Photodermatology, Photoimmunology & Photomedicine

REVIEW ARTICLE

Efficacy of localized phototherapy and photodynamic therapy for psoriasis: a systematic review and meta-analysis

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SUMMARY

Localized phototherapy including topical psoralen plus ultraviolet A (PUVA) and targeted ultraviolet B (UVB), and photodynamic therapy (PDT) have been increasingly used in the treatment of localized psoriasis. Yet, there are no systematic reviews or meta-analyses that scientifically evaluated the pooled efficacy of these treatments in psoriasis. We searched Medline, Embase, and Cochrane databases during the period of January 1980 to June 2012. Our systematic search resulted in 765 studies, 23 of them were included in the review. The primary outcome was 75% reduction in severity score from baseline. A meta-analysis using random effect model found topical PUVA to be more effective than non-laser targeted UVB [odds ratio: 3.48 (95% confidence interval 0.56–21.84), $P = 0.183$]. The pooled effect estimate of the efficacy (75% reduction in severity score) of topical PUVA, targeted UVB, and PDT were as follows: 77% (topical PUVA), 61% (targeted UVB), and 22% (PDT). Topical PUVA and targeted UVB phototherapy are very effective in the treatment of localized psoriasis. Topical PUVA seems more effective than non-laser targeted UVB phototherapy. On the other hand, PDT has low efficacy and high percentage of side effects in treating localized psoriasis.

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Psoriasis is a chronic inflammatory disease that affects the skin and/or the joints with a worldwide prevalence that ranges from 0.6% to 4.8% (1). Treatment of psoriasis depends on the severity of the disease. The majority of psoriatic patients present with mild or localized disease that can be treated with topical medications such as corticosteroids, vitamin D analogs, retinoids, anthralin, or tar (1).

When these topical treatments are found to be ineffective, the next level of therapy entails the use of phototherapy, systemic medications, or biologics. Of these, phototherapy remains an attractive option because of its efficacy and cost effectiveness (2).Localized phototherapy offers the advantage of subjecting skin lesions to significantly high doses of radiation while sparing nearby uninvolved skin (3). Targeted ultraviolet B (UVB) phototherapy [excimer (308-nm) laser, excimer (308-nm) light, and localized narrowband (NB)-UVB (311–313-nm) light], topical psoralen plus ultraviolet A (PUVA), and photodynamic therapy (PDT) are localized forms of phototherapy that have been used to treat psoriatic lesions not responding to topical treatments. For simplicity and clarity, treatments using UVB and those using PUVA photochemotherapy are collectively referred to as 'phototherapy' in this study.

Despite the ever increasing use of localized phototherapy to treat psoriasis, the research evidence to support these clinical practices arises from a handful of relatively small clinical trials and a number of nonrandomized case series. Moreover, findings from these underpowered studies, which represented the best available data, formed the basis of recommendation from the American Academy of Dermatology. These recommendations included the use of targeted UVB phototherapy for pediatric and adult psoriasis with less than 10% body surface area involvement and topical PUVA for adult psoriasis on the palms and soles (2).There are no systematic reviews or meta-analyses that pooled or evaluated the efficacy of these localized forms of phototherapy.

In this study, we aimed to conduct a systematic review and meta-analyses to provide a pooled estimate of the efficacy and short-term safety of targeted UVB phototherapy(including excimer (308-nm) laser, excimer (308-nm) light, and localized NB-UVB (311–313-nm) light), topical PUVA, and PDT in the treatment of localized plaque psoriasis including palmoplantar psoriasis. We also performed a meta-analysis of all published clinical trials that compared the UVB to PUVA.

METHODS

We searched Medline, Embase, and Cochrane databases during the period of January 1980 to June 2012. The key words were 'psoriasis' in combination with all of the following words: excimer laser, excimer light, 308 nm, targeted ultraviolet B, targeted UVB, targeted phototherapy, localized UVB, localized phototherapy, topical psoralen and ultraviolet A, topical PUVA, cream PUVA, gel PUVA, lotion PUVA, paint PUVA, soak PUVA, photodynamic therapy, and PDT. The search was limited to clinical trials performed in humans and reported in English literature.

The eligible studies were randomized and nonrandomized clinical trials as well as case series that evaluated the efficacy of targeted UVB phototherapy, topical PUVA, and PDT in the treatment of plaque psoriasis. Our primary outcome was the percentage of patients who showed at least 75% reduction in their severity score. However, the scoring system of localized treatments usually focuses on lesions on one area of the body. As such, it is different from the same scoring system used to assess the response to the entire body in systemic therapy. Our secondary outcome was the side effects, including painful erythema and blistering from studies evaluating targeted UVB phototherapy and topical PUVA as well as pain from studies evaluating PDT.

Because phototherapy alone is not the optimal treatment for pustular, guttate, and erythrodermic psoriasis, we excluded these subtype of psoriasis from our search. We also excluded all UV-based phototherapy delivered to the entire body surface. Studies that did not report the percentage of patients achieving 75% improvement and studies without adequate description of the treatment protocol were also excluded. Case series with less than 10 patients were excluded as well.

