM, French LE, Hofbauer GF. Herpes simplex virus reactivation as a complication of photodynamic therapy.Photodermatol Photoimmunol Photomed. 2011 Feb;27(1):51-2	It was a case-report not a RCT
17. Arits AH, van de Weert MM. Pain during topical photodynamic therapy: uncomfortable and unpredictable. J Eur Acad Dermatol Venereol. 2010 Dec;24(12):1452-7	It was not a RCT
18. Buinauskaite E, Zalinkevicius R, Buinauskiene J,. Pain during topical photodynamic therapy of actinic keratoses with 5-aminolevulinic acid and red light source: randomized controlled trial. Photodermatol Photoimmunol Photomed. 2013 Aug;29(4):173-81	It was a RCT but with AK´s and pain as outcomes not facial photodamage improvement
19. Pavan K. Nootheti, Mitchel P. Goldman. Aminolevulinic Acid-Photodynamic Therapy for Photorejuvenation. Dermatol Clin 25 (2007) 35–45.	It was not a RCT
20. Karrer. R.-M. Szeimies. Photodynamische Therapie nichtonkologischer Indikationen. Hautarzt. 2007 Jul;58(7):585-96.	It was not a RCT
21. Woodhall KE, Goldman MP, Gold MH, Biron J. Benefits of Using a Hydroquinone/Tretinoin Skin Care System in Patients Undergoing Intense Pulsed Light Therapy for Photorejuvenation: A Placebo-Controlled Study. J Drugs Dermatol. 2009 Sep;8(9):862-7	It evaluates IPL + hidroquinone/tretinoin without the use of a chromophore
22. Boulos PR, Kelley JM, Falcão MF, Tremblay JF. In the Eye of the BeholderFSkin Rejuvenation Using a Light-Emitting Diode Photomodulation Device. Dermatol Surg. 2009 Feb;35(2):229-39	No es un ECA, no evalúa la TFD
23. Von Felbert V, Hoffmann G, Hoff-Lesch S. Photodynamic therapy of multiple actinic keratoses: reduced pain through use of visible light plus water-filtered infrared A compared with light from light-emitting diodes. Br J Dermatol. 2010 Sep;163(3):607-15	It was a RCT but with AK´s improvement as outcome not facial photodamage improvement
24. Yuan-Hong Li, Yan Wu. A Split-Face Study of Intense Pulsed Light on Photoaging Skin in Chinese Population. Lasers Surg Med. 2010 Feb;42(2):185-91	It was a RCT but with IPL as intervention without the use of a chromophore
25. Kim JE, Chang S, Won CH, Kim CH. Combination Treatment Using Bipolar Radiofrequency-Based Intense Pulsed Light, Infrared Light and Diode Laser Enhanced Clinical Effectiveness and Histological Dermal Remodeling in Asian Photoaged Skin. Dermatol Surg. 2012 Jan;38(1):68-76.	It was not a RCT
26. Karrer S, Kohl E, Feise K. Photodynamic therapy for skin rejuvenation: review and summary of the literature – results of a consensus conference of an expert group for aesthetic photodynamic therapy. J Dtsch Dermatol Ges. 2013 Feb;11(2):137-48	It was not a RCT
27. Kearney C, Brew D.. Single-Session Combination Treatment with Intense Pulsed Light and Nonablative	It was a RCT but with IPL and Non ablative fractional

Fractional Photothermolysis: A Split-Face Study. Dermatol Surg. 2012 Jul;38(7 Pt 1):1002-9	photothermolysis as interventions without the use of a chromophore
28. Chan CS, Saedi N, Mickle C, Dover JS. Combined Treatment for Facial Rejuvenation Using an Optimized Pulsed Light Source Followed by a Fractional Non-Ablative Laser. Lasers Surg Med. 2013 Sep;45(7):405-9	It was a RCT but with the use of an optimized pulsed light source followed by a fractional non-ablative laser as interventions
29. Morton CA, Szeimies RM, Sidoroff A, Braathen LR. European guidelines for topical photodynamic therapy part 2: emerging indications--field cancerization, photorejuvenation and inflammatory/infective dermatoses. J Eur Acad Dermatol Venereol. 2013 Jun;27(6):672-9	It was not a RCT
30. Avram D, Goldman M. Effectiveness and safety of ALA-IPL en treating actinic keratoses and photodamage. J drugs dermatol. 2004; 3:32-39	It was not a RCT
31. Braun M. Intense pulsed light versus advanced fluorescent technology pulsed light for photodamaged skin a Split face pilot comparison. J drugs dermatol. 2007;6:1024-1028	It was not a RCT
32. Corti MA. Mainetti C. Methylaminolevulinic acid based photodynamic therapy: the patient view. Photomed Laser Surg. 2010 Oct;28(5):697-702	It was not a RCT
33. Serrano G, Lorente M, Reyes M. Photodynamic therapy with low-strength ALA, repeated applications and short contact periods (40-60 minutes) in acne, photoaging and vitiligo. J Drugs Dermatol. 2009 Jun;8(6):562-8.	It was not a RCT
34. Lowe NJ, Lowe P. Pilot study to determine the efficacy of ALA-PDT photorejuvenation for the treatment of facial ageing. J Cosmet Laser Ther. 2005 Dec;7(3-4):159-62.	It was not a RCT
35. Gold MH. Therapeutic and aesthetic uses of photodynamic therapy part one of a five-part series: the use of photodynamic therapy in the treatment of actinic keratoses and in photorejuvenation. J Clin Aesthet Dermatol. 2008 Jul;1(2):32-7	It was not a RCT
36. Redbord KP, Hanke CW. Topical photodynamic therapy for dermatologic disorders: results and complications. J Drugs Dermatol. 2007 Dec;6(12):1197-202.	It was not a RCT
37. Marmur ES, Phelps R. Ultrastructural changes seen after ALA-IPL photorejuvenation: a pilot study. J Cosmet Laser Ther. 2005 Mar; 7(1):21-4.	It was not a RCT
38. Gold MH. The evolving role of aminolevulinic acid hydrochloride with photodynamic therapy in photoaging. Cutis. 2002 Jun; 69(6 Suppl):8-13	It was not a RCT
39. Piccioni A, Fargnoli MC, Schoinas S, Suppa M, Frascione P, Ginebri A, Chimenti S, Peris K. Efficacy and tolerability of 5-aminolevulinic acid 0.5% liposomal spray and intense pulsed light in wrinkle reduction of photodamaged skin. J Dermatolog Treat. 2011 Oct;22(5):247-53	It was not a RCT

Supplementary Material 4. Included studies and their risk of bias assessment.

