Odovtos-International Journal of Dental Sciences (Odovtos-Int. J. Dent. Sc.), Online First, 2025. ISSN: 2215-3411
https://doi.org/10.15517/9dvb5957

ODOVTOS
International Journal of Dental Sciences

UNIVERSIDAD DE COSTA RICA FOd Facultad de Odontología

https://revistas.ucr.ac.cr/index.php/Odontos

BASIC RESEARCH:

Photobiomodulation and Antimicrobial Photodynamic Therapy as Adjuvant Strategies in Medication-Related Osteonecrosis of the Jaws: A Narrative Review

Terapia fotobiomoduladora y terapia fotodinámica antimicrobiana como estrategias coadyuvantes en la osteonecrosis de los maxilares asociada a medicamentos: Revisión narrativa

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Received: 15-VII-2025 Accepted: 1-X-2025

ABSTRACT: Medication-related osteonecrosis of the jaw (MRONJ) is a severe complication associated with antiresorptive and antiangiogenic therapies, characterized by persistent bone exposure, pain, and infection. Its multifactorial pathophysiology involves alterations in bone remodeling, angiogenesis, immune response, and local infection. In this context, light-based adjunctive strategies such as photobiomodulation therapy (PBM) and antimicrobial photodynamic therapy (aPDT) have emerged, showing promising outcomes in early stages of the disease. This narrative review examines the available scientific evidence on the use of PBM and aPDT in the prevention and treatment of MRONJ. A literature search was conducted in PubMed, Scopus, and Google Scholar up to April 2025. PBM acts by stimulating mitochondria and modulating inflammation, thereby enhancing wound healing and bone regeneration. aPDT combines localized antimicrobial effects with tissue biostimulation, proving effective in infected lesions resistant to antibiotics. Both therapies have demonstrated clinical benefits in early-stage MRONJ and in preventive settings, particularly when combined with minor surgical procedures and autologous biomaterials. Despite their potential, the current literature mainly consists of observational studies and case reports, which limits the strength of the evidence. Randomized controlled trials and standardized protocols are necessary to validate their routine use in clinical practice. PBM and aPDT represent safe, minimally invasive, and well-tolerated therapeutic options with relevant applications in patients at high risk of developing MRONJ or those with early-stage established disease.

KEYWORDS: Osteonecrosis; Jaw; Photodynamic therapy; Photobiomodulation; Bisphosphonates; Wound healing.

RESUMEN: La osteonecrosis de los maxilares asociada a medicamentos (MRONJ) es una complicación grave relacionada con terapias antirresortivas y antiangiogénicas, caracterizada por exposición ósea persistente, dolor e infección. La fisiopatología multifactorial involucra alteraciones en la remodelación ósea, angiogénesis, respuesta inmunitaria e infección local. En este contexto, han emergido estrategias lumínicas coadyuvantes como la terapia fotobiomoduladora (PBM) y la terapia fotodinámica antimicrobiana (aPDT), con resultados prometedores en etapas iniciales de la enfermedad. Esta revisión narrativa examina la evidencia científica disponible sobre el uso de PBM y aPDT en la prevención y tratamiento de la MRONJ. Se realizó una búsqueda en PubMed, Scopus y Google Scholar hasta abril de 2025. La PBM actúa estimulando mitocondrias y modulando la inflamación, lo que favorece la cicatrización y regeneración ósea. La aPDT combina efectos antimicrobianos localizados con bioestimulación tisular, siendo eficaz en lesiones infectadas y resistentes a antibióticos. Ambas terapias han mostrado beneficios clínicos en estadios tempranos y en contextos preventivos, especialmente al combinarse con cirugía menor y biomateriales autólogos. A pesar de su potencial, la literatura se compone en su mayoría de estudios observacionales y reportes de caso, lo que limita la solidez de la evidencia. Se requieren ensayos clínicos controlados y protocolos estandarizados para validar su uso rutinario en la práctica clínica. PBM y aPDT representan opciones terapéuticas seguras, mínimamente invasivas y bien toleradas, con aplicaciones relevantes en pacientes con riesgo elevado de desarrollar MRONJ o con enfermedad establecida en etapas tempranas.

PALABRAS CLAVE: Osteonecrosis; Mandíbula; Terapia fotodinámica; Fotobiomodulación; Bisfosfonatos; Cicatrización de heridas.