Two of the authors (F. Almutawa and D. Heckman) assessed the eligibility of the studies and extracted the following data from the original articles: authors, year, method, number of patients, types of targeted phototherapy, treatment protocol, outcome, adverse effects, and number of withdrawals. The quality of the randomized clinical trials were assessed by the Jadad scoring system using a 0–5 score that assessed the randomization, blinding, and withdrawals; a higher score indicates data of higher quality (4).

STATISTICAL ANALYSES

Our primary outcome was 75% reduction in psoriasis from the baseline. Our analyses composed of two steps. The first step was meta-analysis of randomized control studies that compared topical PUVA vs. targeted UVB phototherapy. We combined these studies to compute the odds ratio (OR) and 95% confidence level for the primary outcome. We evaluated the heterogeneity between the

studies using Cochrane Q statistics and I^2. We used the fixed effect meta-analytical model in the absence of significant heterogeneity between studies. When significant heterogeneity was identified, we used random effects model to obtain the pooled estimate, as per the widely used recommendations of the Cochrane Collaborations (5). Meta analyses were done using Comprehensive Meta Analyses program (6). We plotted the individual study estimates and overall pooled estimates in a forest plot. On the basis of the pooled risk estimate, we computed the number needed to treat.

The second step of our analysis was to quantify the patient outcome, defined by a 75% reduction in psoriasis score after each of the phototherapy and PDT treatment. We computed the pooled weighted estimates of each treatment separately using all available research publications, including randomized and nonrandomized studies. We also plotted the individual study estimates and overall pooled estimates with interval measures. To obtain the pooled estimates of each of the therapies, MetaXL (MetaXL, version 1.3, 2012; EpiGear, Wilston, Queensland, Australia) was used.

Because of insufficient reported data, we were unable to carry out all subgroup comparisons and sensitivity analyses that we initially intended to do. However, there were a sufficient number of studies to perform subgroup analysis of the three different modalities of targeted UVB, namely, excimer (308-nm) laser, excimer (308-nm) light, and NB-UVB (311–313-nm) light. We also performed a subgroup analysis to compare the different treatment protocols based on the starting dose and the frequency of treatment.

RESULT

Our systematic search resulted in 765 studies, 23 of them met the inclusion criteria and were included in the systematic review (Fig. 1). Of the 23 studies, 13 evaluated targeted UVB (7–19), 4 evaluated topical PUVA (20–23), 3 compared topical PUVA vs. targeted UVB (24–26), and 3 evaluated PDT (27–29). Six of the included studies were randomized controlled trials (RCTs) and 17 were case series. Of the six RCTs, only three compared the efficacy of targeted UVB phototherapy vs. topical PUVA (24–26). From these three studies, we directly compared the efficacy of topical PUVA vs. targeted UVB phototherapy. We then obtained the overall efficacy estimates of each type of the targeted phototherapy treatments by pooling the patient outcomes from the 23 included studies. In both of these assessments, our primary outcome of interest was a 75% reduction in severity score from baseline. Some of the studies have two groups that the authors used to compare

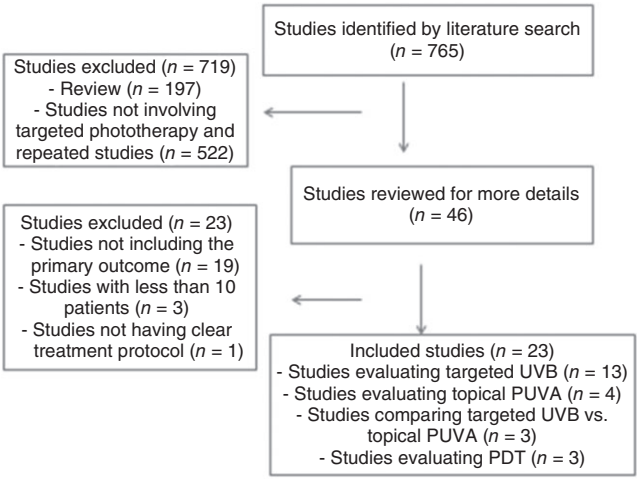


Fig. 1. Flow chart. UVB, ultraviolet B; PUVA, psoralen plus ultraviolet A; PDT, photodynamic therapy.

two different treatment protocols; we refer to these groups in the figures as groups A and B.

Topical PUVA vs. targeted UVB phototherapy

Three RCTs compared the efficacy of topical PUVA with targeted UVB phototherapy (24–26). Two of them used localized NB-UVB (311–313-nm) light (24, 26) and one used excimer (308-nm) light as the source of targeted UVB phototherapy (25); none of them used excimer (308-nm) laser. Neumann *et al.* found no difference between excimer (308-nm) light and topical PUVA (25), whereas Asawanonda *et al.* and Sezer *et al.* studies showed topical PUVA to be more effective than localized NB-UVB (311–313-nm) light (24, 26). A meta-analysis using both the fixed effects and the random effects model of the above studies to compare topical PUVA vs. targeted UVB phototherapy favored topical PUVA (Fig. 2). Fixed effects models showed significantly better patient outcome using PUVA compared with targeted UVB. However, Cochrane Q statistics (6.244, df = 2) showed significant heterogeneity between studies ($P = 0.044$) and I^2 was almost closer to 70%. Therefore, our conclusion was based on the random effects model, which indicated that PUVA had a statistically nonsignificant ($P = 0.183$) advantage over targeted UVB. The pooled OR based on the random effects model was 3.48 [95% confidence interval (CI) 0.56–22.84].