ALA Trials

Touma et al, 2004

Methods	Split-face randomized, controlled trial
Participants	**Location:** Boston, Massachusetts, USA (1 Site) **Setting of recruitment:** Patients from a general dermatology practice. **Sample size:** 18 patients (11 women and 7 men) **Number randomized:** 18 patients (36 Split-faces) **Number completed:** 17 patients (34 Split-faces) **Participant (baseline) characteristics:** **Inclusion criteria:** Patients with at least 4 non-hypertrophic AKs and mild to moderate diffuse facial photodamage and aged 41 to 76 years and 48 to 66 years, respectively, were Included. **Exclusion criteria:** corresponded to a history of porphyria or photosensitivity, hyperkeratotic AKs, active infectious disease, pregnancy or lactation, or use of photosensitizing drugs such as tetracycline or retinoids.
Interventions	**Intervention:** (n= 36 split-faces) One session of 5-ALA at 20% (Levulan Kerastick, DUSA Pharmaceuticals Inc.) + Blue light blue light during 16 minutes and 40 seconds (10 J/cm^2) (BLU-U, DUSA Pharmaceuticals, Inc) with 1 hour incubation **Comparator Group** (n=36 split-faces) 5-ALA at 20% (Levulan Kerastick, DUSA Pharmaceuticals Inc.) + blue light during 16 minutes and 40 seconds (10 J/cm^2) (BLU-U, DUSA Pharmaceuticals, Inc) with 2 hours incubation and to 5-ALA at 20% (Levulan Kerastick, DUSA Pharmaceuticals Inc.) + blue light during 16 minutes and 40 seconds (10 J/cm^2) (BLU-U, DUSA Pharmaceuticals, Inc) with 3 hours incubation. **Use of additional interventions (Common to both treatment arms):** 40% urea cream (Carmol 40) or vehicle cream daily for 7 days. Also, lidocaine hydrochloride (3%) in a mildly acidic "acid mantle" base (LidaMantle) or its vehicle was allocated to the entire face 45 minutes before PDT. Before exposure to the blue light, facial skin was examined under Wood's light illumination (model No. 9312; Burton Medical Products, Chatsworth, Calif) to detect coral-red fluorescence.
Outcomes	**Scale used to measure photodamage:** Griffiths scale (0-8). **Outcomes of interest in the review:** Authors did not specify primary or secondary outcomes. Outcomes evaluated were: The number of actinic keratosis, photodamage improvement measured with the validated Griffiths scale from 0 (no damage) to 8 (severe damage), adverse events such as erythema, edema, and crusting recorded as none=0; focal=1; mild=2; moderate=3; and severe=4, pain recorded as none=0; mild=1-3; moderate=4-6; and severe=7-9 and patient and investigator-assessment of global cosmetic improvement graded as: 1= 90% or greater improvement; 2= 75%-90% improvement; 3= 50%-75% improvement; 4=less than 50% improvement; 5= no change; and 6= worsening. **Time-point of outcomes measurement:** Outcomes in all participants were evaluated after 1 day and 1 week, and in 17 of 18 patients after 1 month. Ten

	patients were also assessed at 5 months (6 from the 1-hour group and 4 from the 2-hour group). **Adverse events:** More erythema, edema and crusting was seen in the urea pre-treated split faces compared to the vehicle treated. A herpes simplex reactivation was reported but the intervention used for the affected side of the face was not depicted.
Notes	This study was sponsored by DUSA Pharmaceuticals Inc, Wilmington, Mass, and DOAK Dermatologics, Fairfield, NJ. Author described no "relevant financial interests" but all other probable conflicts of interests were not specified.

Bias	Authors´judgement	Support for judgement
Random sequence generation (selection bias)	Unclear	The method of sequence generation was not reported.
Allocation concealment (selection bias)	Unclear	The method used for allocation concealment was not described.
Blinding of participants and personnel (Performance bias)	Unclear	Although there is an author's statement of a "double-blind fashion" of the study it is unclear if patients were blinded
Blinding of outcome assessment (Detection bias)	Unclear	Although there is an author's statement of a "double-blind fashion" of the study it is unclear if outcome assessors were blinded
Incomplete outcome data (attrition bias)	High risk	Seventeen out of 18 completed the 1 month follow-up and only 5/18 patients completed the 5-months follow-up. No intention to treat analysis (ITT) was specified.
Selective reporting (reporting bias)	Low risk	Selective reporting was not detected
Other bias	Unclear	Neither sample size calculation nor statistical analyses, were specified. The low power of the study might have led to non-statistical significant differences in AK´s quantification, mottled pigmentation and coarse wrinkling. Comparisons were performed from baseline vs post-treatment in the same split-face, but there was no contralateral comparison. Specific baseline characteristics of groups were not included. This was a industry-sponsored trial with positive results.

Alster et al, 2005

Methods	Split-face randomized, controlled trial
Participants	**Location:** Washington, USA (1 Site) **Setting of recruitment:** Patients from a Dermatologic Laser Surgery practice. **Sample size:** 10 patients (8 women and 2 men) **Number randomized:** 10 patients (20 Split-faces) **Number completed:** 10 patients (20 Split-faces)

	Participant (baseline) characteristics: **Inclusion criteria:** Patients with Fitzpatrick´s Skin Phototype I or II with mild to moderate facial photodamage and with an age range of 38-63 years-old. **Exclusion criteria:** Previous facial treatments 6 months prior study entry, pregnancy, lactation, a history of the use of photosensitizers, active infectious disease or any history of photosensitivity.
Interventions	**Intervention:** (n= 20 split-faces) IPL + 5-ALA at 20% (Levulan Kerastick, DUSA Paharmaceuticals Inc.). 5-ALA was applied 60 minutes prior to IPL. **Comparator Group** (n=20 split-faces) IPL alone (Quantum SR, Lumenis, Yokneam, Israel) with energies ranging from 27-30 J/cm2 using a 560 nm filter and a double pulse of 2.4 milliseconds and 4 milliseconds. **Use of additional interventions (Common to both treatment arms):** After procedures, patients were allowed to use a mild hypoallergenic cleanser and moisturizer and a broad-spectrum sunscreen. Two sessions 4-week apart, were performed.
Outcomes	**Scale used to measure photodamage:** Not specified in the article **Outcomes of interest in the review:** Authors did not specify primary or secondary outcomes. Outcomes evaluated were: clinical improvement of facial photodamage from baseline to post-treatment through clinical photographs, according to a quartile clinical grading scale (Minimal improvement: <25%; moderate improvement: 25-50%; marked improvement: 51-75% and excellent improvement: > 75%). **Time-point of outcomes measurement:** Photographs were evaluated at week 4, 12 and 24 after the last session. Mean clinical improvement was assessed, but details regarding the relation of the quartile grading scale and means obtained, were lacking. **Adverse events:** A safety outcome (side effects) was not specified in the methods section, but was included in the analysis. Side effects of erythema, desquamation and mild edema were more frequent in the PDT + IPL treated side. No scarring or hypo or hyper pigmentation was seen in either group.
Notes	Neither financial support nor author´s conflicts of interests, were specified.

Bias	Authors´judgement	Support for judgement
Random sequence generation (selection bias)	Unclear	The method of sequence generation was not reported.
Allocation concealment (selection bias)	Unclear	The method used for allocation concealment was not described.
Blinding of participants and personnel (Performance bias)	High risk	Participants and personnel blinding was not performed
Blinding of outcome assessment (Detection bias)	High risk	Outcome assessor’s blinding was not performed
Incomplete outcome data (attrition bias)	Low risk	All split-faces were included in the analysis
Selective reporting (reporting bias)	Unclear	Safety outcome was not specified in the methods section, but was included in the analysis.

Other bias	Unclear	Neither sample size calculation nor statistical analyses, were specified. The low power of the study might have led to non-statistical significant differences. Comparison for facial photodamage improvement was performed from baseline vs post-treatment in the same split-face, but there was no contralateral comparison. Baseline characteristics of groups were not included.

Dover et al, 2005

Methods	Prospective, single-blinded, split-face randomized, controlled trial
Participants	**Location:** USA (1 Site), the exact city was not specified in the article **Setting of recruitment:** Patients from a "single group" dermatologic practice. **Sample size:** 20 patients (Gender was not specified in the article) **Number randomized:** 20 patients (40 Split-faces) **Number completed:** 20 patients (40 Split-faces) **Participant (baseline) characteristics:** **Inclusion criteria:** individuals with Fitzpatrick´s Skin Phototype I through IV, with a global score for photoaging of 2 or more and a mean age of 55 years (range, 45-70 years). **Exclusion criteria:** Exclusion criteria were not specified.
Interventions	**Intervention:** (n= 40 split-faces) IPL (Quantum SR, Lumenis, Inc. Santa Clara, California, USA) + Topical 5-ALA solution (Levulan Kerastick; DUSA Pharmaceuticals, Inc, Wilmington, Mass). Each split-face was treated with IPL (Quantum SR, Lumenis, Inc. Santa Clara, California, USA) with a wavelength of 515-1200nm. First pulse and second pulse were set at 2.4 and 4 milliseconds, respectively with a delay of 15 milliseconds between pulses. Fluence ranged from 23 to 28 J/cm2. Also, in half of the subjects the fluence was increased from 26 to 28 J/cm2 and in 2 patients, fluence was decreased to 24 J/cm2). In the remaining subjects fluence was unchanged. Fluence for the fourth and fifth treatments was left unchanged as for the third treatment. No data regarding fluence change either on the whole face or on specific split-faces was not provided. **Comparator Group** (n=40 split-faces) IPL alone (Quantum SR, Lumenis, Inc. Santa Clara, California, USA) **Use of additional interventions (Common to both treatment arms):** Skin cooling was performed with the chiller tip set to maximum and treated areas were also covered with clear contact cooling gel (Lumenis, Inc.) before treatment. Each patient received 5 full-face treatments of IPL spaced 3 weeks between treatments. Before the first 3 IPL sessions, split-faces of all patients were treated with 2 coats of 5-ALA solution (Levulan, Kerastick, DUSA Pharmaceuticals, Inc. Wilmington, Massachusetts, USA) with 30-60 minutes of incubation, according to randomization. Incubation times were shorter during initial treatments but it was lengthened according to tolerability. Full-faces were washed with a mild facial cleanser and water before IPL. After performing IPL all patients were allowed to apply a facial moisturizer with sunscreen (Neutrogena Healthy Defense SPF 30 daily moisturizer, Neutrogena Corporation, Los Angeles, California, USA).
Outcomes	**Scale used to measure photodamage:** Global score for photoaging evaluated on a 0-4 scale. **Outcomes of interest in the review:** Authors did not specify primary or secondary outcomes. Endpoints described were global photodamage and

