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BEST EVIDENCE CONSENSUS

Antimicrobial photodynamic therapy for the treatment of periodontitis and peri-implantitis: An American Academy of Periodontology best evidence review

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Abstract

Background: This systematic review evaluates the efficacy of antimicrobial photodynamic therapy (aPDT), as an adjunct to non-surgical or surgical therapy, on clinical and patient-centered outcomes in patients with periodontitis or peri-implantitis.

Methods: Randomized controlled trials (RCTs) with a follow-up duration ≥ 3 months that evaluated mechanical root/implant surface debridement (i.e., scaling and root planing [SRP] or implant surface scaling [ISS]) versus SRP or ISS plus aPDT for the treatment of adult patients (≥ 18 years old) with moderate-to-severe chronic (CP)/aggressive periodontitis (AgP) or peri-implantitis, respectively, were considered eligible for inclusion. The MEDLINE, EMBASE, and CENTRAL databases were searched for articles published up to and including March 2017. Random-effects meta-analyses were used throughout the review using continuous data (i.e., mean changes from baseline), and pooled estimates were expressed as weighted mean differences with their associated 95% confidence intervals. Additionally, summaries are presented of the included RCTs, critical remarks of the literature, and evidence quality rating/strength of recommendation of laser procedures.

Results: Of 729 potentially eligible articles, 28 papers (26 studies) were included in the review. Individual study outcomes and four sets of meta-analysis showed potential statistical significant benefit of aPDT in improving clinical attachment level (CAL) (non-surgical treatment of AgP) and probing depth (PD) (non-surgical treatment of AgP and CP). However, the comparative differences in clinical outcomes were modest (< 1 mm), and the level of certainty for different therapies was considered low-to-moderate (i.e., more information would be necessary to allow for a reliable and definitive estimation of effect/magnitude of therapies on health outcomes). Overall, most of the strengths of clinical recommendations of aPDT were guided by the expert opinion.

Conclusions: aPDT may provide similar clinical improvements in PD and CAL when compared with conventional periodontal therapy for both periodontitis and peri-implantitis patients. The restricted base of evidence for some treatment approaches and conditions precludes additional conclusions.

KEYWORDS
dental scaling; evidence-based dentistry; lasers; periodontitis; photochemotherapy; surgical procedures, operative

Recent scientific evidence-based information gathered by the American Academy of Periodontology (AAP) best-evidence consensus (BEC) papers identified the potential applications of infrared laser tools for the treatment of periodontitis[1] and peri-implantitis.[2]

It has been demonstrated that lasers are thought to promote periodontal wound healing and regeneration, in general, by means of "thorough debridement and decontamination of diseased tissues, and by modulating or activating cell metabolism in the surrounding tissues."[3] Over the last decade, low-intensity diode lasers in conjunction with photosensitizers also have been used to activate topical photosensitizing agents (i.e., antimicrobial photodynamic therapy [aPDT]) to reduce or eliminate periodontopathogenic bacteria as an adjunct to mechanical debridement in periodontitis patients.[3] Historically, aPDT techniques originated accidently at the beginning of the 20th century when Oskar Raab and Hermann von Tappeiner[4] "noticed that *Paramecium* spp. protozoans stained with acridine orange died upon exposure to bright light."[5] Although aPDT procedures have being used in medicine (especially for the treatment of different types of tumors),[6] the term "photodynamic therapy" was first proposed by John Toth in 1981, who observed the "photodynamic chemical effect."[6]

The principles of aPDT involve the use of a non-toxic light-sensitive dye called a "photosensitizer" (PS) combined with harmless visible light (low energy) of the appropriate wavelength to match the absorption spectrum of the PS.[7] This procedure stimulates the dye to form free radicals of singlet oxygen that will act as toxic agents to the bacteria/cell.[8]

A growing body of evidence examines the clinical effectiveness of aPDT when used as an adjunct to conventional non-surgical and surgical treatment of periodontitis and peri-implantitis patients.[8–49] Thus, the aims of this AAP BEC systematic review (SR) are to 1) evaluate the efficacy of the adjunctive use of aPDT in the non-surgical and surgical treatment of patients with periodontitis or peri-implantitis and 2) reflect the clinical significance of the findings for decision-making. The following specific focused questions were addressed in the systematic review: 1) "Does aPDT, when used as an adjunctive treatment, provide superior clinical and patient-preferred outcomes compared with conventional periodontal therapy in patients with moderate to severe periodontitis?" 2) "Does aPDT, when used as an adjunctive treatment, provide superior clinical and patient-preferred outcomes compared with non-surgical and surgical therapies in patients with peri-implantitis?"

1 | MATERIALS AND METHODS

The text of the review was structured in accordance with guidelines from PRISMA,[50] the *Cochrane Handbook of Systematic Reviews of Interventions*,[51] and Check Review checklist.[52] Detailed descriptions of the study protocol (e.g., assessment of validity and data extraction, assessment of methodologic quality and risk of bias of included studies, and data synthesis) used in this SR have been published in a companion paper.[1] The following sections provide a brief description of the specific methodologic aspects of the present review.

1.1 | Inclusion criteria

Only randomized controlled trials (RCTs) of ≥ 3-month duration were included in the review. Studies were considered eligible for inclusion if they specifically involved the following: 1) Treatment of patients (≥ 18 years old) with moderate to severe aggressive (AgP) or chronic periodontitis (CP) (mean probing depth [PD] ≥ 5 mm) and assessment of mechanical root debridement (e.g., hand scaling and root planing [SRP], sonic/ultrasonic instrumentation), with or without surgical flap access, versus aPDT as an adjunct to mechanical root debridement. 2) Treatment of patients (≥ 18 years old) with moderate to severe peri-implantitis (mean PD ≥ 5 mm) and assessment of mechanical implant surface debridement (e.g., hand scaling, sonic/ultrasonic instrumentation), with or without surgical flap access, versus aPDT as an adjunct to mechanical implant surface debridement.

Studies reporting a mean pretreatment PD < 5 mm were also included if outcome measures were reported separately for periodontal sites > 5 mm. Also, studies had to report laser settings, type of dye, and type of instrument tip (e.g., contact tip diameter) used.

1.2 | Exclusion criteria

RCTs with: 1) < 10 patients per group; 2) follow-up period < 3 months or outcomes from periodontal sites < 5 mm in depth; and 3) all non-randomized studies were excluded from this review. Studies in which the type of periodontitis (AgP or CP) was not reported in the original publication and could not be ascertained after contact with the authors were also excluded.

1.3 | Outcome measures

Periodontal and patient-centered outcome measures were assessed in the review. Periodontal outcome measures

included: 1) change (mean and/or percent) in PD; 2) clinical attachment level (CAL); 3) recession of gingival margin (Rec); 4) bleeding on probing (BOP); 5) bone defect fill; and 6) microbial colonization/composition. Patient-centered outcomes included parameters such as: 1) discomfort, 2) esthetics, 3) function, and 4) treatment costs.