Targeted UVB phototherapy

There were 15 studies meeting the inclusion criteria that evaluated excimer (308-nm) laser, excimer (308-nm) light, and NB-UVB (311–313-nm) light for the treatment of

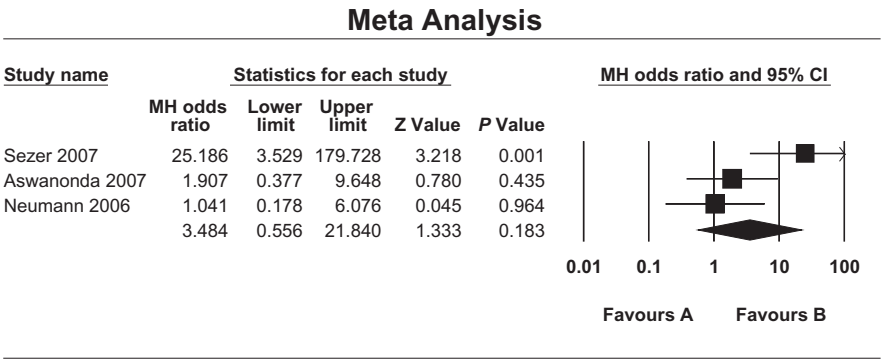


Fig. 2. Comparison of the efficacy of topical psoralen plus ultraviolet A vs. non-laser targeted ultraviolet B phototherapy in psoriasis. (A: targeted ultraviolet B; B: topical psoralen plus ultraviolet A). CI, confidence interval.

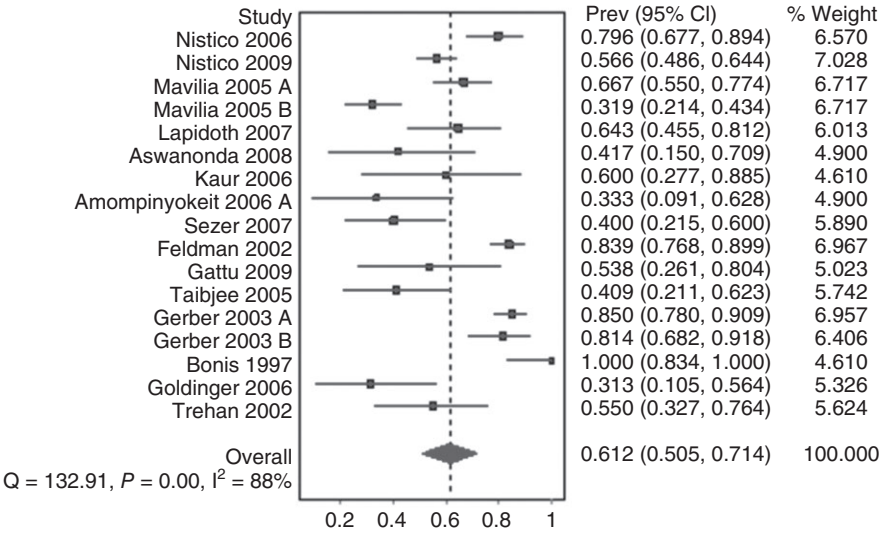


Fig. 3. The efficacy of targeted ultraviolet B phototherapy in psoriasis. CI, confidence interval.

plaque psoriasis (7–19, 24, 26). The pooled weighted estimate of the percentage of patients achieving 75% reduction in their severity score from these studies was 61% (95% CI 50–71%) (Fig. 3). The main side effects, which are painful erythema and blistering, ranged from 0% to 92%. This large difference was attributable to the different treatment protocols used in these studies. The pooled weighted estimate for painful erythema and blistering was 16% (95% CI 4–31%).

By comparing the pooled weighted estimate, the efficacy was higher in studies with higher treatment frequency, two to three treatments per week (66%) than studies with lower treatment frequency, once every 7–14 days (54%) (Fig. 4). The starting dose for targeted UVB studies was either based on minimal erythema dose (MED), or using a fixed dose or skin phototype. There were no large differences between the efficacies in studies using MED as starting dose (63%) (95% CI 50–75%) vs. studies using starting doses based on skin phototype/fixed dose (57%) (95% CI 37–77%) (Fig. 5). The efficacy of different forms of targeted UVB was as follows: 70% for excimer (308-nm) laser, 59% for excimer (308-nm) light, and 49% for localized NB-UVB (311–313-nm) light (Fig. 6).