	specific photodamage (mottled pigmentation, fine lines, tactile roughness and sallowness), recorded on a 5-point scale from 0 to 4. Outcomes were labeled as improvement if there was a decrease in score from baseline of at least 1 grade and was labeled as success if the variable received a severity score of 0 or 1. Other outcomes included were patient´s satisfaction at visit 9 rated as excellent (very satisfied), good (moderately satisfied), fair (slightly satisfied), or poor (not satisfied at all), and patient´s tolerability (erythema, scaling and dryness, edema, oozing/crusting/vesiculation recorded on a 5-point scale from 0 (none) to 4 (severe). Stinging and burning were recorded on a 4-point scale from 0 (none) to 3 (severe). At visit 9, also a complete cosmetic evaluation by the blinded investigator, was made. Telangiectasia and erythema were analyzed post-hoc. **Time-point of outcomes measurement:** Such outcomes were evaluated 1 month after the last session. **Adverse events:** The 5-ALA plus IPL–treated sides had more scaling, dryness, erythema, edema than the IPL-only sides and the intensity of stinging and burning on the 5-ALA plus IPL–treated sides was minimal.
Notes	Pharmaceutical and medical devices industries provided financial support for the study. Although financial disclosures were absent according to author´s, individual conflicts of interests were not fully described.

Bias	**Authors´judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear	The method of sequence generation was not reported.
Allocation concealment (selection bias)	Unclear	The method used for allocation concealment was not described.
Blinding of participants and personnel (Performance bias)	Unclear	It was a single-blinded (investigator) study. Patient´s satisfaction outcome could have been influenced by participants unblinding.
Blinding of outcome assessment (Detection bias)	Low risk	A blinded investigator evaluated photodamage improvement but tolerability assessment was performed by an unblinded investigator.
Incomplete outcome data (attrition bias)	Low risk	All split-faces were included in the analysis and follow-ups were performed in all patients.
Selective reporting (reporting bias)	Unclear	Patient´s satisfaction through photographs evaluation was not specified in the methods section, but was included in the abstract and in the discussion section of the manuscript. Telangiectasia and erythema results were only depicted in the discussion section.
Other bias	Unclear	Sample size calculation was not specified. The power of the study might have led to non-statistical significant differences in some outcomes at different time-points. Fluence changes might have influenced the results. Baseline characteristics of groups were not included.

Bjerring et al, 2009

Methods	Prospective, split-face randomized, trial
Participants	**Location:** Molholm, Denmark (1 Site) **Setting of recruitment:** Not specified in the article **Sample size:** 37 women **Number randomized:** 37 patients (74 Split-faces) **Number completed:** Not specified in the article **Participant (baseline) characteristics:** **Inclusion criteria: I**ndividuals with Fitzpatrick´s Skin Phototype II-III with an average level of periorbital and perioral wrinkles of 4.6 (ranging 1–9) and 4.0 (ranging 1–8), respectively, and according to the Fitzpatrick wrinkle scale, and with a mean age of 50.3 years (range:31–64 years). **Exclusion criteria:** Previous skin tan or sunburning with pigmentation greater than medium, photosensitizing drugs use within 1 week prior to the study, a previous history of Koebner phenomena or light sensitive skin diseases, patients with any clinical suspicion of pre-cancer or skin malignancies, a history of topical retinoids, alpha-hydroxy acids, or topical vitamin C use within 3 months prior to the study, patients with an increase in skin fluorescence higher than 25FDU immediately prior to light exposure.
Interventions	**Intervention:** (n= 74 split-faces) Each split-face was treated with IPL (Ellipse Flex) with a spot size on the skin surface of 10x48mm^2. For the IPL + PDT split-face, a filtered wavelength band from 530–750 nm covering the 580nm and the 635 nm Q- bands of PpIX, was used. A single pass was performed with a double pulse of 2.5 ms duration spaced by 10 ms and with a fluence of 6–7 J/cm2.The chromophore used was 0.5% liposome encapsulated 5-ALA (Photo Spray, Ellipse A/ S) which was sprayed 12-times over the entire face with 5-minute intervals. **Comparator Group** (n=74 split-faces) In the IPL-alone treated split-face, investigators used a waveband from 400–720 nm (PL-W filter) covering all PPIX absorption peaks (Soret band and Q-bands: 407, 505, 540, 580 and 635 nm) and skin irradiation was performed with long pulse durations of 30 ms and low fluences (3.5 J/cm2). A total of 3 passes were performed reaching a total light dose of 10.5 J/cm2. **Use of additional interventions (Common to both treatment arms):** Prior to 5-ALA application, facial skin was washed with a glycolic acid cleanser (Ellipse Exfoliating Gel, Ellipse A/S, Hoersholm, Denmark). Also, PpIX skin concentration was determined with a photometer according to fluorescence measurement (Dia Medico ApS, Gentofte, Denmark).
Outcomes	**Scale used to measure photodamage:** Fitzpatrick´s wrinkle scale **Outcomes of interest in the review:** Authors did not specify primary or secondary outcomes. Efficacy endpoints were assessed through standardized digital photographs and improvement was recorded on a 6-point scale from -1 (worse), 0 (no effect), 1 (slightly better), 2 (fair), 3 (good) and 4 (excellent). Outcomes evaluated were: wrinkle reduction, diffuse redness clearance, dyschromia clearance and telangiectasia improvement. Patient-reported outcomes were also evaluated through the digital photographs and also recorded on the 6-point scale from -1 (worse), 0 (no effect), 1 (slightly better), 2 (fair), 3 (good) and 4 (excellent). Participants also rated their degree of satisfaction according to a 5-point scale as follows: unsatisfied, slightly satisfied, satisfied, very satisfied, and extremely satisfied.

	Time-point of outcomes measurement: Interventions effects in periorbital and perioral wrinkles were categorized according to the Fitzpatrick Wrinkle Scale at baseline and at 3 months post-treatment. **Adverse events:** Safety outcomes included pigmentation disturbances (hypopigmentation, hyperpigmentation), atrophy and scarring (atrophic or hypertrophic) and were recorded on a 4-point scale (none, slight, moderate, severe). At the end of the study no side effects such as atrophy, scarring, hypo- or hyperpigmentation were observed.
Notes	Neither financial support nor author´s conflicts of interests were specified.

