Efficacy evaluation of the photodynamic therapy for oral lichen planus: a systematic review and meta-analysis

CURRENT STATUS: UNDER REVIEW

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DOI:
10.21203/rs.3.rs-16818/v1

SUBJECT AREAS
Dentistry

KEYWORDS
Photodynamic therapy; Oral lichen planus; Efficacy evaluation; Meta-analysis
Abstract
Background Photodynamic therapy (PDT) is a new option for oral lichen planus (OLP) management, while there are different opinions on the efficacy of PDT for OLP. To comprehensively assess the efficacy of PDT in the treatment of OLP, and compare it with steroid therapy. Methods A systematic review and meta-analysis was conducted to assess the curative effect of PDT, five electronic databases were searched, including PubMed, Web of Science (SCI), the Cochrane Library, Embase, and EBSCO, up to December 1, 2019. Random or fixed effects models for pooled estimates calculation were used and the Meta package of R software was applied. Results Pooled estimates revealed that lesion size decreased by 1.53 cm² (95%: 0.71-2.35) after PDT, while partial response (PR) reached 0.77 (95% CI: 0.65–0.85). The visual analog scale score was decreased 3.82 (95%CI:2.80-4.85), and the Thongprasom sign score was decreased 1.33 (95%CI:0.56-2.10) after PDT. Subgroup analyses revealed that the 5-Aminolevulinic acid (5-ALA) was more effective than methylene blue (MB), with the PR was 0.87 (95%:0.80-0.91). Topical use of 5-ALA can yield better response than gargling methylene blue. In terms of VAS, the diode laser showed better clinic partial response in treatment of OLP. But on changes of lesion size, the efficacy of semiconductor laser is higher than diode laser. And the similar efficacy of PDT with topical corticosteroids was confirmed by pooled estimates of five RCT trials with 139 lesions. Conclusion This systematic review indicates that PDT is an effective treatment modality in the management of OLP. Besides, PDT is as effective as topical corticosteroid in treating OLP and could be used for cases resistant to steroids or when steroids are contraindicated.

Introduction
Oral lichen planus (OLP) is a chronic immune-mediated, inflammatory, and psychosomatic condition that frequently affects the oral mucosa in a typical bilateral pattern, often noticed in middle-aged females [1]. OLP has an overall prevalence of about 2.2% [2]. The most common is reticular type which has a white lacy appearance, other forms include erosive, atrophic, bullous, papular and plaque-like forms. It is a kind of oral potentially malignant disorders (OPMD), and has been linked to oral squamous cell carcinoma, the malignant transformation rate was reported about 1.4% [3]. Managing OLP aimed at reducing symptoms and manifestation of lesions. At present, the most
common treatment is pharmacological therapy, the others include surgery, photodynamic therapy and laser therapy. There is a large difference in the curative effect of current treatments. In pharmacologic therapy, topical corticosteroids are usually prescribed, such as triamcinolone acetonide, dexamethasone, and so on [4]. However, long-term treatment with systematic corticosteroids may cause obvious side effects, such as local pigmentation, oral candidiasis, dry mouth and so on [5]. In addition, some studies claimed that patients didn’t responded to drug treatment, and the erosion has not been healed, increasing the risk of canceration [6]. Photodynamic therapy (PDT) is a therapeutic method based on photochemical and photobiological effect mediated by photosensitizer (PS), leading to cell damage of the lesional tissue[7]. It belongs to a kind of minimally invasive treatment, because it has the advantages of good selectivity, small trauma and mild adverse reactions. It is a new option for OLP. Currently there are different opinions on the efficacy of PDT for OLP. A study revealed that PDT appeared to have some effect in the symptomatic treatment of OLP in adult patients[8]. But the authors adopted limited articles and did not perform subgroup analysis. On the contrary, according to the systematic review [9], PDT failed to show any significant effect on treating the signs of OLP. While a meta-analysis reviewed 22 publications, and showed that the partial response rate of OLP lesions was around 70% [10]. This study analyzed effect of PDT on OPMD, only 6 articles were included and in the subgroup analysis the authors did not pay attention to the effect of different factors on the efficacy of OLP. The above three reviews adopted limited articles of OLP and did not analyze the influence of these factors, including sites, type of PS, and administration methods, which may be related to the final therapeutic response. In order to assess the efficacy of PDT in the treatment of OLP, try to give clinicians a comprehensive understanding of the efficacy of PDT in OLP, and compare the efficacy of PDT with steroid therapy, we intend to conduct this systematic review.