Topical PUVA

Six studies evaluating topical PUVA met the inclusion criteria (20–24, 26). The pooled weighted estimate of the efficacy from these studies was 77% (95% CI 62–89%) (Fig. 7). The percentage of patients who developed painful erythema or blisters ranged from 0% to 27% with an average of 5%.

By comparison of the pooled effect estimate, studies with three to four treatments per week showed higher efficacy than studies with one to two treatments per week (87% vs. 50%) (Fig. 8). The starting dose was either based on minimal phototoxic dose (MPD) or a fixed dose. Similar to targeted UVB studies, there were no obvious differences in

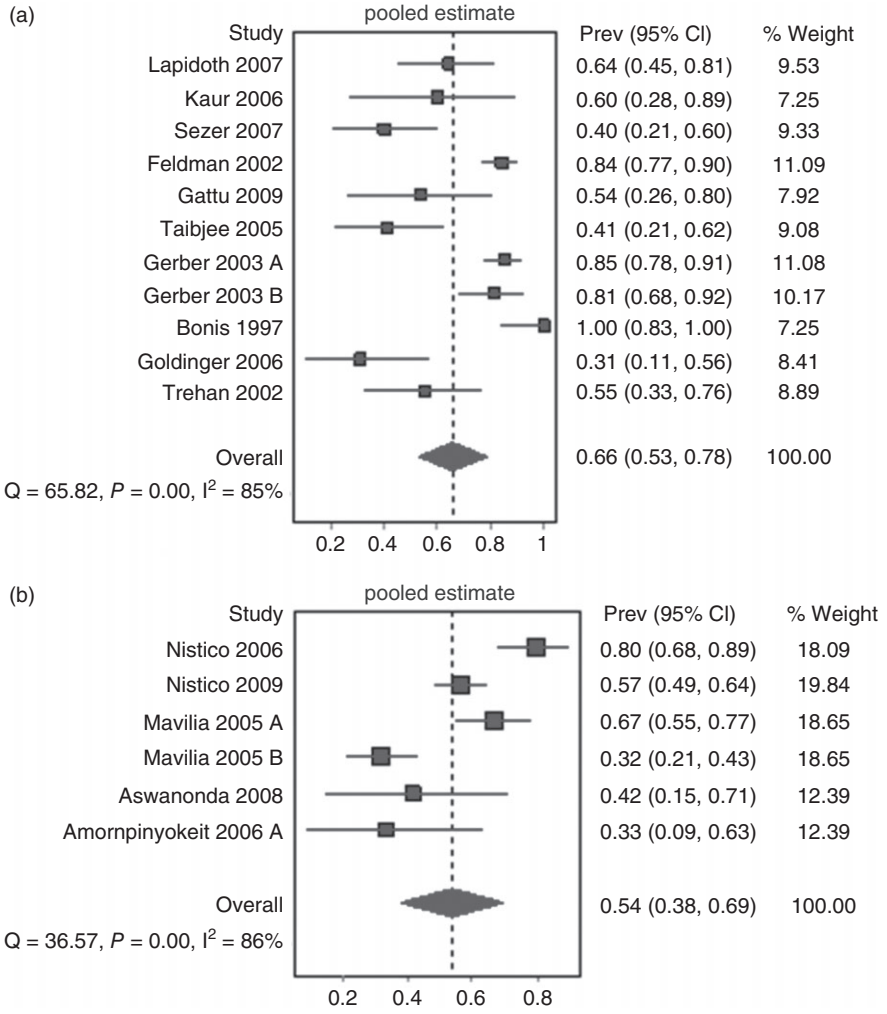


Fig. 4. The efficacy of targeted ultraviolet B phototherapy according to the frequency of treatments: (a) 2–3/week vs. (b) every 7–14 days. CI, confidence interval.

the efficacy of topical PUVA between studies using MPD as a guide for the starting dose (71%) vs. studies using a fixed starting dose (79%) (Fig. 9).

Danno *et al.* investigated the incubation period of topical psoralen and found no difference in the efficacy between 5-min and 2-h incubation periods. However, the 2-h group had a higher percentage of painful erythema and blistering (27%) compared with the 5-min group (0%). The incubation periods of the other studies were between 15–30 min.

PDT

Three studies that investigated aminolevulinic acid (ALA)-PDT met the inclusion criteria (27–29). The pooled efficacy estimate from these studies was 22% (95% CI 10–37%) (Fig. 10). The main side effect was pain that occurred in 80–100% of the patients, and in 30–38% of them, it was described as intolerable. From these studies, groups treated with high doses (10–30 J/cm^2) (27, 28) achieved higher efficacy (33–50%) as compared with groups treated with low doses (5–10 J/cm^2) (10–21%) (28, 29).

DISCUSSION

The aim of this systematic review was to determine the efficacy and the short-term safety of targeted UVB phototherapy, topical PUVA, and PDT in the treatment of localized plaque psoriasis, including palmoplantar psoriasis.