1.4 | Search strategy

Comprehensive search strategies were established to identify studies for inclusion in the systematic review. The MEDLINE (via PubMed), EMBASE, and CENTRAL databases were searched for articles published in the English language up to and including March 2017, based on the search strategy developed for MEDLINE: 1) periodontitis OR chronic periodontitis OR aggressive periodontitis OR attachment loss OR bone resorption OR bone loss OR bone defect OR alveolar bone loss; 2) periodontal treatment OR periodontal therapy OR scaling and root planing OR adjunctive treatment OR adjunctive therapy; 3) periimplantitis OR peri-implant bone loss OR peri-implant defect OR peri-implant tissue loss; 4) implant debridement OR implant surface debridement OR implant scaling OR implant surface disinfection OR implant surface detoxification; 5) [periodontitis OR chronic periodontitis OR aggressive periodontitis OR attachment loss OR bone resorption OR bone loss OR bone defect OR alveolar bone loss] OR [periodontal treatment OR periodontal therapy OR scaling and root planing OR adjunctive treatment OR adjunctive therapy]; 6) [periimplantitis OR peri-implant bone loss OR peri-implant defect OR peri-implant tissue loss] OR [implant debridement OR implant surface debridement OR implant scaling OR implant surface disinfection OR implant surface detoxification]; 7) photodynamic therapy OR antimicrobial photodynamic therapy OR PDT OR aPDT; 8) diode laser OR laser, diode OR semiconductor Diode laser OR diode laser, semiconductor; 9) [photodynamic therapy OR antimicrobial photodynamic therapy OR PDT OR aPDT] OR [diode laser OR laser, diode OR semiconductor Diode laser OR diode laser, semiconductor]; 10) [periodontitis OR chronic periodontitis OR aggressive periodontitis OR attachment loss OR bone resorption OR bone loss OR bone defect OR alveolar bone loss] OR [periodontal treatment OR periodontal therapy OR scaling and root planing OR adjunctive treatment OR adjunctive therapy] AND [photodynamic therapy OR antimicrobial photodynamic therapy OR PDT OR aPDT] OR [diode laser OR laser, diode OR semiconductor Diode laser OR diode laser, semiconductor]; 11) [periimplantitis OR peri-implant bone loss OR peri-implant defect OR peri-implant tissue loss] OR [implant debridement OR implant surface debridement OR implant scaling OR implant surface disinfection OR implant surface detoxification] AND [photodynamic therapy OR antimicrobial photodynamic therapy OR PDT OR aPDT] OR [diode laser OR laser, diode OR semiconductor Diode laser OR diode laser, semiconductor]; 12) [periodontitis OR chronic periodontitis OR aggressive periodontitis OR attachment loss OR bone resorption OR bone loss OR bone defect OR alveolar bone loss] OR [periodontal treatment OR periodontal therapy OR scaling and root planing OR adjunctive treatment OR adjunctive therapy] AND [photodynamic therapy OR antimicrobial photodynamic therapy OR PDT OR aPDT] OR [diode laser OR laser, diode OR semiconductor Diode laser OR diode laser, semiconductor] OR [periimplantitis OR peri-implant bone loss OR peri-implant defect OR peri-implant tissue loss] OR [implant debridement OR implant surface debridement OR implant scaling OR implant surface disinfection OR implant surface detoxification] AND [photodynamic therapy OR antimicrobial photodynamic therapy OR PDT OR aPDT] OR [diode laser OR laser, diode OR semiconductor Diode laser OR diode laser, semiconductor].

Reference lists of any potential articles and OpenGrey[53] database were screened to search for potentially relevant unpublished studies or papers not identified by electronic searching. Additionally, the electronic databases of the following four dental journals were searched: *Journal of Periodontology, Journal of Clinical Periodontology, Journal of Periodontal Research*, and *Journal of Dental Research.*

1.5 | Assessment of validity and data extraction

Two independent reviewers (LC and H-LW) screened the titles, abstracts, and full texts of the articles identified in the search. Disagreements were resolved through discussion until reaching a consensus. When considered necessary, an attempt was made to contact the authors to resolve ambiguity in the reported studies.

1.6 | Assessment of methodologic quality and risk of bias of included studies

The methodologic quality of the trials (see supplementary Appendix 1 in online *Journal of Periodontology*) was evaluated per the Cochrane Collaboration's tool for assessing risk of bias,[51] as adapted by Chambrone et al.[54–57] Based on the same tool, the risk of bias was classified as follows: 1) low, 2) unclear, or 3) high.

1.7 | Statistical analyses

Data were organized into evidence tables and clustered according to the treatment modality and outcome parameters. Random-effects meta-analyses were used throughout the review using continuous data (i.e., mean changes from baseline), and pooled estimates were expressed as weighted mean differences (MDs) with their associated 95% confidence intervals (CIs). The significance of discrepancies in the estimates of the treatment effects from the different trials was assessed

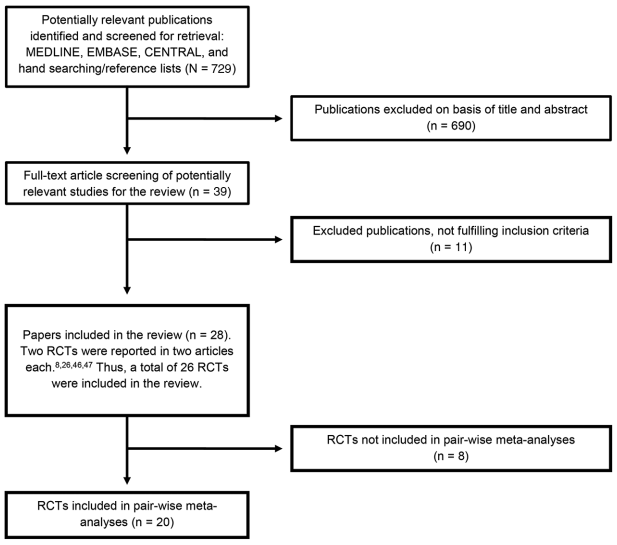

FIGURE 1 Flowchart of manuscripts screened through the review process

by means of the Cochran test for heterogeneity and the I^2 statistic. The analyses were performed using statistical analysis software.*

Additionally, tables include summaries of the included RCTs, critical appraisal of the literature, and evidence quality rating/strength of recommendation of laser procedures (based on the criteria defined by the *American Dental Association Clinical Practice Guidelines Handbook,*[58] which was adapted for the purpose of this review[1]) (see supplementary Tables 1 through 3 in online *Journal of Periodontology*). Based upon the results of this systematic review, the following recommendations were applied:[1] 1) strong; 2) in favor; 3) weak; 4) expert opinion for/supports; 5) expert opinion questions the use; 6) expert opinion against; and 7) against.

2 | RESULTS

2.1 | Description of studies

2.1.1 | Results of the search

The search strategy identified 729 potentially eligible articles (Figure 1), of which 690 articles were excluded after review of titles and/or abstracts. Thirty-nine potentially eligible articles[8,11–49] were screened for eligibility; however, 11 of the papers did not meet inclusion criteria.[11–22] Reasons for exclusion are described in supplementary Table 4 in the online *Journal of Periodontology.*

* Review Manager, v.5.3, Nordic Cochrane Center, The Cochrane Collaboration, Copenhagen, Denmark.

2.1.2 | Included studies

Twenty-eight articles reporting on 26 RCTs were included in this review (Tables 1 through 6).[8,23–49] Data from two RCTs had data reported in two articles each, one describing clinical and the other microbiologic outcomes.[8,26,46,47] Consequently, the articles were included under one study name in Table 1[8,26] and Table 5.[46,47] Of the 26 included studies,[8,23–49] 19 trials[8,23–27,29–33,35,38–42,44,46–48] were conducted according to a split-mouth design, whereas the other RCTs were conducted according to a parallel design.[28,34,36,37,43,45,49] Six studies[8,26,28,32,43–45] were partially or totally supported by companies that provided products (e.g., laser equipment) that were used as interventions in the trials. In total, 69 patients with AgP, 567 patients with CP, and 50 patients with peri-implantitis were treated in the studies, with the results published in full. Two RCTs[27,44] followed participants for a 12-month period, whereas the others covered shorter-term periods (i.e., 3 to 6 months).[8,23–26,28–43,45–49]

2.1.3 | Treatment modalities

aPDT was assessed according to the type and phase of periodontal therapy: 1) non-surgical treatment of AgP and CP (four RCTs[8,23–26]); 2) as part of basic procedures (13 RCTs[27–39]); 3) 3 months after basic procedures (three RCTs[40–42]); 4) at least 1 year of regular periodontal maintenance (three RCTs[43–45]); 5) non-surgical treatment of patients with CP affected by risk factors known to affect the host response to periodontal development and treatment (i.e., smoking [one RCT[46,47]]); and 6) non-surgical treatment of peri-implantitis (two RCTs[48,49]).

2.1.4 | Risk of bias in the included trials

Not all of the included RCTs described randomization and allocation methods in detail, nor examiner and/or patient blinding (Figure 2). Consequently, only the study by Moreira et al.[25] was considered to be at a low risk of bias, whereas 12 were considered to be at unclear risk.[23,24,27,31,33,34,39,43,44,46–49] The remaining trials were considered to be at high risk of bias.

2.2 | Individual study outcomes and pooled estimates

The findings of all included studies, as well as outcomes of four sets of periodontitis meta-analyses (one analysis for the non-surgical treatment of AgP and three analyses for non-surgical treatment of CP), were combined to estimate and assess the level of evidence available per type of disease (AgP, CP, and peri-implantitis) and treatment approach. The generated summaries of evidence and strength of clinical recommendations of procedures are depicted below.