Methods
Study identification and selection criteria
The systematic review and meta-analysis were performed in accordance with the PRISMA statement
as detailed in Additional file 1: Appendix Table 1. Electronic and manual literature searches were conducted in the following five electronic databases: PubMed, Web of Science (SCI), the Cochrane Library, Embase, and EBSCO, up to December 1, 2019. Search terms were as follows: “Photodynamic therapy” OR “PDT”, AND, “lichen planus” OR “oral lichen planus” OR “OLP”.

The inclusion criteria were as follows: (a) original articles, clinical studies, and case series; (b) intervention aims to evaluate the efficacy of PDT in the management of OLP; (c) lesion response was assessed and recorded; (d) articles published only in English language; (e) clinically or histopathological diagnosis for OLP.

The exclusion criteria included: (a) reviews, abstracts, commentaries, letters to the editor, opinion articles and animal studies; (b) inconsistent efficacy evaluation standard such that subsequent analysis cannot be performed; (c) individuals with idiopathic plaque-like lichen planus (non-erosive), lichenoid drug eruptions or showing evidence of dysplasia of the tissue.

Data extraction
Two authors (Z.Y. and D. J.X.) independently searched above databases and assessed the titles and abstracts of all eligible publications. Details, including first author’s name, publication year, type of PS, disease types, method of administration, disease location, number of lesions, were collected from the included studies. Besides, four types of outcome measures were collected for the efficacy evaluation, as follows: (a) the lesion response including complete response (CR) which means lack of visible lesion confirmed by clinical evaluation, and partial response (PR) which means the lesion size decreased at least 20%. (b) area changes of the lesion size; (c) Thongprasom sign (TH): a score of 0 for normal healthy mucosa, 1 for lesions with only white striae, 2 for mixed keratotic and atrophic or erythematous lesions < 1 cm² in size, 3 for keratotic and atrophic or erythematous lesions more than 1 cm² in size, 4 for erosive/ulcerative lesions smaller than 1 cm², and 5 for erosive/ulcerative lesions larger than 1 cm²; (d) visual analog scale (VAS) rated by participants (score:0-10): 0 means no symptoms and 10 means severe symptoms as perceived by the patient.

Other parameters used for qualitative synthesis included that wavelength, energy density of the laser, duration of irradiation and lesion dressing, treatment interval, relapse during follow-up, and
adverse reactions during or after PDT.

Quality assessment
The included RCT studies were assessed by the Cochrane Collaboration's risk of bias assessment tool, with seven fields: random sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, incomplete outcome data, selective reporting, and other bias[12]. The included non-RCT studies were assessed by the Downs-Black Checklist, with 29 items[13]. The quality assessment was independently performed by two authors (H. -Y.Q. and D. -J.X.), and fully discussion would be taken when the conflicts exited, the corresponding authors (Dr. Xu. and Prof. Chen) would make the final decision.

Statistical analysis
The I-squared statistics and heterogeneity statistic Q were calculated for accessing the heterogeneity, and the random effect model was utilized for the heterogeneity when the I^2 statistic was more than 50% or the p value of Q test was less than 0.05.

As mentioned above, the outcome measures chosen by this study were including VAS, TH, size and response (PR and CR). The first three continuous indexes were pooled by the inverse variance method (for the fixed effects model) and the restricted maximum-likelihood (the random effects model). The proportion of the response were pooled by the Inverse variance method (for the fixed effects model) and the DerSimonian-Laird method (for the random effects model).

The publication bias was evaluated by the funnel plot, and a weighted linear regression was used to test the funnel plot asymmetry if the number of the studies was not less than 10, the publication bias could be ignored when the p value was greater than 0.05.

The sensitivity analysis was utilized with the subgroup and influence analyses. The light sources, types of photosensitizer, administration methods of photosensitizer and lesion locations were considered for subgroup analysis, and t test was applied for the differential test between different subgroup. The influence analysis is the pooled estimates calculated by omitting one study at a time.

The Meta package of R software was applied for above analysis [14].

Results
Demographic characteristics of included studies
The literatures selection process was showed in Fig. 1. By searching the mentioned databases, 418 studies were found, and 1 additional record was identified through reviewing the reference list of related studies. By removing the duplicate articles, 225 remained. After screening titles and abstracts, 205 records were excluded. 4 full-text were excluded by reasons that one was case report and three articles were not English. After full-text screening, 16 studies were considered for qualitative assessment, and 13 studies were included for quantitative synthesis [15–30]. All patients are older than 18 years old. In 13 studies, 5 RCT trials compared the efficacy of PDT with topical corticosteroids. One article clearly stated that patients with reticular type were included, and two articles included erosive type. The remaining information is in Table 1 and Additional file 1: Appendix table 3.