Topical PUVA was three times more effective than non-laser targeted UVB phototherapy, as shown by our meta-analysis of three studies comparing these two treatments. However, this was not statistically significant (Fig. 2) (24–26). An average of 61% of patients who were treated by targeted UVB phototherapy achieved more than 75% reduction in their severity score (Fig. 3). Subgroup analysis

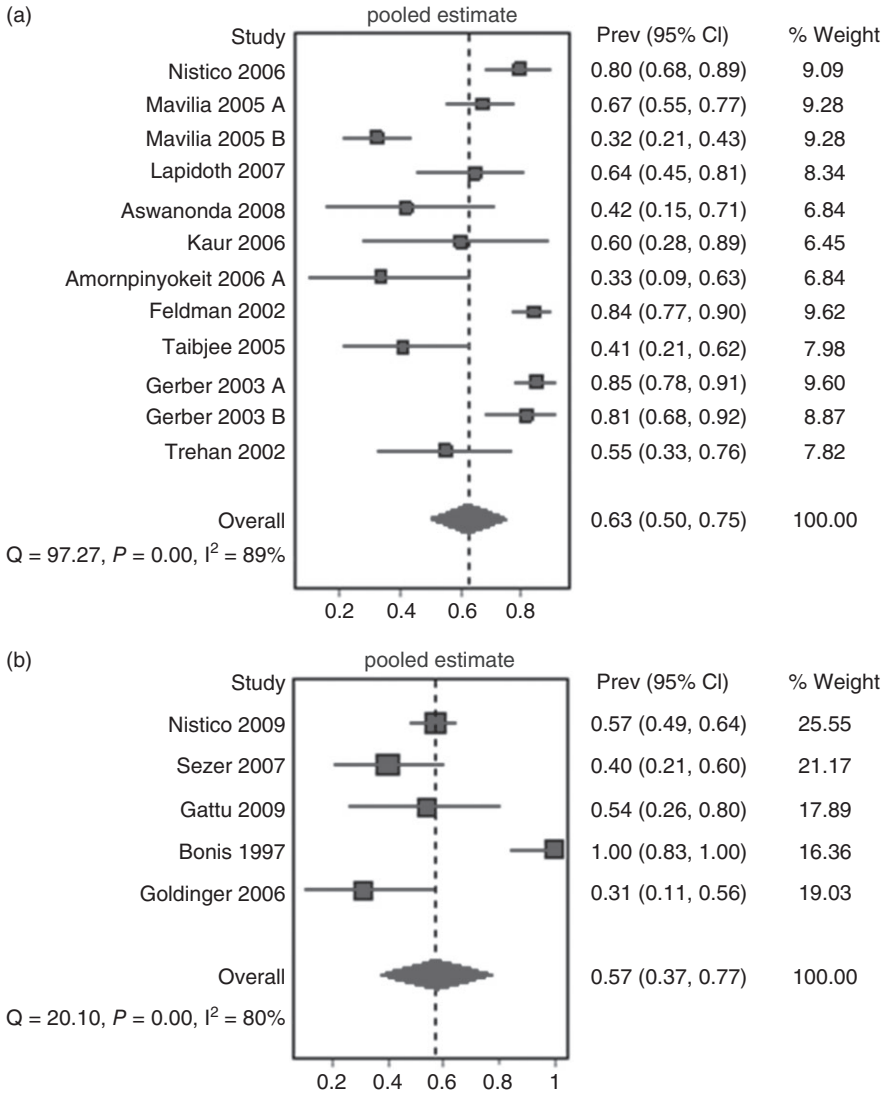


Fig. 5. The efficacy of targeted ultraviolet B phototherapy according to the starting dose: (a) minimal erythema dose vs. (b) non- minimal erythema dose (fixed dose or skin phototype). CI, confidence interval.

of the three modalities of targeted UVB phototherapy showed excimer (308-nm) laser to be more effective (70%) than excimer (308-nm) light (59%) and NB-UVB (311–313-nm) light (49%) (Fig. 6). An average of 16% of the treated patients developed painful erythema or blisters. With regard to topical PUVA, 77% of the patients achieved 75% reduction in their severity score (Fig. 7).

Different variables in the treatment protocols were evaluated in our analysis to find the most effective protocol. When starting doses of the targeted UVB studies were compared, no noticeable differences were noted in the efficacy between studies using MED vs. studies using fixed dose or skin phototype (Fig. 5). Through comparison of two to three treatments per week vs. one treatment every 7–14 days, we found that the higher frequency treatments were more effective (Fig. 4).

A similar evaluation of topical PUVA studies was performed, yielding similar results. There were no noticeable differences in the efficacies of studies using MPD vs. studies using fixed doses (Fig. 9). Furthermore, studies with higher frequencies (three to four treatments per week) were more effective than studies with lower frequencies (one to two treatments per week) (Fig. 8). However, this conclusion should be interpreted with caution, as the studies analyzed had variable increment regimens as well as different total numbers of treatments. Both of these variables, which we were unable to control, could have had an effect on overall efficacy.