Bias	Authors´judgement	Support for judgement
Random sequence generation (selection bias)	Low Risk	Split-faces treated were selected according to a randomization table.
Allocation concealment (selection bias)	Unclear	The method used for allocation concealment was not described.
Blinding of participants and personnel (Performance bias)	Unclear	It was unclear if the study was single (Just investigators) or double-blinded (Investigators and patients.
Blinding of outcome assessment (Detection bias)	Unclear	A blinded investigator evaluated periorbital and perioral photodamage improvement through baseline vs post-treatment patient´s and contralateral facial photographs. It was unclear if blinding was applied for wrinkle reduction, diffuse redness clearance, dyschromia clearance and telangiectasia improvement and side effects assessment. Measures used to assure outcome assessor's blinding were not included in the article.
Incomplete outcome data (attrition bias)	Unclear	It is unclear if all patients completed follow-ups. No intention to treat analysis (ITT) was specified.
Selective reporting (reporting bias)	Low Risk	Selective reporting was not detected
Other bias	Unclear	Wrinkles, dyschromia, diffuse redness, telangiectasias outcomes were measured as ordinal variables but in the analysis section it seems as they have been treated as quantitative variables. Sample size calculation was not specified. The low power of the study might have led to non-statistical significant differences in outcomes when contralateral comparisons were made. Most analysis are centered in baseline vs post-treatment comparisons. Baseline characteristics of groups were not included, and just a mean of baseline fluorescence was depicted.

Xi et al, 2011

Methods	Prospective, double-blind, split-face randomized controlled trial
Participants	**Location:** Shanghai, China (1 Site) **Setting of recruitment:** Hushan Hospital, Fudan University **Sample size:** 26 women **Number randomized:** 26 patients (52 Split-faces) **Number completed:** Not specified in the article **Participant (baseline) characteristics:** **Inclusion criteria:** Participants with Fitzpatrick´s Skin Phototype II-IV and a median age of 48 (range: 39–62 years-old) with at least a modest degree of photodamage defined according to a of 2 or more on a scale from 0 to 4 of global photodamage score, tactile skin roughness, fine lines, coarse wrinkles, and mottled hyperpigmentation. **Exclusion criteria:** Exclusion criteria corresponded to a previous history of photosensitivity or laser/cosmetic treatments within 6 months from recruitment, any use of topical retinoids or other skin care products containing hydroquinones, glycolic acids, or vitamin C within 30 days previous to study initiation, systemic retinoids use within 6 months before study initiation, a "likelihood of becoming pregnant" and active lactation.
Interventions	**Intervention:** (n= 52 split-faces) Topical 5-ALA (Shanghai Fudan-Zhanjiang Bio-Pharmaceutical Co. Ltd., Shanghai, China) with IPL (Lumenis, Inc., Santa Clara, CA) with wavelengths ranging from 520 to 1,200 nm. The spot size of the IPL was 15_35 mm. Either a 560-nm or a 590-nm cutoff filter was used according to the quantification of erythema and telangiectasias. Two or three pulses 3.5 to 4.0 ms were used, with a delay between pluses of 25 to 30 ms. For the double pulsing, fluences ranged from 14 to 17 J/cm2, and for triple pulsing, fluences ranged from 17 to 20 J/cm2. Intense-pulsed-Light features were chosen according to skin conditions and tolerability. Each patient received three full-face IPL treatments at 1-month intervals. The chromophore consisted in a powder commercially available of 0.5%mL of 5-ALA which was dissolved in a facial cream (TOLERIANE Fluide, La Roche-Posay, France). Before the interventions, the face was washed with a mild cleanser. In addition, 0.2mL of 10% ALA was added to certain regions with severe photodamage signs, and the same amount of the facial cream was applied to the contralateral control side. All faces were occluded with aluminum-coated paper and a 1 hour incubation was performed. After incubation, ALA was removed and full faces were covered with a 2- to 3-mm layer of a coupling gel and then irradiated with the IPL device. **Comparator Group** (n=52 split-faces) IPL alone (Lumenis, Inc., Santa Clara, CA) with wavelengths ranging from 520 to 1,200 nm. **Use of additional interventions (Common to both treatment arms):** A chiller tip integrated in the IPL hand piece was used. After IPL therapy, patients washed their faces again and received a cooling spray for 20 minutes. Patients were instructed to use a physical sun-Block (AVENE sunscreen cream, sun protection factor (SPF) 50, Pierre Fabre Corporation, Toulouse, France) and to keep away from hot water for the next 2 to 3 days, and to avoid sun exposure.
Outcomes	**Scale used to measure photodamage:** Dover´s global photodamage scale with few modifications in punctuation for tactile skin roughness, fine lines, coarse wrinkles, and mottled hyperpigmentation. **Outcomes of interest in the review:** Authors did not specify primary or secondary outcomes. Outcomes evaluated were: global photodamage, fine

	lines, mottled pigmentation, tactile skin roughness, and coarse wrinkles. Each score was recorded on a 5-point scale (0–4). An independent investigator recorded scores for each split-face at each treatment session and during the follow-ups. Improvement was defined as a decrease of at least 1 grade in score from baseline and success was defined as a severity score of 0 or 1. Pain was also assessed through the visual analog scale (VAS). Contralateral comparisons of results for all photodamage variables and for pain, were performed A patient-reported outcome of treatment satisfaction was also included and was recorded by each patient on each side of the face as excellent (very satisfied), good (moderately satisfied), fair (slightly satisfied), or poor (not satisfied at all). **Time-point of outcomes measurement:** Interventions effects measurement was performed at 1 and 2 months after final treatment. **Adverse events:** The ALA-IPL PDT side had more erythema and post-inflammatory hyperpigmentation (PIH). No erythema and edema lasted longer than 1 month, and PIH was transient and faded within 2 months.
Notes	This trail was sponsored by Shanghai Fudan-Zhanjiang Bio-Pharmaceutical Co. Ltd. Authors indicated “no significant interest with commercial supporters” but further specific data was not available in the article.

Bias	Authors´judgement	Support for judgement
Random sequence generation (selection bias)	Unclear	The method of sequence generation was not reported.
Allocation concealment (selection bias)	Unclear	The method used for allocation concealment was not described.
Blinding of participants and personnel (Performance bias)	Unclear	Although the study was labeled as double-blind, it was unclear who was also blinded besides the outcome assessors.
Blinding of outcome assessment (Detection bias)	Unclear	A blinded “independent” investigator evaluated outcomes but it was unclear if assessments were performed clinically or through the photographs taken. Measures used to assure outcome assessor’s blinding were not included in the article.
Incomplete outcome data (attrition bias)	High Risk	An ITT analysis was not performed. Two patients withdrew from the study: One due to an allergy to IPL, but it was unclear which side of the face (or whole face) was affected. In the other excluded patient, it was unclear if not meeting study requirements was related to the type of intervention received. The exclusion of these 2 patients in the analysis might have influenced the results due to the low power of the study.
Selective reporting (reporting bias)	Low risk	Selective reporting was not detected.
Other bias	Unclear	This was an industry-sponsored trial with positive results, with scarce specific data on potential conflicts of interest. Sample size calculation was not specified. Variations in

		IPL parameters according to individual features might have influenced final results. Baseline characteristics of groups were not included.