Quality assessment of the included studies
The results of Cochrane Collaboration's risk of bias assessment and Downs-Black Checklist were shown in Additional file 1: Appendix Fig. 1 and Appendix Table 2. As shown in Additional file 1: Appendix Fig. 1, the included RCT studies had low or unclear risk of bias, while as the wide difference of treatment method between the PDT and topical corticosteroids, most of them did not specify blinding. The Additional file 1: Appendix Table 2 shown that majority of the non-RCT studies own high quality in five fields, which include: study quality, external validity, study bias, confounding and power of study.
### Table 2
Parameters without meta-analysis of the studies included

| Author                  | Year  | Wavelength (nm) | Energy density (J/cm²) | Duration of irradiation (s) | Dressing time (min) | Frequency of PDT | Recurrence | Follow-up time (month) |
|-------------------------|-------|-----------------|------------------------|-----------------------------|---------------------|-----------------|------------|-------------------------|
| Aghahosseni, F          | 2006  | 632             | 120                    | 120                         | 5                   | 1 session       | NA         | 3                       |
| Sadaksharam J           | 2012  | 632 ± 5         | 120                    | 1200                        | 5                   | 4 weekly        | NA         | 6                       |
| Sobaniec S              | 2012  | 660             | 90                     | NA                          | 60                  | 2 weekly        | NA         | 5                       |
| Kval SI                  | 2013  | 600-660         | 75                     | NA                          | 60                  | 1 session       | 2          | 6-48                    |
| Saleh WE                 | 2014  | 660             | 100-130                | 120                         | 5                   | 1 session       | NA         | 1                       |
| Jalarm HH                | 2015  | 630             | 1.5                    | 150                         | 10                  | Once 2-weeks    | 0          | 1                       |
| Prasanna SW              | 2015  | 630 ± 10        | 120                    | NA                          | 5                   | Once a week     | NA         | 1                       |
| Maloth KN                | 2016  | 420             | 210                    | 600                         | 30                  | 1 session       | NA         | 1                       |
| Bakhtiaris S             | 2017  | 630             | 7.2-14.4               | 120                         | 10                  | NA              | NA         | 3                       |
| Mostafa D                | 2017  | 660             | 100-130                | 70                          | NA                  | Once a week     | 0          | 2                       |
| Sulewska M               | 2017  | 630             | 150                    | 500                         | 120                 | 10 weekly       | 4          | 12                      |
| Mirza S                  | 2018  | 630             | 1.5                    | 150                         | 10                  | Twice a week    | NA         | 1                       |
| Paiziyeva Z              | 2018  | 632.7           | NA                     | NA                          | NA                  | NA              | NA         | NA                      |
| Rakesh N                 | 2018  | 600-670         | 80                     | NA                          | 120                 | 1 session       | 0          | 48                      |
| Lavae F                  | 2019  | 660             | 19.23                  | 600                         | 10                  | 3 sessions      | NA         | 2                       |
| Sulewska M               | 2019  | 630             | 150                    | 500                         | 120                 | 10 weekly       | 0          | 12                      |

nm: nanometers; J/cm²: Joules per square centimeters; NA: not available

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**Overall pooled estimates of CR and PR**

Ten publications involving 309 lesions assessed the lesion response (complete and partial) after the photodynamic therapy, the details of them could be found in Table 1.

As the recognition criteria of complete response was set strictly, half of included studies had no complete response case, the pooled proportion of complete response by random effects model (Additional file 1: Appendix Fig. 2 showed the heterogeneity exited) was 0.08, which indicates that only 8% of the lesions reached complete response. No publication bias existed as shown in funnel plot (Appendix Fig. 3), and the sensitivity analysis showed that the results were relatively robust.

Results of PR were showed in Fig. 2. Since the heterogeneity was detected by Q test (p value < 0.05) and $I^2$ statistic (71%), the random effects model was applied to pool the overall proportion of PR, which was 0.77 (95% CI: 0.65-0.85). The funnel plot indicated no publication bias existed (Additional file 1: Appendix Fig. 4), and the robust of results was also validated by the sensitivity analysis.