TABLE 1 Non-surgical treatment of AgP (3-month follow-up)[a]

Study	Design	Procedures	Treatment groups	ΔBOP (%)	ΔCAL (mm)	ΔPD (mm)	ΔRec (mm)
Annaji et al.[23]	SM, 15 patients (NS) with localized or generalized AgP and one tooth with PD ≥5 mm in each quadrant	Ultrasonic SRP Diode laser (continuous mode for 30 seconds/tooth using a fiberglass tip) aPDT (toluidine blue O dye 1 mg/mL applied 3 minutes prior to aPDT)	SRP SRP + aPDT (810 nm at 0.1 W) SRP + aPDT (810 nm at 0.1 W) days 0, 7, and 21	NR NR NR	0.28[b] 0.65[b] 0.76[b]	0.29[b] 0.61[b] 0.80[b]	NR NR NR
Chitsazi et al.[24]	SM, 24 patients (NS) with AgP and at least three teeth in each quadrant with ≥4 mm of PD	Ultrasonic SRP Diode laser (fiber-optic tip, dimension not reported, 120 seconds/tooth) + aPDT (toluidine blue photosensitive dye 1 mg/mL applied for 1 minute prior to aPDT)	SRP SRP + aPDT (670 to 690 nm at 75 mW)	62.5[bc] 16.7[b]	0.75[b] 1.29[b]	0.91[b] 1.50[b]	−0.42[b] −0.21
Moreira et al.[25]	SM, 20 patients (NS) with generalized AgP and two pairs of single-rooted contralateral teeth with proximal sites presenting PD and CAL ≥5 mm	Manual and ultrasonic SRP Diode laser (fiber-optic applicator with 600-μm diameter and maximum power 75 mW, power density: 25 mW/cm^2, 10 seconds/pocket) + aPDT (phenothiazine chloride photosensitizer 10 mg/mL, applied for 1 minute) Two contralateral pairs of single-rooted teeth in maxillary quadrants with proximal sites presenting PD and CAL ≥5 mm OHI + SS 1 week prior treatment	SRP SRP + aPDT (670 nm at 75 mW)	49.2[b] 46.2[b]	1.58[b]/1.75[b] [5 to 6 mm/ ≥7 mm] 1.53[b]/2.77[bc] [5 to 6 mm/ ≥7 mm]	2.15[b]/2.56[b] [5 to 6 mm/ ≥7 mm] 2.41[b]/3.96[bc] [5 to 6 mm/ ≥7 mm]	−0.57[b]/−0.84[b] [5-6 mm/ ≥7 mm] −0.87[b]/1.00[b] [5-6 mm/ ≥7 mm]

(Continues)

TABLE 1 (Continued)

Study	Design	Procedures	Treatment groups	ΔBOP (%)	ΔCAL (mm)	ΔPD (mm)	ΔRec (mm)
de Oliveira et al.[8]/ Novaes Jr. et al.[26]	SM, 10 patients (NS) with generalized AgP, with CAL exceeding 5 mm at seven teeth (excluding first molars and central incisors) Outcomes of sites with PD > 5 mm reported separately.	Manual SRP Diode laser (fiber-optic applicator with 600-μm diameter and maximum power 60 mW/cm^2, 10 seconds/pocket) + aPDT (phenothiazine chloride photosensitizer 10 mg/mL, applied for 1 minute) Interproximal surfaces of 10 contralateral maxillary single rooted-teeth with PD ≥5 mm on at least two aspects of the tooth OHI + SS 7 days prior treatment	SRP SRP + aPDT (660 nm at 75 mW)	NR NR	NR NR	NR NR	NR NR

Δ = change from baseline to last follow-up (means); SM = split-mouth; NS = non-smoking; NR = not reported; OHI = oral hygiene instructions; SS = supragingival scaling.
[a]Patients submitted to periodontal and/or antibiotic treatment within the previous 6 months were not considered eligible for inclusion.
[b]Statistically significant within group.
[c]Statistically significant between groups (superior group).

2.3 | Non-surgical treatment of AgP

2.3.1 | Main findings

Four trials[8,23–26] evaluated the adjunctive use of aPDT therapy in the non-surgical treatment of AgP (Table 1). All studies showed significant intragroup improvements for CAL, PD, and BOP; however, only Moreira et al.[25] found a superior mean PD reduction and mean CAL gain at 3-month follow-up for deep pockets (≥ 7 mm) when aPDT therapy was combined with SRP. Additionally, although not reporting the mean PD changes according to the severity of defect (i.e., shallow, moderate, or deep), the RCT reported in the papers by de Oliveira et al.[8] and Novaes et al.[26] described a reduction in the frequency of sites with moderate and deep (≥ 7 mm) pockets following both SRP plus aPDT and SRP at 3-month follow-up.

With respect to bacterial outcome measures, two studies[23,25] found that aPDT therapies, when compared with SRP alone, promoted greater reductions in the levels/proportions of periodontal pathogens from the red and orange complexes (i.e., *Porphyromonas gingivalis, Prevotella intermedia*, *Tannerella forsythia,* and *Treponema denticola*) and *Aggregatibacter actinomycetemcomitans*, particularly in deep pockets[25] and after multiple sessions of aPDT.[23] In contrast, Chitsazi et al.[24] found that SRP and SRP plus aPDT resulted in similar significant reductions in *A. actinomycetemcomitans* counts after 3 months in patients with AgP. In addition, none of the studies reported potential adverse effects related to the tested treatments.

Pooled estimates on the use of SRP plus aPDT versus SRP were conducted with data from three trials[23–25] (Table 7; supplementary Figure 1 in online *Journal of Periodontology*). Annaji et al.[23] and Chitsazi et al.[24] assessed the effect of treatment at sites with PD of 5 to 6 mm, while Moreira et al.[25] separated outcomes for moderate (5 to 6 mm) and deep (≥ 7 mm) pockets; therefore, two subsets of meta-analysis were carried out. A significantly greater reduction in PD was found for SRP plus aPDT than SRP alone (0.29 mm for sites with PD = 5 to 6 mm; 0.75 mm for sites with PD ≥ 7 mm; $P < 0.05$).

2.3.2 | Clinical recommendation summary

SRP plus aPDT versus SRP alone in the treatment of AgP is recommended with a moderate level of certainty. In general terms, outcomes generated by pooled estimates (i.e., meta-analysis) suggest that SRP plus aPDT promoted modest additional clinical benefits over those achieved by SRP alone (within deep pockets [≥ 7 mm] treated with SRP plus aPDT), but the available evidence does not allow an accurate assessment of the clinical significance of the findings. None of the studies presented information on treatment costs.

Pooled estimates on PD reduction and CAL gain (MD) showed a modest additional PD reduction of 0.29 mm for

TABLE 2 Non-surgical treatment of CP

Study	Design	Procedures	Treatment groups	ΔBOP (%)	ΔCAL (mm)	ΔPD (mm)	ΔRec (mm)
Alwaeli et al.[27]	SM, 16 patients with previously untreated CP (number of smokers NR), at least one premolar and one molar in every quadrant with a minimum of four teeth each, and at least one tooth with AL ≥4 mm in every quadrant 12-month follow-up Patients submitted to periodontal and/or antibiotic treatment within the previous 6 months were not considered eligible for inclusion	Manual and ultrasonic SRP Diode laser (fiber-optic tip diameter and maximum power NR, 10 seconds/pocket) + aPDT (phenothiazine chloride photosensitizer, 10 mg/mL, applied for 1 to 3 minutes) OHI + SRP at the beginning of the study	SRP SRP + aPDT (660 nm at 100 mW)	12.7 64.4[a,b]	0.13 1.48[a,b]	0.60[a] 1.51[a,b]	NR NR
Andersen et al.[28]	Parallel, 28 patients (NS) with CP and at least four sites with PD > 6 mm in at least two quadrants of the mouth, with BOP 3-month follow-up Patients submitted to periodontal and/or antibiotic treatment within the previous 4 months were not considered eligible for inclusion	Manual SRP Diode laser (fiber-optic tip dimension NR; energy density of 10 to 29 J/cm^2 moved around the pocket, 60 seconds/pocket) + aPDT (methylene blue dye, 0.05 mg/mL, applied prior to aPDT) aPDT group was excluded from the review because it assessed data of only five patients No information on whether OHI/SS were provided	SRP SRP + aPDT (670 nm at 150 mW)	56.0[a] 59.0[a]	0.36 0.86[a,b]	0.74[a] 1.11[a,b]	NR NR
Balata et al.[29]	SM, 22 patients (NS) with generalized CP and clinical AL ≥5 mm and minimum of two teeth with PD ≥7 mm and two other teeth with a PD ≥5 mm 6-month follow-up Patients submitted to periodontal treatment within the previous 6 months or antibiotics within the previous 3 months were not considered eligible for inclusion	Ultrasonic SRP Diode laser (fiber-optic tip with 600-μm diameter applied at a 90-degree angle with the gingival surface and with no contact with the tissues, 90 seconds/pocket) + aPDT (methylene blue dye, 0.05 mg/mL, applied 2 minutes prior to aPDT) At least two teeth (one with a PD ≥7 mm and another with a PS ≥5 mm) were assigned to one of the treatments OHI + SS 2 weeks prior treatment	SRP SRP + aPDT (660 nm at 100 mW)	23.74[a] 24.85[a]	1.80 (PD = 5 to 6 mm)[a] 3.90 (PD ≥ 7 mm)[a] 1.79 (PD = 5 to 6 mm)[a] 3.57 (PD ≥ 7 mm)[a]	2.03 (PD = 5 to 6 mm)[a] 4.24 (PD ≥ 7 mm)[a] 1.96 (PD = 5 to 6 mm)[a] 3.84 (PD ≥ 7 mm)[a]	NR NR