A recent systematic review evaluating the efficacy of total body PUVA vs. NB-UVB in psoriasis found that starting doses had no effect on the efficacy of treatments (30). This was consistent with our data involving targeted UVB therapy. In contrast to our analysis, the review found that the frequency of treatments had no effect on efficacy (30). However, when the treatment frequencies of total body NB-UVB individual studies were analyzed (while

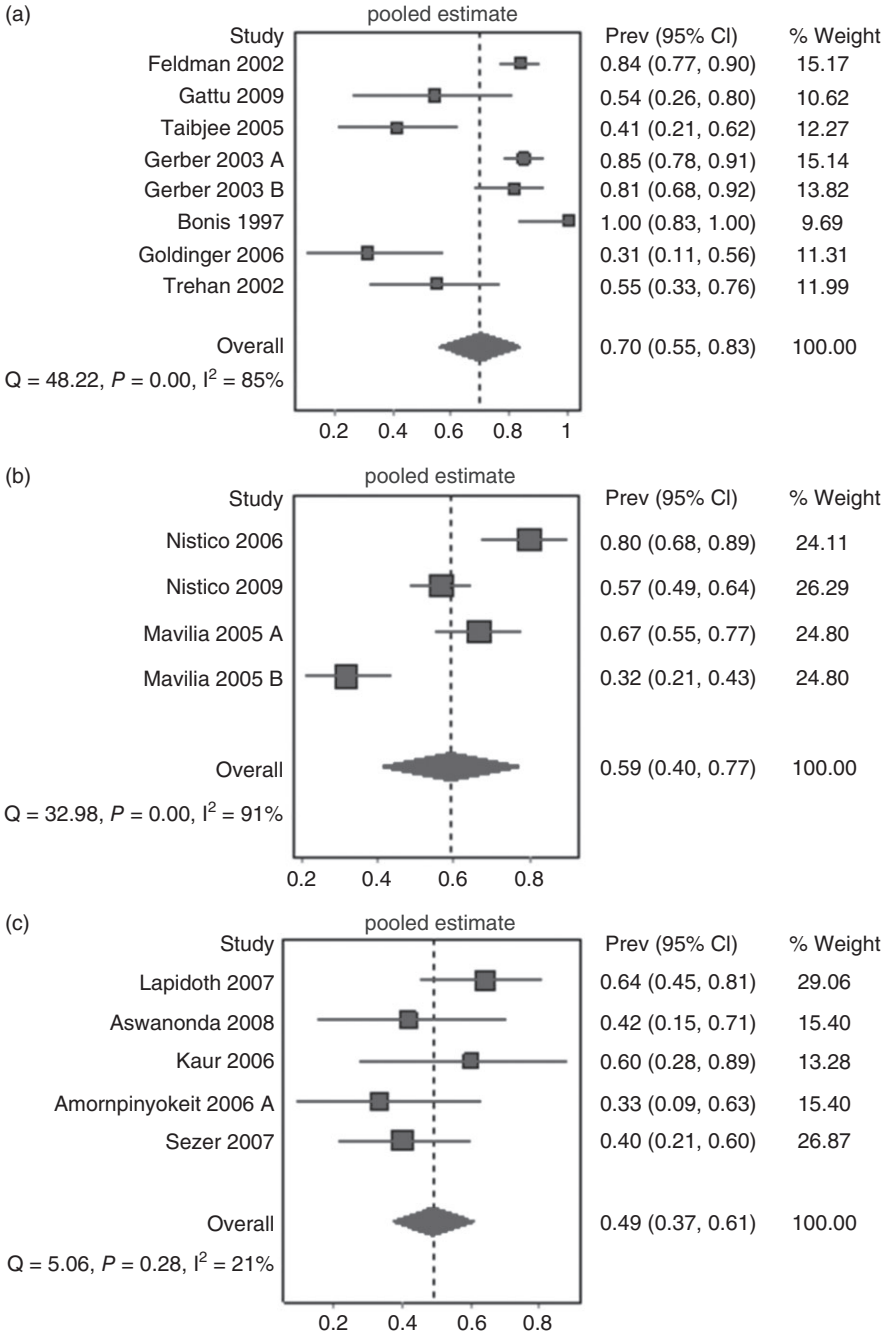


Fig. 6. The efficacy of (a) excimer laser, (b) excimer light, and (c) targeted narrowband-ultraviolet B light in psoriasis. CI, confidence interval.

controlling other variables), it was found that the three treatments per week were more effective than the two treatments per week. Five treatments per week achieved slightly faster remissions when compared with three treatments per week. However, higher frequency treatment was associated with an increased incidence of side effects (31, 32).