**Subgroup analysis for PR**

Light sources: five types of light source were utilized in 10 studies, including diode laser (3 trials),
xenon lamp (1 trials), semiconductor laser (1 trials), metal halide lamp (1 trials) and LED (4 trials). As the standard of CR is so strictly that half of the included studies got no complete response, we just applied subgroup analysis for the PR. The forest plots of different light sources’ groups were showed in the Additional file 1: Appendix Fig. 5, and the Fig. 3A showed the result of random effects model for the pooled PR. While no significant difference (tested by u test, p > 0.05) was detected.

Photosensitizers: three types of photosensitizers were discussed in included studies, namely, 5-ALA (4 trails), MB (5 trails), chlorin e6 derivative (1 trial). From the Fig. 3B and Additional file 1: Appendix Fig. 6, the pooled PR of 5-ALA was 0.86 (95% CI: 0.80–0.91), performed more effective than other two, and the difference is significant (p < 0.05) compared to MB.

Administration methods: five trials used topical application, and the other five used gargle. The Fig. 3C and Additional file 1: Appendix Fig. 7 revealed that the topical application was more effective than gargle method (p < 0.05), the pooled PR of topical application could reach to 0.85 (95% CI: 0.80–0.89).

In addition, two types of lesion locations (BM/L and T/G) were detailed in three studies, including 194 lesions. The odds ratio (OR) was calculated and pooled for comparing the PR of two lesion locations, and the PDT should be regarded as more efficient in BM/L if the OR is greater than 1. According to the Additional file 1: Appendix Fig. 8, the PDT seemed to be more suitable for BM/L, while it was not statistically significant (pooled OR: 1.75, 95% CI: 0.43–7.05).

Changes of the lesions
The variables of lesion size and TH were included to assess the changes of the lesions after PDT.

The lesion size was recorded in 6 publications before and after PDT, and 245 lesions were identified for meta-analysis. The forest plot in Fig. 4A showed the lesion size was decreased by 1.53 cm² (95%: 0.71–2.35) after PDT. The heterogeneity was existed within the six studies, as the I-squared statistic was 85% and the p value of Q test was lower than 0.01, while sensitivity analysis (Additional file 1: Appendix Fig. 9) validated the pool estimates was stability. Publication bias could be ignored according to the funnel plot (Additional file 1: Appendix Fig. 10). Through subgroup analysis, we found the lesion size of using semiconductor laser decreased more than using diode laser (tested by u test,
p < 0.05, Fig. 3D), and the lesions located in BM/L were decreased more than those located in the T/F/G (pooled MD:0.37, 95% CI:0.05–0.68, showed in Additional file 1: Appendix Fig. 11), while no statistical significant differences detected within photosensitizers and administration methods (Fig. 3E and Fig. 3F).

As to the TH score, five trails including 88 lesions were involved. Due to the heterogeneity exited (Fig. 4B), the random effects model was recommended, and the TH score was decreased 1.33 (95%CI:0.56–2.10) after PDT, result was validated to be robust with the sensitivity analysis (Additional file 1: Appendix Fig. 12). The metal halide lamp performed better than LED and xenon lamp with the subgroup analysis of light sources (Fig. 3G), while the photosensitizers and administration methods showed no significant differences (Fig. 3H and Fig. 3I).

**Improvement of clinical pain symptom**

The clinical pain symptom was measured by VAS, and six studies with 88 lesions used VAS to assess the improvement of pain after PDT. Figure 4C showed the VAS score was decreased 3.82 (95%CI:2.80–4.85). The heterogeneity exited (p value < 0.05 and $I^2 = 92\%$), while the result was robust (Additional file 1: Appendix Fig. 13). Unlike the lesion changes, subgroup analysis revealed the efficacy of using diode laser is better than using metal halide lamp and LED in relieving pain ($u$ test p < 0.05, Fig. 3J), the differences were not found in subgroup of photosensitizers and administration methods (Fig. 3K and Fig. 3L). As the information shortage, the subgroup analysis of sites was not performed.
### Table 1
Characteristics of the studies with lesion response and lesion size changes after PDT.