(Continues)

TABLE 2 (Continued)

Study	Design	Procedures	Treatment groups	ΔBOP (%)	ΔCAL (mm)	ΔPD (mm)	ΔRec (mm)
Berakdar et al.[30]	SM, 22 patients (NS) with CP and four teeth having at least one site with a PD ≥5 mm and BOP 6-month follow-up No information on whether the patients submitted to periodontal treatment within the previous 6 months were considered eligible for inclusion	Manual SRP Diode laser (fiber-optic tip dimension NR; 60 seconds/pocket) + aPDT (methylene blue dye, 0.05 mg/mL, applied prior to aPDT) Professional tooth cleaning 3 weeks prior to treatment	SRP SRP + aPDT (670 nm at 150 mW)	77.3[a] 86.4[a]	NR[a] NR[a]	2.4[a] 2.9[a,b]	NR NR
Birang et al.[31]	SM, 20 patients (NS) with CP with the presence of three or more quadrants of mouth, each containing at least three sites with PD of 4 to 7 mm and CAL of 2 mm or greater 3-month follow-up Patients submitted to antibiotic treatment within the previous 2 months were considered not eligible for inclusion	Ultrasonic SRP Diode laser (fiber-optic tip with 300-μm diameter and maximum power 0.5 W/cm^2; pockets were initially irradiated for 10 seconds, and than granulation tissue removal was performed for 25 seconds) + aPDT (indocyanine green dye, 1 mg/mL, applied prior to aPDT) Laser applied after SRP and 2 weeks later OHI 1 week prior to treatment	SRP SRP + aPDT (810 nm at 0.5 W)	NR NR	0.83[a] 0.92[a]	0.92[a] 0.89[a]	NR NR
Braun et al.[32]	SM, 20 patients (NS) with CP and clinical AL > 3 mm 3-month follow-up Patients submitted to periodontal and/or antibiotic treatment within the previous 6 months were not considered eligible for inclusion Outcomes of sites with PD > 5 mm reported separately	Manual and ultrasonic SRP Diode laser (fiber-optic tip with 600-μm diameter and maximum power 60 mW/cm^2, 10 seconds/pocket) + aPDT (phenothiazine chloride photosensitizer 10 mg/mL applied for 3 minutes)	SRP SRP + aPDT (660 nm at 100 mW)	NR NR	NR NR	1.22[a] 1.43[a]	NR NR
Dilsiz et al.[33]	SM, 24 patients (NS) with CP and presence of ≥4 non-adjacent teeth with PD ≥5 mm 6-month follow-up Patients submitted to periodontal treatment within the previous 6 months were not considered eligible for inclusion	Manual and ultrasonic SRP Diode laser (fiber-optic tip with 300-μm diameter, 60 seconds/pocket) + aPDT (methylene blue dye, 10 mg/mL, applied 3 minutes prior to aPDT) OHI + supra- and subgingival ultrasonic SRP (first visit) Manual SS was applied to all groups at second visit	SRP SRP + aPDT (808 nm at 100 mW)	46[a] 50[a]	1.50[a] 1.54[a]	1.42[a] 1.54[a]	NR NR

(Continues)

TABLE 2 (Continued)

Study	Design	Procedures	Treatment groups	ΔBOP (%)	ΔCAL (mm)	ΔPD (mm)	ΔRec (mm)
Ge et al.[34]	Parallel, 58 patients (nine smokers) with CP and at least four sites of PD = 6 to 9 mm in at least two quadrants of the mouth 3-month follow-up Patients submitted to periodontal and/or antibiotic treatment within the previous month were not considered eligible for inclusion	Manual and sonic SRP Diode laser (fiber-optic tip, 60 seconds/pocket) + aPDT (methylene blue dye, 0.1 mg/mL applied prior to aPDT) OHI + SS prior to treatment (moment not reported)	SRP SRP + aPDT (670 nm at 140 mW) SRP + aPDT (670 nm at 140 mW) Weeks 0 and 6	NR[a] NR[a,b] NR[a,b]	NR[a] NR[a] NR[a]	NR[a] NR[a] NR[a]	NR NR NR
Lui et al.[35]	SM, 24 patients (NS) with CP and at least two single-rooted teeth on each side of the mouth having PD ≥5 mm and interproximal AL of ≥3 mm 3-month follow-up Patients submitted to periodontal treatment within the previous 6 months or antibiotic treatment within the previous 3 months were not considered eligible for inclusion	SRP Diode laser applied twice: Day 0: laser (immediately after SRP, fired at the orifice of the gingival margin at a distance of 1 cm, 5 to 10 seconds/tooth, giving no more than 4 J/cm^2 of energy) Day 1: aPDT (fiber-optic tip, 300-μm diameter, 30 seconds/tooth) + aPDT (methylene blue dye, 10 mg/mL, applied 3 minutes prior to aPDT) OHI immediately prior SRP	SRP SRP + laser (940 nm at 1.5 W) + aPDT (940 nm at 0.5 W)	49[a] 55[a]	0.50[a] 0.60[a]	1,30[a] 1.60[a]	−0.80[a] −1.00[a]
Monzavi et al.[36]	Parallel, 50 patients (NS) with CP and presence of at least three teeth exhibiting PD ≥5 mm with BOP 3-month follow-up Patients submitted to antibiotic treatment within the previous 6 months were not considered eligible for inclusion	Manual and ultrasonic SRP Diode laser (fiber-optic tips, dimensions NR; 10 seconds/pocket) + aPDT (indocyanine green dye 1 mg/mL applied prior to aPDT) Laser applied after SRP and 7, 17, and 27 days later OHI prior to treatment	SRP SRP + aPDT (810 nm at 200 mW)	52[a] 100[a,b]	1.55[a] 1.36[a]	0.63[a] 2.54[a]	NR NR
Polansky et al.[37]	Parallel, 58 patients (seven smokers) with moderate to severe CP and at least three periodontal pockets of 5 to 8 mm 3-month follow-up Patients submitted to periodontal and/or antibiotic treatment within the previous 6 months were not considered eligible for inclusion	Ultrasonic SRP Diode laser (fiber-optic tip with 300 μm diameter, 60 seconds/pocket) + aPDT (phenothiazine chloride photosensitizer, 10 mg/mL, applied 3 minutes prior to aPDT) OHI over 6 weeks prior to treatment	SRP SRP + aPDT (680 nm at 75 mW)	41[a] 53[a]	1.35[a] 1.35[a]	1.03[a] 1.24[a]	NR NR

(Continues)

TABLE 2 (Continued)

Study	Design	Procedures	Treatment groups	ΔBOP (%)	ΔCAL (mm)	ΔPD (mm)	ΔRec (mm)
Srikanth et al.[38]	SM, 30 patients with moderate or advanced CP and at least two periodontal pockets ≥5 mm with radiographic evidence of bone loss per quadrant (27 patients completed the study) 6-month follow-up Patients submitted to periodontal and/or antibiotic treatment within the previous 6 months were not considered eligible for inclusion	Manual and ultrasonic SRP Diode laser (supragingival application without fiber-optic tip: 5 seconds/pocket) + aPDT (indocyanine green dye, 5 mg/mL, applied prior to aPDT)	SRP SRP + aPDT (810 nm at 0.7 W)	NR NR	1.40[a] 2.47[a,b] (baseline means statistically different)	2.06[a] 2.74[a] (baseline means statistically different)	NR NR
Theodoro et al.[39]	SM, 37 patients with CP and at least three non-adjacent sites with a PD of 5 to 9 mm and BOP (33 patients completed the study) 6-month follow-up Patients submitted to periodontal and/or antibiotic treatment within the previous 6 months were not considered eligible for inclusion	Manual SRP Diode laser (supragingival application without fiber-optic tip, power density of 0.4 W/cm^2 and energy density of 64.28 J/cm^2, 150 seconds/pocket) + aPDT (toluidine blue dye, 0.1 mg/mL, applied prior to aPDT) OHI + SS	SRP SRP+aPDT (660 nm at 0.03 W)	69.7[a] 48.4[a]	1.98[a] 1.56[a]	2.71[a] 2.33[a]	−0.64 −0.77

Δ = change from baseline to last follow-up (means); SM = split-mouth; NR = not reported; OHI = oral hygiene instructions; NS = non-smoking; SS = supragingival scaling; AL = attachment loss.