Overall, PDT in our review showed low efficacy and a high percentage of pain (that was intolerable in one third of the patients). This result was supported by the British Association of Dermatologists guidelines, which did not support the use of ALA-PDT in the treatment of psoriasis (33). The included PDT studies examined various ALA concentrations, radiation doses, and light sources in an attempt to increase the efficacy and reduce pain. It is possible that photosensitizers other than ALA might play a role in the treatment of psoriasis in the future. For example, a study by Salah *et al.* used methylene blue (0.1%) with light-emitting diode light (570 nm,

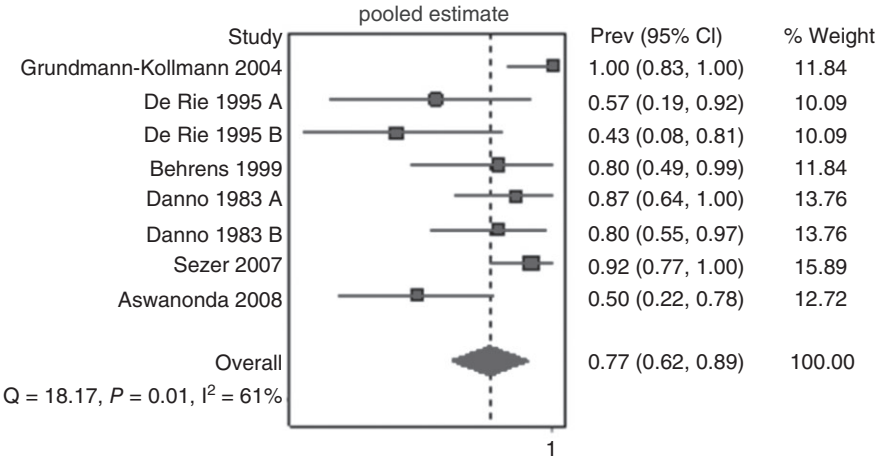


Fig. 7. The efficacy of topical psoralen plus ultraviolet A in psoriasis. CI, confidence interval.

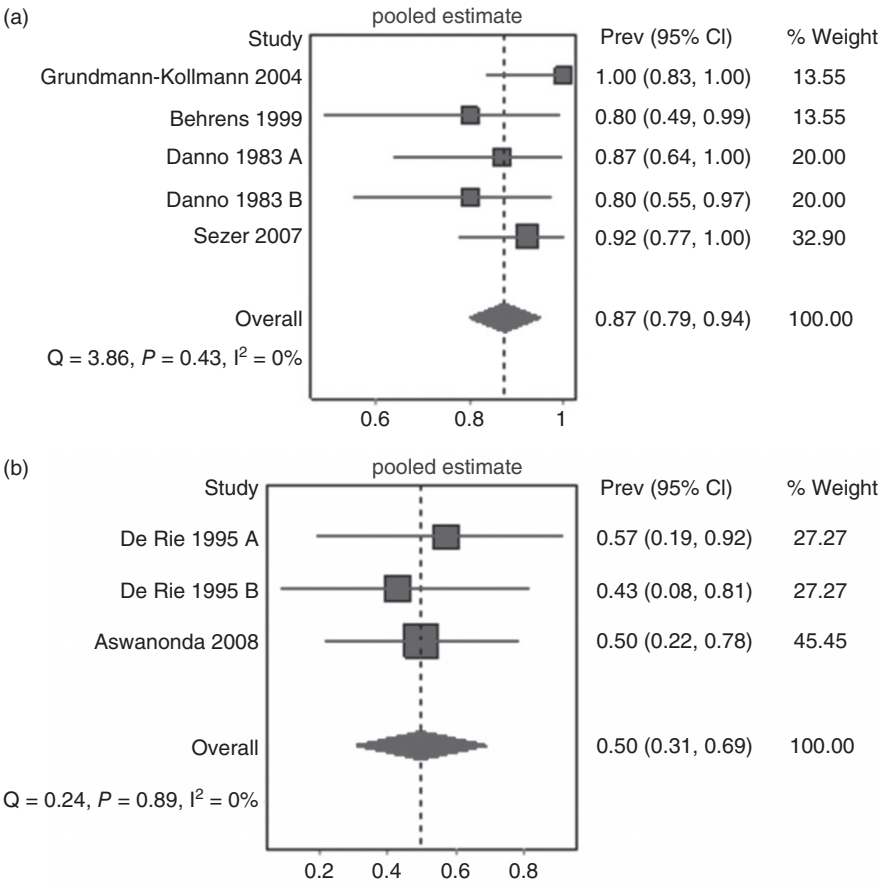
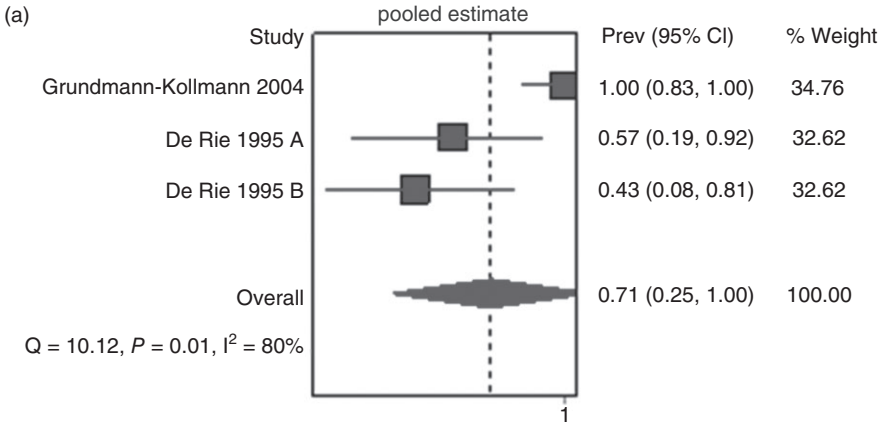


Fig. 8. The efficacy of topical psoralen plus ultraviolet A according to the frequency of treatments: (a) 3–4/week vs. (b) 1–2/week. CI, confidence interval.