| Author          | Year | Light Sources | Photosensitizer | Lesion Types | Administration Method | Lesion Locations | Sample Size | CR (Mean) | CR (SD) | PR (Mean) | PR (SD) | CR (Mean) | CR (SD) | PR (Mean) | PR (SD) |
|-----------------|------|---------------|-----------------|--------------|-----------------------|-----------------|-------------|-----------|--------|-----------|--------|-----------|--------|-----------|--------|
| Aghahosseini F  | 2006 | diode laser   | MB mixed         | gargle       | mixed                 | mixed           | 26          | 4         | 12      | 1.8       | 0.7    | 1         | 0.9    |           |         |
| Sadaksaharam J | 2012 | xenon lamp    | MB mixed         | gargle       | mixed                 | mixed           | 20          | 0         | 10      |           |        |           |        |           |         |
| Sobani ec S    | 2013 | semiconductor laser | chlorin e6 derivative | mixed | topical | mixed | 48          | 14        | 25      | 6        | 4.5     | 2.7     | 2.62     |        |           |         |
| Prasanna SW    | 2015 | metal halide lamp | MB mixed         | gargle       | mixed                 | mixed           | 15          | 0         | 13      | 3         | 1.6    | 0.8      | 1      |           |         |
| Maloth KN      | 2016 | LED           | 5-ALA mixed      | topical      | mixed                 | mixed           | 10          | 0         | 8       | 2.22     | 0.79   | 1.41     | 0.74   |           |         |
| Bakhtiari S    | 2017 | LED           | MB mixed         | gargle       | mixed                 | mixed           | 15          | 0         | 2       |           |        |         |        |           |         |
| Mostafa D      | 2017 | diode laser   | MB mixed         | gargle       | mixed                 | mixed           | 19          | 7         | 9       |           |        |         |        |           |         |
| Sulewska M     | 2017 | LED           | 5-ALA erosive    | topical      | mixed                 | mixed           | 22          | 5         | 11      | 1.49     | 1.45   | 1.37     | 1.78   |           |         |
| Prasanna SW    | 2015 | metal halide lamp | MB mixed         | gargle       | mixed                 | mixed           | 10          | 0         | 10      |           |        |         |        |           |         |
| Sulewska M     | 2017 | LED           | 5-ALA reticular  | topical      | mixed                 | mixed           | 124         | 46        | 63      | 3.99     | 3.73   | 1.48     | 1.98   |           |         |

PDT: photodynamic therapy; GaAlAs: Gallium-Aluminum-Arsenide; LED: light emitting diode; TB: toluidine blue; 5-ALA: 5 aminolevulinic acid; MB: Methylene Blue; BM/L: buccal mucosa and/or lips; T/G: tongue and/or gingival mucosa; mixed: with different required information or information were not mentioned; CR: complete response; PR: partial response; NR: no response. SD: standard deviation.

A: lesion size, B: TH score, C: VAS.

### Other factors in the PDT

The wavelength of 630–660 nm and the energy density of 80–150 joules per square centimeters (J/cm²) were commonly used. Duration of irradiation ranged between 120 s and 600 s. Range of dressing time was from 5 to 120 minutes. The frequency of PDT application ranged from 1 to 10 times throughout the study period at one- to two-week intervals. Details were showed in Table 2.

Majority of patients experienced no discomfort or only minor adverse effects (pain, mild burning sensation) during treatments and disappeared immediately. Most studies conducted with a usual follow-up time of 1–12 months. In all studies, 6 patients in 2 studies were reported relapse after PDT.

However, most studies did not report the cancerous patient.

### Comparison with topical corticosteroids

To get a considerate understand of the efficacy of PDT, five RCT trials with 139 lesions were included.
to compare the PDT with topical corticosteroids, the effect indicators included PR (recorded in 2 trials, 68 lesions in total), TH (recorded in 4 trials, 109 lesions in total) and VAS (recorded in 4 trials, 109 lesions in total), details were given in Additional file 1: Appendix table 3. The pooled estimates indicated varied results of comparisons. The efficacy of PDT performed better than topical corticosteroids (pooled OR: 6.15, 95%CI: 1.65–22.97) on PR, the forest plot was given in Additional file 1: Appendix Fig. 14. As for the TH score (Additional file 1: Appendix Fig. 15), the pooled mean difference is 0.62 (95%CI: -0.46–1.71), which indicated the two treatments own similar efficacy in decreasing the lesion size. And the pooled mean difference of VAS (Additional file 1: Appendix Fig. 16) is -0.30 (95%CI: -1.99–1.40), indicated the similar improvement for pain between the two treatments.

Discussion
The pooled estimates of lesion response, changes of size, VAS, and TH, revealed that PDT could not only reduce the lesions size, but also reduce pain of the patients. PDT is a new noninvasive treatment that is assumed to be effective for OLP.