Haddad et al, 2011

Methods	Randomized full-face trial
Participants	24 Exclusion criteria corresponded to **Location:** Sao Paulo, Brazil (1 Site) **Setting of recruitment:** Skin cancer section of the plastic surgery division of the surgery department of the Federal University of Sao Paulo, Brazil. **Sample size:** 24 individuals (gender was not specified) **Number randomized:** 24 patients (Full-face) **Number completed:** 21 patients **Participant (baseline) characteristics:** **Inclusion criteria:** individuals with SPT I-IV with at least 5 AK´s on face or scalp and moderate to severe photodamage indicated by fine wrinkles, mottled pigmentation, and textural alterations. Actinic keratosis must not have been treated during the last 6 months. Patient´s age was not depicted. **Exclusion criteria:** A history of porphyria or photosensitivity, any active infectious disease, systemic retinoid use within the last year, keloids o hypertrophic scars history, SPT V-VI, pregnancy or lactation, use of any systemic photosensitizing drug, uncontrolled diabetes, hypertension or cardiovascular disease.
Interventions	**Intervention:** (n= 24) IPL ((Vasculight, ESC, Lumenis, Inc. Santa Clara, California, USA) at 20 J + 5-ALA (Levulan, Kerastick, DUSA Pharmaceuticals, Inc. Wilmington, Massachusetts, USA). All IPL´s were performed with a 515 nm cutoff filter, double pulse (3ms/6ms) with a delay of 10 ms. **Comparator Group** (n=24) IPL ((Vasculight, ESC, Lumenis, Inc. Santa Clara, California, USA) at 25 J + 5-ALA (Levulan, Kerastick, DUSA pharmaceuticals, Inc. Wilmington, Massachusetts, USA) vs IPL ((Vasculight, ESC, Lumenis, Inc. Santa Clara, California, USA) at 40 J + 5-ALA (Levulan, Kerastick, DUSA Pharmaceuticals, Inc. Wilmington, Massachusetts, USA) vs IPL ((Vasculight, ESC, Lumenis, Inc. Santa Clara, California, USA) at 50 J + 5-ALA (Levulan, Kerastick, DUSA Pharmaceuticals, Inc. Wilmington, Massachusetts, USA) vs IPL (Vasculight, ESC, Lumenis, Inc. Santa Clara, California, USA) alone. **Use of additional interventions (Common to both treatment arms):** Patients were allowed to perform a single application of non-micronized sunscreen after sessions and were instructed to avoid sun exposure for the first 48 hours post-treatment.
Outcomes	**Scale used to measure photodamage:** Griffiths scale (0-8). **Outcomes of interest in the review:** Authors did not specify primary or secondary outcomes. Actinic keratosis were numbered from 1-5 and they must have been non hyperkeratotic, <1 cm in diameter, dry, yellowish, rough and with scales. Photodamage was measured with the 0-8 Griffiths scale. Also global response assessment was rated on a 0-7 scale as follows: 0= Complete response, 1= ~90 % improvement, 2= ~75 % improvement, 3= ~50 % improvement, 4= ~10 % improvement, 5= no improvement and 6= worsening of the condition. Follow-ups were performed 5-7 days and 8 weeks post-treatment. Tolerability was evaluated at 24-48 hours post-treatment according to the eryhthema, crusting, edema and erosion presentation and it was recorded on a 0-4 scale (0=none, 1=minimal, 2=mild, 3=moderate, 4=severe).

	Patient discomfort was also recorded on a 0-3 scale (0=none, 1=minimal, 2=moderate, 3=severe). **Time-point of outcomes measurement:** Outcomes assessment was performed through standardized clinical photographs taken at day 2 and at 8 weeks post-treatment. **Adverse events:** Erythema, edema, crusts and erosions were evaluated 48 hours after sessions. Erythema was more frequent in all groups and edema was greater in the 25, 40 and 50J groups compared to the control group. Discomfort during treatments was significantly greater only in the 25J group when compared to the 20J group.
Notes	ALA was supplied by DUSA Pharmaceuticals at no cost. Authors only depict disclosures regarding consultancies for laser companies or DUSA pharmaceuticals.

Bias	Authors´judgement	Support for judgement
Random sequence generation (selection bias)	Unclear	The method used for random sequence generation was not described.
Allocation concealment (selection bias)	Unclear	The method used for allocation concealment was not described.
Blinding of participants and personnel (Performance bias)	Unclear	Participants blindness was not specified
Blinding of outcome assessment (Detection bias)	Unclear	Authors state that 2 independent physicians evaluated outcomes through photographs but blindness was not specified.
Incomplete outcome data (attrition bias)	High Risk	An ITT analysis was not performed. Three patients withdrew from the study: Two did not attended the follow-up visits and 1 died due to a heart attack but it was unclear to which arm of the study they belonged. The exclusion of these 3 patients in the analysis might have influenced the results due to the low power of the study.
Selective reporting (reporting bias)	Unclear	Photodamage comparison was included in the methods section but statistical analysis of this variable was not included in the results.
Other bias	Unclear	Sample size calculation was not specified. The majority of comparisons were intra-patient, not vs the control group. Baseline characteristics of groups were not included. This positive trial was partially sponsored by the pharmaceutical industry.

MAL Trials

Ruiz-Rodriguez et al, 2007

Methods	Pilot, prospective, split-face randomized, controlled trial
Participants	**Location:** Madrid, Spain (1 Site) **Setting of recruitment:** Patients from an ambulatory dermatologic clinic. **Sample size:** 4 Women **-Number randomized:** 4 patients (8 Split-perioral areas) **-Number completed:** 4 (8 Split-perioral areas) **Participant (baseline) characteristics:** **Inclusion criteria:** Female patients with Fitzpatrick Skin type II or III, with mild to moderate rhytides and no actinic keratosis. Patient´s age and exclusion criteria were not depicted.
Interventions	**Intervention:** (n= 8 split-perioral areas) Fraxel Laser SR750, Reliant Technologies Inc, Palo Alto, CA) alone. **Comparator Group** (n= 8 split-perioral areas) Fraxel Laser SR750 + Methyl Aminolevulinate with a 3 hour incubation + red light (PhotoCure ASA, Oslo, Norway). The perioral area was treated with 2 sessions of fractional laser rejuvenation (Fraxel SR750, Reliant Technologies Inc, Palo Alto, CA), with a 3-weeks +/- 3 days interval. The first laser session consisted of 8 passes with energy levels of 8mJ/cm2 at a density setting of 250 MTZ/cm2 up to a density of 2,000 MTZ/cm2. The second session consisted of 8 passes with energy levels of 8mJ/cm2 at a density setting of 250 MTZ/cm2 and 2 additional passes using energy levels of 15 to 18 mJ/cm2 at a density setting of 125 MTZ/cm2 up to a 2,250 MTZ/cm2 density. Immediately after each laser treatment, topical Methyl Aminolevulinate with a 3 hour incubation was applied and treatment area was exposed to red light (PhotoCure ASA, Oslo, Norway) in a dose of 37J/cm2 according to split-face randomization. **Use of additional interventions (Common to both treatment arms):** Mepivacaine infraorbital and sub-mental nerve blocks were performed for local anesthesia and the Cryo 5 Cold Air device was used for pain and to minimize thermal injury. Strict sun avoidance and sun protection was advised after each session.
Outcomes	**Scale used to measure photodamage:** Not specified in the article **Outcomes of interest in the review:** Authors did not specify primary or secondary outcomes. Outcomes evaluated were: improvement of superficial perioral wrinkles from baseline to post-treatment through clinical photographs. (Arbitrary classification of improvement as excellent, good, fair or poor), and patient´s satisfaction by comparing each split-face after treatment (Arbitrary classification of improvement as excellent, good, fair or poor). Safety outcome was not specified in the methods section, but was included in the analysis. **Time-point of outcomes measurement:** Outcomes were evaluated at week 4 and at week 12 after the last session. **Adverse events:** More erythema, edema and desquamation were observed in the Laser + PDT split-face. Herpes simplex recurrence was reported but we were unable to determine to which treated side of the face corresponded. Transient post-inflammatory hyperpigmentation was described in one patient of the PDT + laser group.
Notes	Neither financial support nor author´s conflicts of interests were specified.

Bias	**Authors´judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear	The method of sequence generation was not reported.

Allocation concealment (selection bias)	Unclear	The method used for allocation concealment was not described.
Blinding of participants and personnel (Performance bias)	Unclear	Measures used for blinding were not specified. It was not clear if patients were blinded for satisfaction assessment.
Blinding of outcome assessment (Detection bias)	Low risk (For perioral photodamage improvement)	Quote: "A blinded investigator evaluated each side of the perioral area".
Incomplete outcome data (attrition bias)	Low risk	All split-faces were included in the analysis.
Selective reporting (reporting bias)	Unclear	Safety outcome was not specified in the methods section, but was included in the analysis.
Other bias	Unclear	Only superficial wrinkles were evaluated but other photodamage features were not included. Neither sample size calculation nor statistical tests used in analysis, were specified. The low power of the study might have led to non-statistical significant differences. Baseline characteristics of groups were not included. Potential conflicts of interests and financial support were not described.