565 mW/cm^2, 5 J/cm^2) resulted in 68% of the patients achieving ≥ 75% reduction in their severity score after a mean of nine treatments (34).

There were limitations to our analyses. Despite the increasing use of targeted phototherapy for psoriasis, there were a limited number of randomized controlled studies that assessed efficacy and safety. Moreover, this handful of studies recruited only a small number of patients with the largest trial including only 163 patients (11). The heterogeneity of the treatment protocols in regard to the starting dose, increment, treatment frequency, and the use of different severity scores to assess efficacy was another limitation. It should also be clear that the end points in the included studies did not use the



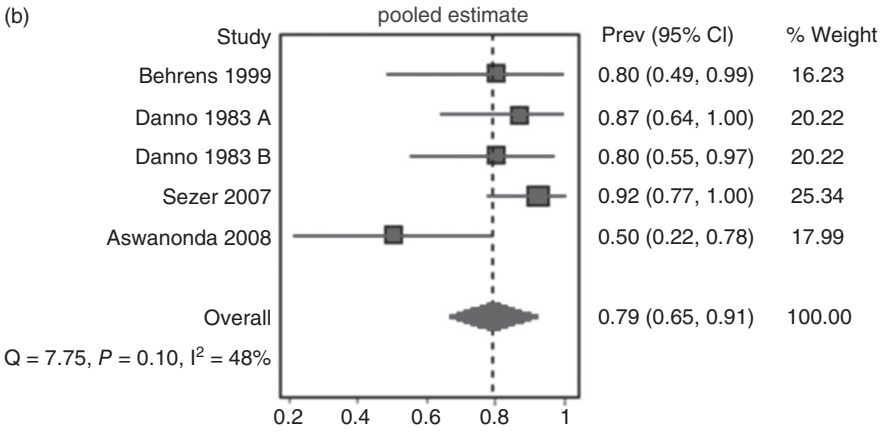


Fig. 9. The efficacy of topical psoralen plus ultraviolet A according to the starting dose: (a) minimal pigment dose vs. (b) fixed dose. CI, confidence interval.

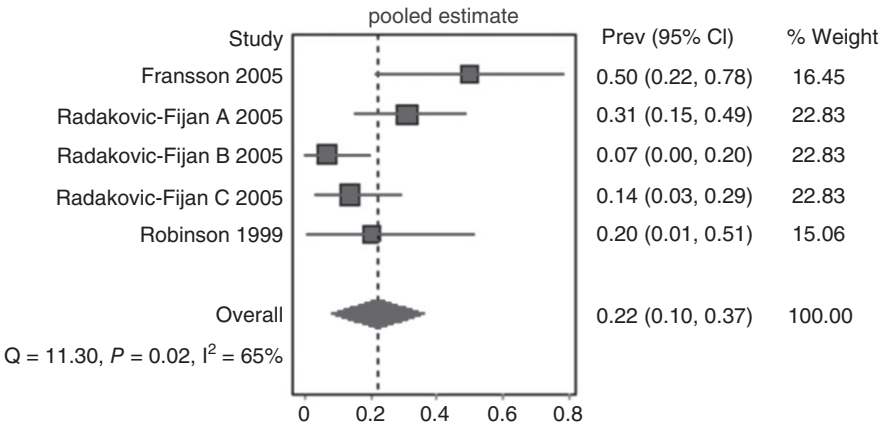


Fig. 10. The efficacy of photodynamic therapy in psoriasis. CI, confidence interval.

scoring system such as psoriasis area severity index and psoriasis severity index in the same manner that it is used in the evaluation of systemic therapy.

We suggest that future studies on localized phototherapy should use a randomized controlled design with appropriate blinding; an appropriate and consistent scoring system should be developed and used to assess therapeutic response on these localized areas. Studies should also use clearly described protocols in regard to starting doses, increments, frequencies, total cumulative doses, and total number of treatments to reach the end points. Studies comparing different treatment protocols such as starting dose, treatment frequency, and increment regimen would help to develop the optimal protocol with the highest possible efficacy and safety.

CONCLUSIONS

Despite the limitations of this systematic review, it can be concluded that topical PUVA and targeted UVB phototherapy are very effective in the treatment of localized psoriasis. Both should be considered if topical treatments fail prior to progressing to systemic treatments or biologics. Topical PUVA therapy appears to be more effective than non-laser targeted UVB phototherapy. However, some studies showed that the efficacy of excimer (308-nm) laser approximates that of topical PUVA. PDT with ALA showed low efficacy and high incidence of side effects when used to treat localized psoriasis.

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