We found that topical use of 5-ALA had a higher efficacy compared to gargling MB in terms of PR. The relatively poor outcome from MB can be possibly due to the short gargle time of only five minutes. The time of topical use 5-ALA can continue 30–120 minutes. The longer the PS stays on the lesions, the better efficacy of PDT. Constant saliva secretion and frequent tissue movement may impair drug absorption. Thus, high local concentration of PS may achieve better potency. In 4 studies of using 5-ALA as PS, the range of 5-ALA was from 4–5%. Therefore, the topical use of 5% ALA may be recommended as the optimal modality.

When 5% ALA is used, wavelength of 630 nm is recommended. Because 635 nm corresponds to the absorption peak of 5-ALA. In studies involving gargling MB, the chosen wavelength of 632–660 nm did not reach the maximum absorption wavelength of MB (around 665 nm), which also explain partially why the effect of MB was less than 5-ALA. Therefore, it is important to choose suitable wavelength to adapt PS.

In terms of VAS, the diode laser showed better clinic partial response in treatment of OLP, perhaps because of its one wave length of light, which made it more effective. We recommended the diode
laser as the first option when the patients want to relieve pain. But on changes of lesion size, the efficacy of semiconductor laser is higher than diode laser.

Some scholars [26] supported a hypothesis that PDT stimulates healing processes which become even more evident over long-term observation, particularly within masticatory mucosa. This tentative hypothesis needs to be confirmed by a greater number of cured cases. In the study of [23], the mean size reduction was 62.91%, which was significant, showing a slightly higher value for the lesions on the buccal mucosa and lips (63.54%) than the gingiva and tongue (61.43%). While in our study, the lesions on BM/L and T/F/G achieved similar effect from PDT.

Previous study had compared the cellular apoptosis level in reticular and erosive OLP, and the results showed a significantly increased apoptosis in the erosive type and a marked reduction in the thickness of oral epithelium in erosive oral lichen planus compared to the reticular type, which indicated that a higher inflammation and cell destruction in erosive OLP [31]. PS tends to accumulate in abnormal hyperplasia and tumor tissue, some researchers believe that it may be related to the defect of the cell membrane structure. We speculated that PDT of erosive OLP is more effective than reticular OLP. However, the subgroup analysis of disease type in our study, has no statistical significance based on u test. The reason may be that two studies were included for erosive OLP, and only one for reticular OLP.

PDT of OLP has fewer adverse reactions, Majority of patients experienced no discomfort or only minor adverse effects (pain, mild burning sensation) during treatments and disappeared immediately. At present the definite recurrence rate of OLP after PDT is unknown, but the onset features of OLP include easy recurrence. In all studies, 6 patients in 2 studies were found recurrence after PDT, but 3 studies reported no recurrence in 1–12 months follow-up. OLP is a chronic disease, thus the follow-up periods need to be longer. PDT can reduce the risk of malignant transformation. A study revealed that the malignant transformation rate of OLP is about 1.4%, but all above studies did not record the malignant rate [3]. So, the long-term effects remain unclear, there is an urgently need to carry out large sample, multi-center clinical research to explore and verify the influencing factors of the efficacy of PDT.
Currently the most common treatment for OLP is topical corticosteroids [4]. We compared the efficacy of PDT to the methods of topical corticosteroid. The similar efficacy of PDT and corticosteroid therapy was confirmed. In spite of several side effects of steroid, PDT has rare side effects. Therefore, PDT can be used as one of the optional treatment methods for resistant or recurrent OLP.

A few weaknesses of this study need to be addressed. Insufficient trials met the included criteria, which reduced the significance of the results, especially for the subgroup analysis and the comparison with topical corticosteroids. Outcome measures were varied in the different trials, that hindered data combination. In addition, the heterogeneities of wavelength, energy density, etc. may lead to low statistical power. Although above disadvantages exist in this study, it provides clinicians a comprehensive view of the efficacy of PDT in OLP. More high-quality clinical studies are required to improve the reliability of the results.

**Conclusions**

PDT is an effective treatment in the management of OLP, the overall PR could reach to 0.75, and topical using 5% ALA is suggested to be the priority when choosing the photosensitizer. Besides, PDT is as effective as topical corticosteroid in treating OLP, which indicates PDT could also be used for cases resistant to steroids or when steroids are contraindicated.

**Declarations**

**Authors’ Contribution:** Dr. Xu and Prof. Chen had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Concept and design: He, Chen.