Ruiz-Rodriguez et al, 2008

Methods	Prospective, split-face randomized, controlled trial
Participants	**Location:** Madrid, Spain (1 Site) **Setting of recruitment:** Patients from an ambulatory dermatologic clinic. **Sample size:** 10 Women (20 Split-faces) **Number randomized:** 9 patients (18 Split-faces) **Number completed:** 4 (8 Split-perioral areas) **Participant (baseline) characteristics:** **Inclusion criteria:** Female patients with a mean age of 55 years (range: 45-65 years-old) with Fitzpatrick´s Skin Phototype II or III, with mild to moderate clinical photodamage characterized by "mild rhytids", pigmentation and telangiectasia). **Exclusion Criteria**: Exclusion criteria corresponded to isotretinoin use 6 months previous to study initiation, previous laser, botulin toxin, fillers in the last year, tanning or actinic keratosis, pregnancy, any active infection, allergy history to MAL, skin photosensitivity, migraine or seizures disorders triggered by light, photosensitizing drugs, job or sports related high UV exposure after sessions, facial keloid scar history, or local hypertrichosis, any medical or skin condition that could put the patient at risk , any other issue that could interfere with patients participation or assessments.
Interventions	**Intervention:** (n= 20 split-faces) Each split-face was treated with Methyl Aminolevulinate with a 3 hour incubation + red light (PhotoCure ASA, Oslo, Norway). Three sessions were performed at 2-week intervals with first visit at 2 months after the third session. Two grams of MAL were applied to each split-

	face. A plastic occlusive dressing was used during incubation time. The non-treated side was shielded during red light exposure. **Comparator Group** (n= 20 split-faces) Methyl Aminolevulinate (with 1 hour incubation + red light (PhotoCure ASA, Oslo, Norway). **Use of additional interventions (Common to both treatment arms):** Co-interventions such as anesthesia or pain killers, were not administered.
Outcomes	**Scale used to measure photodamage:** No formal scale was used. Mild to moderate clinical photodamage characterized by "mild rythids, preferable with pigmentation and telangiectasias"). **Outcomes of interest in the review:** Authors did not specify primary or secondary outcomes. Endpoints described were improvement of fine lines, mottled pigmentation, telangiectasias, tactile roughness and skin tightness recorded on a 5-point scale from 0 (none) to 4 (severe) at two months post-treatment, and tolerability (erythema, scaling, edema and pain) recorded on a 5-point scale from 0 (none) to 4 (severe), at 3-5 days post-treatment. Photodamage improvement was labeled as "excellent", "good", "fair" or "poor" by comparing baseline vs post-treatment photographs. **Time-point of outcomes measurement:** Outcomes were evaluated at 2 months post-treatment. **Adverse events:** Safety outcome was described in the results section but not in the methods section. Erythema, edema and desquamation were more frequent in the 3hr MAL incubation when compared to the 1 hr incubation.
Notes	Neither financial support nor author´s conflicts of interests were specified.

Bias	Authors´judgement	Support for judgement
Random sequence generation (selection bias)	Unclear	The method of sequence generation was not reported.
Allocation concealment (selection bias)	Unclear	The method used for allocation concealment was not described.
Blinding of participants and personnel (Performance bias)	Unclear	It was unclear if the study was single or double-blinded.
Blinding of outcome assessment (Detection bias)	Unclear	A blinded investigator evaluated photodamage improvement through baseline vs post-treatment patient´s photographs but blinding of side effects assessment was not specified. Measures used to assure outcome assessor's blinding were not described.
Incomplete outcome data (attrition bias)	Unclear	Nine out of ten patients completed follow-ups. No intention to treat analysis (ITT) was specified.
Selective reporting (reporting bias)	Unclear	Safety outcome was not specified in the methods section, but was included in the results section of the manuscript.
Other bias	Unclear	Side-effects outcomes were measured as ordinal variables but in the analysis section these were treated statistically as quantitative variables. Sample size calculation was not specified. The lack of an ITT analysis could have an impact in efficacy

		results due to the small sample size of the study. Similarly, the low power of the study might have led to non-statistical significant differences in all outcomes. A qualitative comparison of clinical facial photodamage improvement was performed from baseline vs post-treatment in the same split-face, but there were neither contralateral comparisons, nor statistical comparisons for this outcome. Baseline characteristics of groups were not included.

Sanclemente et al, 2011 and 2012

Methods	Prospective, split-face, double-blind, placebo-controlled randomized trial
Participants	**Location:** Medellin, Colombia (1 Site) **Setting of recruitment:** Patients from an ambulatory dermatologic clinic. **Sample size:** 49 Women (98 Split-faces) **Number randomized:** 49 patients (98 Split-faces) **Number completed:** 48 (96 Split-perioral areas) **Participant (baseline) characteristics:** **Inclusion criteria:** Female with Fitzpatrick´s Skin Phototype II-IV with symmetrical scores of 2 or 3 according to Dover´s global photodamage scale, with an age range between between 35-75 years old. **Exclusion Criteria**: Exclusion criteria corresponded to pregnancy or lactation, any active infectious skin disorder, previous history of any photosensitizing disorder or drug induced photosensitization, participants requiring concurrent treatment that could have interfered with study objectives and/or assessments, subjects with less than 6 months of previous rejuvenation treatments or topical retinoids use 15 days before recruitment.
Interventions	**Intervention:** (n= 98 split-faces) Each split-face was treated either with 0.5 grams of MAL (Galderma, La Defense Cedex, France) with a 3 hour incubation + red-light (Galderma, La Defense Cedex, France). Interventions were applied according to randomization through an allocation sequence obtained using a computerized random number generator. Allocation was concealed in sealed envelopes. Interventions were applied by two nurses, but the only endpoint assessed by them was pain after each session. Patients and outcome assessors were masked to interventions. Patients had two split-face treatments 2–3 weeks apart, but thereafter and due to ethical reasons, patients received two sessions of the active intervention on the split-face initially exposed to placebo and all split-faces initially receiving the active intervention were exposed to placebo. A 3mm punch skin biopsy was performed at baseline and 1 month after the second session. During incubation time, a dark plastic occlusive dressing was used. **Comparator Group** (n= 98 split-faces) 0.5 grams of a moisturizing cream (Galderma, La Defense Cedex, France) with a 3 hour incubation, + red-light (Galderma, La Defense Cedex, France). **Use of additional interventions (Common to both treatment arms):** Following sessions, patients were instructed to wash their faces and to apply a facial moisturizer and a sunscreen. Patients also were instructed for sun-protection and sun-exposure avoidance and for pain killer use (500 mg acetaminophen tablets q.i.d.).
Outcomes	**Scale used to measure photodamage:** A modified Dover´s scale. **Outcomes of interest in the review:** The primary outcome was the Dover´s

	modified global photodamage severity score 1 month after the second session which was recorded on a 0-4 scale. Primary outcome was assessed by the same blinded dermatologist. Secondary outcomes included the specific photodamage severity score for fine lines, coarse lines, tactile roughness, mottled pigmentation, sallowness, erythema, sebaceous hyperplasia and telangiectasia, one month after the second session. These primary and secondary endpoints were labelled as “improvement” if there was a 1-grade decrease in scores from baseline, and as “success” if there was a decrease in scores to a severity score of 0 or if there was a >1 grade of decrease in scores from baseline. Lack of improvement was defined as having the same severity score as baseline after treatment. Other secondary outcomes were: The Dover´s modified global photodamage severity score, measured 1 month after the fourth session of each split-face vs. the severity score of the same split-face obtained after session 4. Also, one month after the fourth session, severity scores of each split-face, were compared. Outcomes assessments beyond the 1-month follow-ups after session 4 were not considered as objectives in this study. Safety outcomes such as pigmentation disturbances (hypopigmentation, hyperpigmentation), atrophy and scarring (atrophic or hypertrophic) were recorded on a 4-point scale (none, slight, moderate, severe) throughout the study. Other secondary outcomes included were: pain measured with the visual analogue scale immediately after session 1 and session 2 (rated from 0 to 10); patient global photodamage assessment at the end of the study (0 to 100% point scale); therapy tolerability 3 to 7 days after session 1 and session 2 (rated from0 to 3) and patient satisfaction at the end of the study (0 to 4 point scale).All these secondary endpoints were also assessed by a blinded investigator. Histopathological outcomes such as epidermal and dermal layer thickness, perivascular inflammation, solar elastosis, perifollicular fibrosis, telangiectasias, number of elastic and collagen fibers, and grade of reticular degeneration were assessed in another publication (Sanclemente et al, 2012). These outcomes were assessed through a 0-4 rated scale and were labelled again as “improvement” if there was a 1-grade decrease in scores from baseline, and as “success” if there was a decrease in scores to a severity score of 0 or if there was a >1 grade of decrease in scores from baseline. Lack of improvement was defined as having the same severity score as baseline, after treatment. **Time-point of outcomes measurement:** Outcomes were evaluated at 1 month after the fourth session of each split-face vs. the severity score of the same split-face obtained after session 4. Also, one month after the fourth session, severity scores of each split-face, were compared. **Adverse events:** Adverse effects were labelled according to Karch-Lasagna algorithm. One patient had a severe local allergic reaction and a superficial bacterial infection associated either with the moisturizer or the sun-block used after the session but no related to MAL, because the reaction was observed on both split-faces.
Notes	The trial was sponsored by Galderma Laboratories. Author´s conflicts of interests were specified.