[a]Statistically significant within group.

[b]Statistically significant between groups (superior group).

TABLE 3 Non-surgical treatment of patients with CP – residual pockets after active periodontal therapy

Study	Design	Procedures	Treatment groups	ΔBOP (%)	ΔCAL (mm)	ΔPD (mm)	ΔRec (mm)
Campos et al.[40]	SM, 13 patients (NS) with CP and at least two contralateral single-rooted teeth with residual PD ≥5 mm and BOP 12 weeks after one session of full-mouth SRP 3-month follow-up Patients submitted to antibiotic treatment within the previous 6 months were not considered eligible for inclusion	Manual and ultrasonic SRP Diode laser (fiber-optic tip with 600-μm diameter and energy density: 129 J/cm^2, 10 seconds/pocket) + aPDT (methylene blue 10 mg/mL, applied for 1 minute)	SRP SRP + aPDT (660 nm at 60 mW)	40.00[a] 77.78[a,b]	0.51[a] 1.43[a,b]	1.14[a] 2.17[a,b]	−1.10[a] −1.03[a]
Correa et al.[41]	SM, 15 patients (NS) with CP and at least two contralateral single-rooted teeth with residual PD ≥5 mm with BOP 12 weeks after one session of full-mouth SRP 3-month follow-up Patients submitted to antibiotic treatment within the previous 6 months were not considered eligible for inclusion	Manual and ultrasonic SRP Diode laser (fiber-optic tip with 600-μm diameter and energy density: 129 J/cm^2, 10 seconds/pocket) + aPDT (methylene blue 10 mg/mL, applied for 1 minute)	SRP SRP + aPDT (660 nm at 60 mW)	60.00[a] 80.00[a]	0.30 1.30[a,b]	1.60[a] 2.30[a,b]	−1.30[a] −1.10[a]
Kolbe et al.[42]	SM, 22 patients (NS) with CP and at least three single-rooted teeth with residual PD ≥5 mm and BOP 12 weeks after one session of full-mouth SRP 6-month follow-up Patients submitted to antibiotic treatment within the previous 6 months were not considered eligible for inclusion	Manual and ultrasonic SRP Diode laser (fiber-optic tip with 600-μm diameter and energy density: 129 J/cm^2, 10 seconds/pocket) + aPDT (methylene blue 10 mg/mL, applied for 1 minute)	SRP SRP + aPDT (660 nm at 60 mW)	71.43[a] 71.43[a]	1.21 0.95[a]	1.88[a] 1.60[a]	−0.67[a] −0.64[a]

Δ = change from baseline to last follow-up (means); SM = split-mouth; NS = non-smoking.

[a]Statistically significant within group.

[b]Statistically significant between groups (superior group).

TABLE 4 Non-surgical treatment of patients with CP – treatment of residual sites following regular maintenance (3 to 4 months) for at least 1 year after active periodontal therapy

Study	Design	Procedures	Treatment groups	ΔBOP (%)	ΔCAL (mm)	ΔPD (mm)	ΔRec (mm)
Chondros et al.[43]	Parallel, 24 patients (seven smokers) with CP, undergoing PM, and with at least one site per quadrant exhibiting PD ≥4 mm with BOP 6-month follow-up Patients submitted to antibiotic treatment within the previous 6 months were not considered eligible for inclusion	Ultrasonic SRP Diode laser (fiber-optic applicator with 600-μm diameter and power density of 75 mW/cm^2, 60 seconds/tooth) + aPDT (phenothiazine chloride photosensitizer 10 mg/mL)	SRP SRP + aPDT (670 nm)	10.00 50.00[a,b]	0.50[a] 0.70[a]	0.90[a] 0.80[a]	−0.40[a] −0.20
Lulic et al.[44]	SM, 10 patients (two smokers) with CP, undergoing PM, and with residual PD ≥5 mm with/without concomitant BOP 12-month follow-up Patients submitted to antibiotic treatment within the previous 3 months were considered not eligible for inclusion	Manual SRP Manual and ultrasonic SRP Diode laser (fiber-optic applicator with 600-μm diameter and maximum power 75 mW, 60 seconds/pocket) + aPDT (phenothiazine chloride photosensitizer, 10 mg/mL, applied for 3 minutes) Laser applied after SRP and 1, 2, 7, and 14 days later OHI prior to treatment	SRP SRP + aPDT (670 nm)	−3.00 20.00[a]	−0.20 −0.09	0.07 0.27	NR NR
Rühling et al.[45]	Parallel, 54 patients (NS) with CP, undergoing PM, with at least two teeth with PD > 4 mm 3-month follow-up Patients submitted to antibiotic treatment within the previous 6 months were not considered eligible for inclusion	Ultrasonic SRP Diode laser (fiber-optic applicator, diameter not reported, 60 seconds/pocket) + aPDT (tolonium chloride photosensitizer, 50 mg/mL, applied for 30 seconds)	SRP SRP + aPDT (635 nm at 100 mW)	NR NR	−0.10 0.00	0.80[a] 0.60[a]	NR NR

Δ = change from baseline to last follow-up (means); PM = periodontal maintenance; SM = split-mouth; OHI = oral hygiene instructions; NR = not reported; NS = non-smoking.

[a]Statistically significant within group.

[b]Statistically significant between groups (superior group).

TABLE 5 Non-surgical treatment of smokers with CP

Study	Design	Procedures	Treatment groups	ΔBOP (%)	ΔCAL (mm)	ΔPD (mm)	ΔRec (mm)
Queiroz et al.[46,47]	SM, 20 smoking patients with CP and at least two bilateral sites with PD ≥5 mm 3-month follow-up Smokers were identified as smoking ≥10 cigarettes per day for ≥5 years Patients submitted to periodontal treatment within the previous 6 months were not considered eligible for inclusion	Manual and ultrasonic SRP Diode laser (fiber-optic applicator with 600-μm diameter and maximum power 75 mW, power density: 25 mW/cm^2, 10 seconds/pocket) + aPDT (phenothiazine chloride photosensitizer 10 mg/mL, applied for 1 minute) OHI 2 weeks prior treatment SS 1 week prior treatment	SRP SRP + aPDT (660 nm at 60 mW)	NR NR	1.41[a] 1.60[a]	1.58[a] 1.81[a]	−0.20 −0.29

Δ = change from baseline to last follow-up (means); SM = split-mouth; OHI = oral hygiene instructions; SS = supragingival scaling; NR = not reported.

[a]Statistically significant within group.

[b]Statistically significant between groups (superior group).

moderate sites (5 to 6 mm) treated with SRP plus aPDT. Additional PD reduction of 0.75 mm and CAL gain of 0.63 mm were identified when deep sites (≥ 7 mm) were used for analysis.[25] Sites with PD ≥ 7 mm appeared to present superior gains in PD reduction.