Acquisition, analysis, or interpretation of data: All authors.

Drafting of the manuscript: He, Xu.

Critical revision of the manuscript for important intellectual content: All authors.

Statistical analysis: He, Deng.

Administrative, technical, or material support: Chen, Xu.

**Funding**

The authors gratefully acknowledge support received from the National Natural Science Foundation of
Acknowledgments

Not applicable

Availability of data and materials

Not applicable

Ethics approval and consent to participate

Not applicable

Consent for publication

Not applicable

Competing interests

The authors declare that they have no competing interests.

References

1. Panta P, Andhavarapu A, Patil S. A Holistic Intervention for Oral Lichen Planus. The journal of contemporary dental practice. 2019;20;7:765-7.

2. Cheng Y-SL, Gould A, Kurago Z, Fantasia J, Muller S. Diagnosis of oral lichen planus: a position paper of the American Academy of Oral and Maxillofacial Pathology. Oral surgery, oral medicine, oral pathology and oral radiology. 2016;122;3:332-54.

3. Richards D. Malignant transformation rates in Oral Lichen Planus. Evidence-based dentistry. 2018;19;4:122.

4. Oberti L, Alberto L, Massimo P, Francesco C, Dorina L. Clinical Management of Oral Lichen Planus: A Systematic Review. Mini Rev Med Chem. 2019;19;13:1049-59.

5. Amanat D, Ebrahimi H, Zahedani MZ, Zeini N, Pourshahidi S, Ranjbar Z. Comparing the effects of cryotherapy with nitrous oxide gas versus topical corticosteroids in the treatment of oral lichen planus. Indian Journal of Dental Research. 2014;25;6:711.

6. Bornstein MM, Kalas L, Lemp S, Altermatt HJ, Rees TD, Buser D. Oral lichen planus
and malignant transformation: a retrospective follow-up study of clinical and histopathologic data. 2006;37;4:261-71.

7. Chen Q, Dan H, Tang F, Wang J, Li X, Cheng J, et al. Photodynamic therapy guidelines for the management of oral leucoplakia. International journal of oral science. 2019;11;2:1-5.

8. Akram Z, Javed F, Hosein M, Al-Qahtani MA, Alshehri F, Alzahrani AI, et al. Photodynamic therapy in the treatment of symptomatic oral lichen planus: a systematic review. Photodermatology, photoimmunology & photomedicine. 2018;34;3:167-74.

9. Jajarm HH, Asadi R, Bardideh E, Shafae H, Khazaei Y, Emadzadeh M. The effects of photodynamic and low-level laser therapy for treatment of oral lichen planus—a systematic review and meta-analysis. Photodiagnosis and photodynamic therapy. 2018;23:254-60.

10. Jin X, Xu H, Deng J, Dan H, Ji P, Chen Q, et al. Photodynamic therapy for oral potentially malignant disorders. Photodiagnosis and Photodynamic Therapy. 2019.

11. Shamseer L, Moher D, Clarke M, Ghersi D, Liberati A, Petticrew M, et al. Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015: elaboration and explanation. BMJ. 2015;349:g7647-g.

12. Higgins JP, Altman DG, Gøtzsche PC, Jüni P, Moher D, Oxman AD, et al. The Cochrane Collaboration’s tool for assessing risk of bias in randomised trials. Bmj. 2011;343:d5928.

13. Downs SH, Black N. The feasibility of creating a checklist for the assessment of the methodological quality both of randomised and non-randomised studies of health care interventions. Journal of Epidemiology & Community Health. 1998;52;6:377-84.

14. Schwarzer G. meta: An R package for meta-analysis. R news. 2007;7;3:40-5.
15. Bakhtiari S, Azari-Marhabi S, Mojahedi SM, Namdari M, Rankohi ZE, Jafari S. Comparing clinical effects of photodynamic therapy as a novel method with topical corticosteroid for treatment of Oral Lichen Planus. Photodiagnosis Photodyn Ther. 2017;20:159-64.

16. Mostafa D, Moussa E, Alnouaem M. Evaluation of photodynamic therapy in treatment of oral erosive lichen planus in comparison with topically applied corticosteroids. Photodiagnosis Photodyn Ther. 2017;19:56-66.

17. Aghahosseini F, Arbabi-Kalati F, Fashtami LA, Djavid GE, Fateh M, Beitollahi JM. Methylene blue-mediated photodynamic therapy: a possible alternative treatment for oral lichen planus. Lasers Surg Med. 2006;38;1:33-8.