Bias	Authors´judgement	Support for judgement
Random sequence generation (selection bias)	Low Risk	Patients were randomized to receive either the active intervention or placebo, according to an allocation sequence obtained using a computerized random number generator with

		the EPI-Info 6.0 software (CDC, Atlanta, GA, USA).
Allocation concealment (selection bias)	Low-Risk	Allocation was concealed in sealed envelopes Which were opened by the two nurses only involved in pain assessment.
Blinding of participants and personnel (Performance bias)	Low Risk	Patients were masked before applying both interventions.
Blinding of outcome assessment (Detection bias)	Low Risk	Dermatologists were blind to therapy assignment. The same dermatologist assessed the primary outcome throughout the study and another dermatologist assessed all secondary outcomes throughout the study.
Incomplete outcome data (attrition bias)	Low Risk	48 out of 49 randomized patients were analyzed because 1 patient was excluded due to a severe allergic reaction. However, since the trial had a split-face design, such exclusion did not alter final results.
Selective reporting (reporting bias)	Low Risk	Selective reporting was not detected
Other bias	Unclear	This was a industry-sponsored trial with positive results.

Palm et al, 2011

Methods	Prospective, randomized split-face trial
Participants	**Location:** La Jolla, California, USA (1 Site) **Setting of recruitment:** Patients from a Dermatology/Cosmetic Laser clinic. **Sample size:** 18 participants (11 women and 7 males) **Number randomized:** 18 patients (36 Split-faces) **Number completed:** 18 patients (36 split-faces). Facial photodamage was evaluated in 14 patients (28 split-faces). **Participant (baseline) characteristics:** **Inclusion criteria:** Individuals with a mean age of 58.4 years (Range: 37-82), with Fitzpatrick´s Skin Phototype I-III and with moderate to severe photodamage on the head or upper trunk in respect to rhytides, pigmentation, erythema and actinic keratosis. **Exclusion Criteria**: Exclusion criteria corresponded to history of photosensitivity, porphyria or allergy to nuts or nut products; skin active infection or inflammatory disease; microdermabrasion or light to medium skin peels within one month of study enrollment; non ablative laser, light or radiofrequency treatment or topical chemotherapeutic agent use within 3 months before enrollment; pregnancy, lactation or any other medical history that could interfere with study performance.
Interventions	**Intervention:** (n= 36 split-faces) Patients were randomized to receive one session of either Methyl Aminolevulinate (with a 1 hour incubation + Pulsed Dye laser (Cynergy, Cynosure, Westford Massachusetts, USA) at 595 nm with

	a 7 mm spot size and fluences ranging from 10 to 12 J/cm2 and a pulse width of 40 milliseconds + IPL (Lumenis, New York, NY, USA) + red light (Galderma, La Defense Cedex, France). **Comparator Group** (n= 36 split-faces) Methyl Aminolevulinate with a 1 hour incubation + Pulsed Dye laser (Cynergy, Cynosure, Westford Massachusetts, USA) at 595 nm + IPL (Lumenis, New York, NY, USA) + blue fluorescent light (Blu-U, DUSA Pharmaceuticals, MA, USA) at a peak wavelength of 407 nm, a light dose of 10J/cm2 during 16 minutes and 40 seconds. **Use of additional interventions (Common to both treatment arms):** All patients were cleaned with acetone soaked gauze scrubs and treated with vibrational microdermabrasion (Vibraderm, Grand Praire, TX, USA) for 5 minutes prior to starting therapy. Each patient was supplied with an aerosolized water mist (Thermal water spray) and a fan, if needed. Patients were instructed to apply a sun-block and to avoid sun-exposure for 36 hours after treatment.
Outcomes	**Scale used to measure photodamage:** A 5-point photodamage scale (0-4) which evaluated rhytides, pigmentation, erythema and actinic keratosis. **Outcomes of interest in the review:** Authors did not specify primary or secondary outcomes. Efficacy outcomes were recorded with a 5-point scale (0=none to 4= severe) which evaluated the severity of photodamage degree in rhytides, pigmentation, erythema and actinic keratosis. Participants also rated the severity of photodamage with another 5-point scale (0=none to 4= severe) not specified in the study. **Time-point of outcomes measurement:** Outcomes assessment was performed through clinical photographs taken at days 0, 2, 7 and 30. Efficacy outcomes were assessed at 30 days post-treatment. **Adverse events:** At days 2 and 7, post-treatment, local secondary effects such as erythema, edema, crust and blistering, as well as pain, were also recorded on a 5-point scale (0=none to 4= severe). Pigmentation was not included in safety outcomes in the methods section. No differences of pain, erythema, edema, crusting were found when both groups were compared. No hypopigmentation or scarring was observed.
Notes	MAL and Red Light were supplied by Galderma Laboratories at no cost. Although disclosures regarding study sponsoring were depicted, specific author´s potential conflicts of interest were not described in full.

Bias	Authors´judgement	Support for judgement
Random sequence generation (selection bias)	Low Risk	A computer generated randomization schedule was used.
Allocation concealment (selection bias)	Unclear	The method used for allocation concealment was not described.
Blinding of participants and personnel (Performance bias)	High Risk	Participants and personnel blinding was not performed
Blinding of outcome assessment (Detection bias)	High Risk	Outcome assessors were not blind.

Incomplete outcome data (attrition bias)	Low Risk	All included patients were analyzed. No withdrawals were reported.
Selective reporting (reporting bias)	Unclear	Pigmentation safety outcome was not described in the methods section but was included in the results. As the reason for not including this outcome might have been related to an unexpected finding by authors, this domain was rated as unclear instead of at high risk of bias.
Other bias	Unclear	Sample size calculation was not specified. The low power of the study might have led to non-statistical differences. Variations in IPL parameters according to individual features, interventions multiplicity and unpredictable chromophore activation by lights used, might have influenced final results.