When comparing clinical outcomes in the four included RCTs, the effectiveness of SRP also appeared to impact the results of therapy. As described previously,[1] in the study by Annaji et al.,[23] treatment groups presented poorer clinical improvements when compared with other studies reporting outcomes from 5- to 6-mm pockets. This difference in clinical improvements seemed to be directly associated with the type and perhaps quality of performed instrumentation (single session of ultrasonic scaling and lack of adequate root planing), rather than adjunctive aPDT therapy. In addition, photophysically, this paper presents a very uncommon combination of laser and dye.[23] Technically, however, it is unclear whether optimal settings for the toluidine blue O dye were applied in the study. An infrared laser was used with a dye with an absorption peak of about 632 nm. Moreover, any differences among the groups in clinical outcomes might be due to repeated flushing of the periodontal pocket due to irrigation with the dye and saline, rather than the aPDT (i.e., sham procedures should have been done to overcome this possibility). Overall, based on the outcomes of individual studies and on the pooled estimates, the statistically significant reduction in PD and gain in CAL achieved with SRP plus aPDT reflect only modest clinical benefit.

No adverse events or harms were reported. Benefit-harm assessment (net benefit rating) compared with SRP: modest clinical benefits of SRP combined with aPDT outweigh potential for harm.

Strength of clinical recommendation of procedures compared with SRP: non-surgical treatment of AgP by SRP plus aPDT – expert opinion questions the use (evidence is lacking; level of certainty is low; expert opinion questions the use).

2.4 | Non-surgical treatment of CP

2.4.1 | Main findings

Thirteen trials[27–39] evaluated the use of aPDT as an adjunct to SRP for the non-surgical treatment of CP (Table 2). It has been shown that the use of SRP plus aPDT promoted significant improvements in BOP, CAL and PD.[27–39] Moreover, no significant adverse effects were reported within the included studies.

On the other hand, four RCTs[27,28,30,38] (approximately one-third of trials evaluating the non-surgical treatment of CP as part of basic procedures) demonstrated additional CAL and/or PD gains at moderate-deep pockets with SRP + aPDT when compared with manual and/or ultrasonic/sonic debridement (SRP). Alwaeli et al.,[27] Andersen et al.,[28] and Berakdar et al.[30] found that sites treated with aPDT presented

TABLE 6 Treatment of patients with peri-implantitis

Study	Design	Procedures	Treatment groups	ΔBOP (%)	ΔCAL (mm)	ΔPD (mm)	ΔRec (mm)
Romeo et al.[48]	SM 10 patients with at least 1 implant with peri-implantitis and PD ≥4 mm and BOP were considered eligible for inclusion in the study 6-month follow-up Patients submitted to periodontal treatment within the previous 3 months were not considered eligible for inclusion	Piezoelectric ablator with a non-metal tip + ISS (plastic scalers) + irrigation with 0.2% chlorhexidine digluconate solution Diode laser (fiber-optic tip with 600-μm diameter, 10 seconds/pocket) + aPDT (methylene blue, 10 mg/mL, applied for 1 minute) OHI Statistical analysis NR	ISS ISS + aPDT (670 nm at 75 mW)	90 100	NR NR	2.00 3.00	−0.54 −0.34
Bombeccari et al.[49]	Parallel, 40 patients with at least one implant with peri-implantitis, PD ≥5 mm, and BOP; light smokers (< 10 cigarettes per day) were considered eligible for inclusion in the study 6-month follow-up Patients submitted to periodontal treatment within the previous 3 months were not considered eligible for inclusion	Open-flap surgery + ISS (plastic scalers) + irrigation with 0.2% chlorhexidine digluconate solution Diode laser (fiber-optic applicator with 300-μm diameter, 20 seconds per application: five consecutive applications with 30-second intervals) + aPDT (toluidine blue dye, 0.1 mg/mL, applied 1 minute prior to aPDT)	ISS ISS + aPDT (810 nm at 1W)	NR NR	0.10 0.54	0.30 1.00[a,b]	−0.54[a] −0.34[a,b]

Δ = change from baseline to last follow-up (means); SM = split-mouth; ISS = implant surface scaling; OHI = oral hygiene instructions; NR = not reported.

[a]Statistically significant within group.

[b]Statistically significant between groups (superior group).

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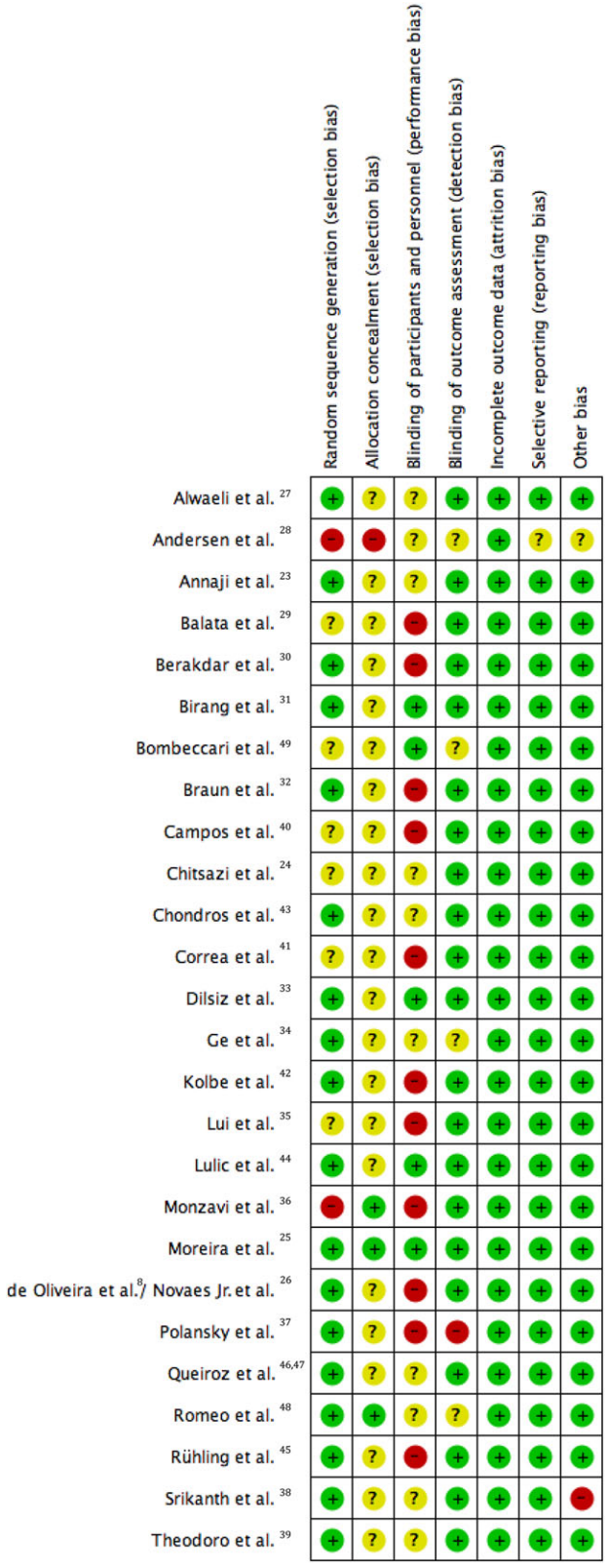

FIGURE 2 Risk of bias summary: review authors' judgments about risk of bias items for each included study

superior PD reduction and/or CAL gain at 3,[28] 6,[30] and 12[27] months when compared with those treated by SRP alone, especially for patients with "meticulous strict supragingival plaque control."[27] Srikanth et al.[38] also identified superior clinical improvements for SRP plus aPDT (810 nm at 0.7 W) compared with SRP alone; however, the aPDT group presented with significantly higher mean PD and CAL prior to treatment, a methodologic limitation known to impact the relative changes from baseline and statistical analysis. Additionally, greater reductions in BOP for sites treated by SRP plus aPDT than those treated by SRP at the end of the follow-up period were also identified in some trials;[27,34,36] however, in one of them,[34] baseline values were not published in the original paper.

Of the three studies[31,37,39] that reported on the effect of treatment on periodontopathogens, two trials[31,37] found that SRP plus aPDT and SRP alone were essentially comparable in reducing levels of different bacteria (e.g., *A. actinomycetemcomitans, T. forsythia, Campylobacter rectus, Eikenella corrodens, Fusobacterium nucleatum, P. gingivalis, P. intermedia, T. denticola*) at 12[31,37] weeks after treatment. In one trial,[39] the use of SRP plus aPDT promoted superior reductions in the values of *A. actinomycetemcomitans*, *P. gingivalis*, *P. intermedia*, *Prevotella nigrescens*, and *T. forsythia* 6 months after treatment.[39]

In terms of patient-centered outcomes, none provided observations.