18. Jayachandran Sadaksharam KPTNNPS. Treatment of oral lichen planus with methylene blue mediated photodynamic therapy – a clinical study. Photodermatology, Photoimmunology & Photomedicine. 2012;28;2:97-101.

19. Sobaniec S, Bernaczyk P, Pietruski J, Cholewa M, Skurska A, Dolińska E, et al. Clinical assessment of the efficacy of photodynamic therapy in the treatment of oral lichen planus. Lasers in Medical Science. 2012;28;1:311-6.

20. Kvaal SI, Angell-Petersen E, Warloe T. Photodynamic treatment of oral lichen planus. Oral Surg Oral Med Oral Pathol Oral Radiol. 2013;115;1:62-70.

21. Wafaa Elsaid Omar Hassan Khashaba SyEnaMDM. Photodynamic Therapy of Oral Erosive lichen Planus in Diabetic and Hypertensive Patients. Mansoura Journal of Dentistry. 2014;1;3:119-23.

22. Lavaee F, Shadmanpour M. Comparison of the effect of photodynamic therapy and topical corticosteroid on oral lichen planus lesions. Oral Dis. 2019.

23. Sulewska M, Duraj E, Sobaniec S, Graczyk A, Milewski R, Wroblewska M, et al. A clinical evaluation of efficacy of photodynamic therapy in treatment of reticular oral
lichen planus: A case series. Photodiagnosis Photodyn Ther. 2019;25:50-7.

24. Maloth KN, Velpula N, Kodangal S, Sangmesh M, Vellamchetla K, Ugrappa S, et al. Photodynamic Therapy - A Non-invasive Treatment Modality for Precancerous Lesions. J Lasers Med Sci. 2016;7;1:30-6.

25. Prasanna SW, Ingle E, Aruna PR, Pravada C, Koteeswaran D, Ganesan S. Photodynamic therapy of oral leukoplakia and oral lichen planus using methylene blue: A pilot study. Journal of Innovative Optical Health Sciences. 2015;08;01.

26. Sulewska M, Duraj E, Sobaniec S, Graczyk A, Milewski R, Wroblewska M, et al. A clinical evaluation of the efficacy of photodynamic therapy in the treatment of erosive oral lichen planus: A case series. Photodiagnosis Photodyn Ther. 2017;18:12-9.

27. Mirza S, Rehman N, Alrahlah A, Alamri WR, Vohra F. Efficacy of photodynamic therapy or low level laser therapy against steroid therapy in the treatment of erosive-atrophic oral lichen planus. Photodiagnosis Photodyn Ther. 2018;21:404-8.

28. Jajarm HH, Falaki F, Sanatkhani M, Ahmadzadeh M, Ahrari F, Shafaee H. A comparative study of toluidine blue-mediated photodynamic therapy versus topical corticosteroids in the treatment of erosive-atrophic oral lichen planus: a randomized clinical controlled trial. Lasers Med Sci. 2015;30;5:1475-80.

29. Rakesh N, Clint JB, Reddy SS, Nagi R, Chauhan P, Sharma S, et al. Clinical evaluation of photodynamic therapy for the treatment of refractory oral Lichen planus - A case series. Photodiagnosis Photodyn Ther. 2018;24:280-5.

30. Paiziyeva Z, Puriene A. The effectiveness of the combined use of a polysaccharide film with photodynamic action in complex therapy of oral lichen planus in the oral cavity. Drug Invention Today. 2018;10;12.

31. Brant JMC, Vasconcelos AC, Rodrigues LV. Role of apoptosis in erosive and reticular
oral lichen planus exhibiting variable epithelial thickness. Brazilian dental journal. 2008;19;3:179-85.

Figures

Figure 1

Flow diagram of study selection
Figure 2

Forest plot of proportions of PR after PDT
A–J showed the results of subgroup analysis with random effects model, three factors were considered for subgroup analysis, namely, light sources (A, D, G, J), photosensitizers (B, E, H, K), administration methods (C, F, I, L). The three plots at the first column represent the results of PR, the plots at the second column represent the results of size, the plots at the third column represent the results of TH, the plots at the fourth column represent the results of VAS. The plots at the third column represent the results of VAS. The full red lines in the plots indicate the pooled overall estimates and the dashed red lines indicate the lower limits and upper limits of their 95%CI.
Figure 4

Forest plots of mean difference between before and after PDT in three effect indicators. A: lesion size, B: TH score, C: VAS.

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