Torezan et al, 2013

Methods	Prospective, split-face, randomized trial
Participants	**Location:** Sao Paulo, Brazil (1 Site) **Setting of recruitment:** Patients from Hospital das Clinicas at the University of Sao Paulo, Brazil. **Sample size:** 10 participants (9 females and 1 male) **Number randomized:** 10 patients (20 split-faces) **Number completed:** 10 patients (20 split-faces). **Participant (baseline) characteristics:** **Inclusion criteria:** Individuals with a with a mean age of 65,2 years-old, with SPT I-III with at least 3 facial actinic keratosis and clinical signs of photoaging. Age range of patients was not depicted. **Exclusion Criteria**: Exclusion criteria corresponded to pregnant or nursing women, patients with a history of photosensitivity-related disorders, participants with an active infectious disease, or individuals with a past history in the last 6 months of laser or any cosmetic treatment.
Interventions	**Intervention:** (n= 20 split-faces) Methyl Aminolevulinate (with 90 minutes incubation + red light (PhotoCure ASA, Oslo, Norway) + 7-8 passes of microneedling with a dermaroller with 192 stainless steel needles 1.5 mm long and 0.1 mm wide (Dermaroller, Wolfenbùttel, Germany), after MAL application. One gram of MAL was applied on each Split-face and a plastic film and aluminum foil was used for incubation. After the incubation period, the dressing was removed, and the skin was cleansed with a 0.5% chlorhexidine solution before red light exposure with an irradiance of 50 mW/cm^2 and a total light dose of 37 J/cm^2. **Comparator Group** (n= 20 split-faces) Gentle curettage and thereafter Methyl Aminolevulinate (with 90 minutes incubation + red light (PhotoCure ASA, Oslo, Norway) **Use of additional interventions (Common to both treatment arms):** Patients were instructed to use a cold spring water spray and to avoid sun exposure during the first 48 hours and to apply a SPF 50 sun-block.
Outcomes	**Scale used to measure photodamage:** A 5-point scale adapted from Dover *et al.* and Zane *et al.* that included global photoageing, mottled pigmentation, fine lines, sallowness, roughness, facial erythema, telangiectasias and coarse wrinkles.

	Outcomes of interest in the review: Authors did not specify primary or secondary outcomes. Outcomes included were: improvement in global photoageing, mottled pigmentation, fine lines, sallowness, roughness, facial erythema, telangiectasias and coarse wrinkles rated through a 5-point scale adapted from Dover *et al.* and Zane *et al,* and improvement in the quantity of actinic keratosis. Another outcome included was pain intensity recorded with the visual analogue scale (VAS) and rated as follows: 0 = absence of pain, 10 = most-severe pain). Outcomes were evaluated by 2 dermatologists not involved in the study. **Time-point of outcomes measurement:** Outcomes assessment was performed through clinical photographs (Canfield Imaging Systems, Fairfield, NJ) taken at days 30 and 90. **Adverse events:** Side effects such as erythema, crusting and pain were more common and intense on the Microneedling+PDT side, with lower resolution time on the conventional MAL-PDT split-face vs de MN assisted split-face. (5 days vs 10 days, respectively). One female patient developed an infection with no sequelae on the MN-assisted PDT side after 7 days post -treatment.
Notes	Neither study sponsors nor conflicts of interest were specified in the article, but after contacting the main author we were informed that the trial was not sponsored by the industry. Also, although the main author was a Galderma Laboratories consultant at the time the trial was performed, Dr. Torezan has replied that this Lab has not influenced the results of the study.

Bias	Authors´judgement	Support for judgement
Random sequence generation (selection bias)	Low Risk	Simple randomization through coin tossing was used, according to main author.
Allocation concealment (selection bias)	High Risk	According to main author, allocation concealment was not performed.
Blinding of participants and personnel (Performance bias)	Low Risk	As no participants related outcomes were included, the lack of blinding of patients might have not affected the results
Blinding of outcome assessment (Detection bias)	Low Risk	An independent (Blind) assessor evaluated outcomes, according to main author explanation.
Incomplete outcome data (attrition bias)	Low Risk	All included patients were analyzed, according to main author explanation.
Selective reporting (reporting bias)	Low Risk	Selective reporting was not detected.
Other bias	Unclear	Sample size calculation was not specified in the article but the main author confirmed that the number of participants was lower than calculated (10 patients instead of 13). Baseline characteristics of groups were not included.

Sanclemente et al, 2016

Methods	Prospective, unicentre, phase IIb trial, double blind, randomized placebo-controlled trial.
Participants	**Location:** Medellin, Colombia (1 Site) **Setting of recruitment:** Patients from an ambulatory dermatologic clinic. **Sample size:** 60 patients (54 Women and 6 males) **Number randomized:** 60 patients (60 full-faces) **Number completed:** 60 (60 full-faces). **Participant (baseline) characteristics:** **Inclusion criteria:** Individuals with Fitzpatrick´s Skin Phototype I-IV with scores of 2 or 3 according to Dover´s global photodamage scale. Inclusion criteria corresponded to adult patients 35-75 years-old willing to participate, with symmetric facial photodamage grade 2 or 3 according to Dover's scale. **Exclusion Criteria**: Exclusion criteria were nursing or pregnancy; previous history of photosensitizing disorders; active infectious skin diseases or a history of facial herpes simplex; subjects with less than 6 months of any previous rejuvenation procedure; a previous history of the use of systemic isotretinoin in the last year; a history of hypersensitivity to the active product; and subjects requiring concurrent treatment that would have interfered with study's objectives and/or assessments.
Interventions	**Intervention:** (n= 60 full-faces) The face of each participant was treated either with 1 gram of MAL (Galderma, La Defense Cedex, France) + 2 hours of daylight exposure. MAL or matching placebo were applied <30 min before sun exposure for 2 h (3 sessions, 2-4 weeks apart) in a double-blind fashion (investigators and patients). Patients of both groups were allowed to stay under a gazebo if ambient temperature and/or sun-exposure were uncomfortable. Also, patients receiving placebo were allowed to receive the active intervention after data analysis and prove of efficacy. **Comparator Group** (n= 60 full-faces). One gram of matching placebo + 2 hours of daylight exposure. **Use of additional interventions (Common to both treatment arms):** A subtle abrasion of whole faces with sandpaper 400 grit, was performed in all patients in order to enhance product/placebo skin penetration. Thereafter, a SPF30 sunscreen (Galderma, La Defense Cedex, France) was applied to the entire face of both groups of participants, in order to avoid sunburn, and 15 minutes after sun-block application, either MAL or placebo, were applied.
Outcomes	**Scale used to measure photodamage:** Dover´s scale. **Outcomes of interest in the review:** The primary outcome was measured with the Dover's photodamage scale, 1 month after the third daylight PDT session. Primary outcome was labeled as ''success if there was a decrease in global photodamage score to a severity score of 0 or if there was a >1 grade of decrease in scores of global photodamage from baseline. Failure or lack of improvement was defined as having the same severity score found at baseline, after therapy''. Secondary outcomes included were: pain evaluation after each session measured with the visual analog scale (VAS), specific photodamage severity score for sallowness, mottled pigmentation, fine lines, tactile roughness, coarse lines, and erythema measured 1 month after the third daylight PDT session, measured with the Dover's photodamage scale. Other secondary included outcomes were sun irradiance quantification during daylight exposure and, quality of life assessment before/after treatment measured with the validated version of the Colombian Skindex-29 Instrument. **Time-point of outcomes measurement:** All outcomes were measured at 1 month after the third daylight PDT session.

	Adverse events: Safety outcomes included were the assessment of any adverse event at all times, and therapy tolerance measured at 1 week after all sessions.
Notes	This trial was partially sponsored by Galderma Laboratories. Author´s conflicts of interests were specified.

Bias	Authors´judgement	Support for judgement
Random sequence generation (selection bias)	Low Risk	Allocation sequence was generated by an external statistician according to a simple random sampling without replacement.
Allocation concealment (selection bias)	Low Risk	Concealment was warranted by sending the allocation sequence by the external statistician to the pharmacist chemist who was entailed to label and supply the active intervention and matching placebo according to a ‘‘A’’ or ‘‘B’’ code’s assignment list. The coded list was thereafter sent to the nurse in charge of the application of the interventions, and she also was masked to the generated allocation sequence.
Blinding of participants and personnel (Performance bias)	Low Risk	Patients were blind to both interventions
Blinding of outcome assessment (Detection bias)	Low Risk	Outcome assessors were blind to both interventions
Incomplete outcome data (attrition bias)	Low Risk	An intention to treat analysis (ITT) of primary outcome and secondary outcomes, was performed.
Selective reporting (reporting bias)	Low Risk	Selective reporting was not detected
Other bias	Unclear	This positive trial was partially sponsored by the pharmaceutical industry. An imbalance of baseline characteristics such as gender, skin phototype and global photodamage score, was detected. A priori sub-group analysis was not performed.