Pooled estimates comparing the use of SRP plus aPDT to SRP alone, performed with data from 11 trials,[27–33,36–39] identified an additional significant reduction of 0.43 mm in mean PD for sites with PD = 5 to 6 mm (Table 7; supplementary Figure 2 in online *Journal of Periodontology*) and a high level of heterogeneity (90.0%).

2.4.2 | Clinical recommendation summary

SRP plus aPDT versus SRP for the non-surgical treatment of CP is recommended with a moderate level of certainty.

The overall estimates on SRP plus aPDT suggested modest additional clinical benefits to those achieved by SRP alone. None of the studies presented information on treatment costs. Pooled estimates on PD reduction and CAL gain (MD) showed a modest additional PD reduction of 0.43 mm for moderate sites (5 to 6 mm) treated with SRP plus aPDT. For the 13 included trials, the quality of SRP did not seem to impact the results of therapy.

Overall, based on outcomes of individual studies and on pooled estimates, the statistically significant adjunctive improvements in PD and CAL achieved with SRP plus aPDT were considered to represent questionable additional clinical benefit. No adverse events or harms were reported. Benefit-harm assessment (net benefit rating) compared to SRP:

TABLE 7 Summary of meta-analyses – overall estimates (MD; 95% CI)

Comparison	Outcomes	Statistical method	Effect size in mm	*P* value	χ^2	*P* value (Q)	I^2 (%)
AgP – basic procedures SRP + aPDT versus SRP	ΔPD[23–25]	MD (95% CI)	0.29 (0.17 to 0.41)	<0.001	1.57	0.46	0
	ΔPD[23–25] (PD ≥7 mm[25])	MD (95% CI)	0.75 (0.19 to 1,421	0.02	15.66	<0.001	87
	ΔCAL[23–25]	MD (95% CI)	0.22 (–0.15 to 0.58)	0.25	4.85	0.09	59.0
	ΔCAL[23–25] (PD ≥7 mm[25])	MD (95% CI)	0.63 (0.22 to 1.04)	0.002	3.84	0.15	48.0
CP – basic procedures SRP + aPDT versus SRP	ΔPD[27–33,36–39]	MD (95% CI)	0.43 (0.04 to 0.82)	0.03	100.33	<0.001	90.0
	ΔPD[27–33,36–39] (PD ≥7 mm[29])	MD (95% CI)	0.40 (–0.02 to 0.81)	0.06	95.63	<0.001	90.0
	ΔCAL[27–31,33,36–39]	MD (95% CI)	0.30 (–0.08 to 0.67)	0.12	42.94	<0.001	81.0
	ΔCAL[27–31,33,36–39] (PD ≥7 mm[29])	MD (95% CI)	0.28 (–0.12 to 0.67)	0.17	41.71	<0.001	81.0
CP – residual sites following basic procedures SRP + aPDT versus SRP	ΔPD[40–42]	MD (95% CI)	0.44 (–0.20 to 1.20)	0.25	6.97	0.03	71
	ΔCAL[40–42]	MD (95% CI)	0.51 (–0.35 to 1.37)	0.25	6.27	0.04	68
CP – residual sites during periodontal maintenance SRP + aPDT versus SRP	ΔPD[43–45]	MD (95% CI)	0.08 (–0.57 to 0.73)	0.80	21.19	<0.001	91.0
	ΔCAL[43–45]	MD (95% CI)	0.43 (–0.04 to 0.89)	0.07	4.69	0.10	57.0

Δ = change from baseline to last follow-up.

modest clinical benefits of SRP plus aPDT outweigh potential for harm.

Strength of clinical recommendation of procedures compared to SRP: non-surgical treatment of CP by SRP plus aPDT – expert opinion questions the use (evidence is lacking [for the different protocols]; the level of certainity is low; expert opinion questions the use).

2.5 | Non-surgical treatment of CP – residual sites after active periodontal therapy and during periodontal maintenance

2.5.1 | Main findings

Six studies[40–45] appraised the use of SRP plus aPDT for the non-surgical treatment of patients with CP with sites with residual pocketing. In three studies,[40–42] single-rooted teeth with PD ≥ 5 mm with BOP 3 months after one session of full-mouth SRP were treated with SRP alone or SRP plus aPDT. Two of these trials[40,41] showed significant additional gains for the combined therapy for both CAL gain and PD reduction over mechanical treatment alone, whereas one did not find differences between SRP alone and SRP associated with aPDT.[42] Moreover, Correa et al.[41] observed that SRP plus aPDT may decrease the levels of *A. actinomycetemcomitans*, when compared to SRP alone, at short-term (3-month) follow-up. In addition, Kolbe et al.[42] reported no significant differences among treatments in terms of pain/morbidity ($P > 0.05$).[42]

Table 4 presents information on the other three RCTs[43–45] examining the clinical response of sites with residual pocketing (PD ≥ 5 mm) to targeted retreatment in patients with CP after undergoing regular periodontal maintenance every 3 to 4 months for at least 1 year. None of these studies[43–45] reported significant additional improvements in PD or CAL measures associated with the treatment of residual pockets with aPDT therapies. Regarding microbial outcome measures, Chondros et al.[43] found that aPDT resulted in a decrease in *F. nucleatum* and *Eubacterium nodatum* after 3 months and an increase in *E. corrodens*, *T. denticola*, and *Capnocytophaga species* after 6 months, when compared with SRP alone. Rühling et al.[45] reported a significant reduction (about 30% to 40%) in microbial counts immediately after conventional ultrasonic debridement or aPDT; however, microbial counts returned to baseline levels after 3 months, irrespective of treatment.

Pooled estimates evaluating PD reduction and CAL gain at residual sites did not identify significant differences among therapies, neither 3 months following basic procedures nor during regular periodontal maintenance (Table 7; supplementary Figs. 3 and 4 in online *Journal of Periodontology*).

2.5.2 | Clinical recommendation summary

SRP plus aPDT for the non-surgical treatment of CP is recommended with low certainty for residual sites identified after

active periodontal therapy or during regular maintenance (3 to 4 months) for at least 1 year after active periodontal therapy. In general terms, SRP plus aPDT did not promote additional improvements to those accomplished by SRP alone in the treatment of residual sites. None of the studies presented information on treatment costs. Pooled estimates on PD reduction and CAL gain (MD) did not show statistically significant differences between SRP plus aPDT and SRP alone.

In the six included RCTs,[40–45] the quality of SRP did not appear to have adversely impacted the results of therapy. Overall, based on the outcomes of the individual studies and on the pooled estimates of treatment effects for residual sites, the base of evidence is insufficient to fully support the statistically significant additional improvements in PD and CAL achieved with SRP plus aPDT, when compared with SRP, identified in two studies.[40,41]

The availability of additional new information could allow for a reliable estimation of effects on health outcomes. No adverse events or harms were reported. Benefit-harm assessment (net benefit rating) compared to SRP: No additional clinical benefit was identified for SRP plus aPDT in the treatment of sites with residual PD during regular periodontal maintenance. Potential clinical benefits of SRP plus aPDT in the treatment of residual sites after basic procedures might outweigh potential for harm.

Strength of clinical recommendation of procedures compared with SRP: 1) treatment of sites with residual PD after active non-surgical treatment of CP by SRP plus aPDT – expert opinion questions the use (evidence is lacking; the level of certainty is low; expert opinion questions the use); 2) treatment of residual sites during regular periodontal maintenance of patients with CP by SRP plus aPDT – expert opinion questions the use (evidence is lacking; the level of certainty is low; expert opinion questions the use).

2.6 | Non-surgical treatment of CP in patients with systemic conditions/disease known to impact disease progression – smoking

2.6.1 | Main findings

The unique RCT available in the literature by Queiroz et al.[46,47] assessed the effects of SRP plus aPDT, compared with SRP alone, on 40 bacterial species in smokers with CP.[46,47] These two papers did not find significant differences in microbial species among treatment groups.[46,47]

2.6.2 | Clinical recommendation summary

SRP plus aPDT versus SRP alone for the non-surgical treatment of CP in smokers recommended with low certainty and low benefit. The unique study did not present information on treatment costs. Pooled estimates could not be calculated for PD reduction and CAL gain.

No adverse events or harms were reported. Benefit-harm assessment (net benefit rating) compared to SRP: benefits of SRP combined with aPDT are uncertain but outweigh potential for harm.

Strength of clinical recommendation of procedures compared with SRP: 1) non-surgical treatment of smokers with CP by SRP plus aPDT – expert opinion questions the use (evidence is lacking; the level of certainty is low; expert opinion questions the use).

2.7 | Non-surgical treatment of peri-implantitis

2.7.1 | Main findings

Two trials[48,49] assessed the use of implant surface scaling (ISS) plus aPDT in the treatment of peri-implantitis, one using non-surgical[48] therapy and the other an open-flap approach.[49]

Romeo et al.[48] evaluated aPDT therapy associated with mechanical debridement and found 2- and 3-mm PD reduction in control and test groups, respectively, 6 months after non-surgical treatment of peri-implantitis sites presenting mean baseline PD of 5 mm. Despite the somewhat pronounced arithmetic changes from baseline, the authors of this study did not provide statistical analysis comparing the outcomes between ISS plus aPDT versus ISS alone. In another trial, Bombeccari et al.[49] reported a minute significant improvement in PD 6 months after open-flap surgery (OFS) + ISS + aPDT compared to OFS + ISS (1.0 versus 0.3 mm). Overall, in this trial,[49] there were no significant differences between treatments in terms of the total anaerobic bacteria counts. Both therapies failed in satisfactory improving clinical outcomes.

2.7.2 | Clinical recommendation summary

ISS plus aPDT versus ISS for the treatment of peri-implantitis is recommended with low level of certainty. In general, ISS plus aPDT did not lead to additional gains to those accomplished by ISS alone. None of the studies presented information on treatment costs. Pooled estimates could not be calculated for PD reduction and CAL gain.

No adverse events or harms were reported. Benefit-harm assessment (net benefit rating) compared to SRP: no additional clinical benefit was identified for ISS plus aPDT.

Strength of clinical recommendation of procedures compared with SRP: 1) treatment of peri-implantitis by ISS plus aPDT – expert opinion questions the use (evidence is lacking; level of certainty is low; expert opinion questions the use).

3 | DISCUSSION

The findings of this AAP BEC review showed that SRP plus aPDT may promote short-term statistically significant

improvements in CAL and PD. Some studies (Tables 1 through 6) also showed alterations in the position of the gingival margin (i.e., increase in Rec depth) after treatment. No adverse effects were reported, a condition supporting the safety of the aPDT-based procedures assessed in this review. On the other hand, few trials and pooled estimates identified additional gains in clinical outcomes when compared with those expected after conventional (SRP) approaches to mechanical debridement of both root surfaces and implant surfaces. Additionally, the very limited data on the use of aPDT in the treatment of peri-implantitis did not show any additional potential clinical benefit compared with ISS alone.

Of the four sets of meta-analyses, significant but small additional gains in clinical outcomes were observed with SRP plus aPDT to SRP alone for the following comparisons: 1) non-surgical treatment of AgP using SRP plus aPDT (PD reduction and CAL gain mainly in sites with baseline PD $\geq$ 7 mm) and 2) non-surgical treatment of CP using SRP plus aPDT (PD reduction). It might be considered that the extension/clinical significance of additional gains (0.30 to 0.75 mm) promoted with SRP plus aPDT over SRP alone seems imprecise.[59] Such a degree of inaccuracy should be assumed to be due to the small number of studies included within some analysis (non-surgical treatment of AgP patients), differences in study protocols (e.g., SRP and aPDT protocols), and disease severity at baseline (i.e., potential for differing clinical improvements in PD and CAL, favoring deeper sites).[59] Thus, all of these conditions may have impacted the calculation of pooled estimates.

3.1 | Quality of the evidence and potential biases in the review process

Only one RCT[25] was considered to be at low risk of bias, while the other trials were assessed as unclear or as high risk of bias. It should be noted that for most of the trials information on the methods of randomization, allocation, and patient masking were not reported or met. However, the lack of patient masking, per se, did not seem to have interfered in the overall outcomes of each individual trial. Additionally, to reduce potential heterogeneity among studies in terms of combining data from trials with shallow versus deep mean PD baseline values, this SR protocol (inclusion/exclusion criteria) considered eligible for inclusion only reporting PD $\geq$ 5 mm.[59] On the other hand, it may have precluded the inclusion of additional data into the meta-analysis sets.

Also, the degree of heterogeneity identified for some estimates appeared to be linked to the severity of disease (baseline PD), type of mechanical debridement performed, and the type of dye (Tables 1 through 6). The absorption coefficient by the bacteria depends on the photosensitizer and the specific laser wavelength and can have different effects on the periodontal tissues.

3.2 | Agreements and disagreements with other studies or reviews

Outcomes of previous recent reviews did not identify additional relevant clinical improvements associated with aPDT procedures at least 3 months after therapy.[9–11] In the present BEC systematic review, some additional significant gains were identified for SRP plus aPDT [non-surgical treatment of CP and AgP]. However, these small clinical improvements remain uncertain because of the lack of an outright "gold standard" aPDT procedure, as well as the restricted extent of the additional gains identified by both the individual study outcomes and pooled estimates. Furthermore, due to lack of data, potential cost-benefits of aPDT therapy could not be assessed.

Evidence from studies that could not be included in this SR may shed light on the potential positive effects and cost-benefits of aPDT. For instance, Romanos and Brink[60] evaluated in a study with 10 patients the antimicrobial effects of aPDT (660 nm, 400-μm fiber, phenothiazine chloride, 10 mg/mL) compared with those of other laser wavelengths (i.e., Nd:YAG [1,064 nm, 2 W] and diode [980 nm, 2 W]) in conjunction with SRP and SRP alone in the treatment of deep periodontal pockets ($\geq$ 5 mm) after initial therapy. The authors found that aPDT led to the greatest bacterial reduction 1 and 3 months after treatment. The bacteria reduction in the control (only SRP group) was similar to the Nd:YAG laser + SRP group. A significant reduction in BOP was found during the entire examination period at the sites where aPDT was used in conjunction with SRP. The tissue was irradiated for 20 seconds with the laser* using a 75-mW power setting after irrigation of the pocket using a photosensitizer.† The photosensitizer was left in the sulcus for 60 seconds before the residual dye was washed out using saline solution. These outcomes suggest that aPDT therapy could be an alternative treatment in patients with a compromised medical history as well as a beneficial option during the recall phase of treatment.

More information on aPDT use at periodontitis and peri-implantitis sites would be necessary to allow for a reliable and definitive estimation of effect/magnitude of therapies on health outcomes. It should be highlighted that the reported protocols are quite heterogeneous (i.e., types of dye used, time of laser exposure, power level, diameter of fiber, duration of exposure, whether SRP and/or ultrasonics were used). The calculated meta-analyses provided only a snapshot or bigger picture of the potential role of adjunct aPDT therapy, rather than combining protocols that are fairly similar (i.e., no optimal/gold standard aPDT protocol could be established). Consequently, these conditions should be accounted for when interpreting the results of this SR.

* Minilaser 2075 dent, HELBO Photodynamic Systems, Bredent Medical, Walldorf, Germany.

† HELBO Blue, HELBO Photodynamic Systems, Bredent Medical.

4 | CONCLUSIONS

Despite the safety and the significant clinical improvements promoted by antimicrobial photodynamic therapy, these gains did not lead to standout additional benefits over traditional forms of treating moderate to severe periodontitis and peri-implantitis.

Within the limits of this SR, based on both individual study outcomes and pooled estimates, it can be concluded that:1) aPDT, when used as an adjunctive treatment, may provide similar clinical improvements in PD and CAL when compared with conventional periodontal therapy in patients with moderate to severe periodontitis. The extension of some statistical gains achieved with the combined therapy does not seem to represent potential clinical relevance. 2) aPDT, when used as an adjunctive treatment, did not show evidence (at this moment in time) of improving the outcomes of implant surface scaling/debridement alone. The extremely limited evidence considered eligible for inclusion in the SR and the impossibility of performing pooled estimates (i.e., meta-analysis) precludes additional conclusions.

4.1 | Implications for research and future practice

Advances in the development of new photosensitizers for better antibacterial effects in the treatment of periodontitis and peri-implantitis should be performed to improve the clinical outcomes using this technology. The effects of aPDT on the stages of periodontal supportive therapy should be compared with other alternative treatment options since this approach is not associated with antimicrobial resistance and has no implications with systemic diseases or higher costs compared with the use of other laser wavelengths. At peri-implantitis sites, based on the outcomes of both included studies, the use of aPDT beyond the control treatment does not appear to bring additional clinical improvements. Thus, further studies focusing on standardized protocols need to be performed to warrant a meta-analysis and future recommendations.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of the article.

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