INTRODUCTION

Medication-related osteonecrosis of the jaws (MRONJ) is a serious complication associated with antiresorptive therapies (e.g., bisphosphonates, denosumab) and antiangiogenic agents commonly used in the treatment of oncologic and metabolic bone diseases (1). According to the diagnostic criteria established by the American Association of Oral and Maxillofacial Surgeons (AAOMS), MRONJ is defined by the presence of exposed bone (or bone that can be probed through a fistula) in the maxillofacial region for at least eight weeks, in patients with a history of antiresorptive or antiangiogenic therapy and no prior craniofacial radiotherapy (2). The pathogenesis of MRONJ is multifactorial, involving suppression of bone remodeling, inhibition of angiogenesis, local infection or inflammation, and immune system dysregulation (2). Antiresorptive agents suppress osteoclastic activity, particularly in the alveolar bone, promoting the accumulation of microdamage and reduced remodeling, such that a dental extraction may trigger necrosis (3). In recent years, two light-based treatment modalities have gained attention as adjunctive therapies for MRONJ: photobiomodulation therapy (PBM), also referred to as low-level laser therapy (LLLT), and antimicrobial photodynamic therapy (aPDT) (4, 5). Studies suggest that both therapies may contribute to improved outcomes in MRONJ, either by preventing its onset in at-risk patients or by treating established lesions in conjunction with conventional measures (6-8). This narrative review aims to summarize the current evidence on the use of photobiomodulation therapy and antimicrobial photodynamic therapy as adjunctive strategies for the prevention and treatment of MRONJ.

MATERIALS AND METHODS

SEARCH STRATEGY

A comprehensive literature search was conducted in PubMed, Scopus, and Google Scholar to identify publications on the use of photobiomodulation (PBM) and antimicrobial photodynamic therapy (aPDT) in the management of medication-related osteonecrosis of the jaws (MRONJ), covering the period from January 2000 to April 2025. Boolean operators (AND, OR) and free-text terms were applied, including: Medication-Related Osteonecrosis of the Jaw, Bisphosphonate-Related Jaw Osteonecrosis, MRONJ, Bisphosphonate-induced osteonecrosis of the jaws, Photobiomodulation, Photo-Biomodulation, Low-Level Laser Therapy, Antibacterial photodynamic therapy, Antimicrobial Photodynamic Therapy, and Photodynamic therapy. The detailed search strategies for each database are provided in Table 1.

Table 1. Search strategies applied in each database.

Database	Search Strategy
PubMed	("Medication-Related Osteonecrosis of the Jaw"[All Fields] OR "Bisphosphonate-Related Jaw Osteonecrosis"[All Fields] OR "MRONJ"[All Fields] OR "Bisphosphonate-induced osteonecrosis of the jaws"[All Fields]) AND ("Photobiomodulation"[All Fields] OR "Photo-Biomodulation"[All Fields] OR "Low-Level Laser Therapy"[All Fields] OR "Antibacterial photodynamic therapy"[All Fields] OR "Antimicrobial Photodynamic Therapy"[All Fields] OR "Photodynamic therapy"[All Fields])
Scopus	TITLE-ABS-KEY(“Medication-Related Osteonecrosis of the Jaw” OR “Bisphosphonate-Related Jaw Osteonecrosis” OR “MRONJ” OR “Bisphosphonate-induced osteonecrosis of the jaws”) AND TITLE-ABS-KEY(“Photobiomodulation” OR “Photo-Biomodulation” OR “Low-Level Laser Therapy” OR “Antibacterial photodynamic therapy” OR “Antimicrobial Photodynamic Therapy” OR “Photodynamic therapy”)
Google Scholar	(“Medication-Related Osteonecrosis of the Jaw” OR “Bisphosphonate-Related Jaw Osteonecrosis” OR “MRONJ” OR “Bisphosphonate-induced osteonecrosis of the jaws”) AND (“Photobiomodulation” OR “Photo-Biomodulation” OR “Low-Level Laser Therapy” OR “Antibacterial photodynamic therapy” OR “Antimicrobial Photodynamic Therapy” OR “Photodynamic therapy”). Additionally, the filter “Review articles” was selected to restrict results to review-type publications.

INCLUSION CRITERIA

The inclusion criteria were: (a) availability of abstract and full text, (b) English language, (c) presence of at least one of the specified terms in the title or abstract, (d) clinical trials, animal studies, case reports, or observational research directly addressing PBM or aPDT in MRONJ, and (e) systematic reviews, meta-analyses, and official position papers, which were considered to provide background and context but were not included in the interpretative synthesis.

EXCLUSION CRITERIA

The following studies were excluded: (a) those not meeting the AAOMS diagnostic definition of MRONJ (e.g., osteoradionecrosis or other non–drug-related etiologies, unless MRONJ data were analyzed separately), (b) editorials, guidelines, or opinion papers without original data, which were not included in the qualitative synthesis but were occasionally retained to provide clinical context, (c) *in vitro* studies without animal or clinical data, (d) protocols using only ablative lasers without photobiomodulatory or photodynamic properties, (e) studies lacking essential intervention parameters (e.g., wavelength, energy, photosensitizer, number of sessions), (f) mixed series including MRONJ and other conditions without separate analysis, (g) reports with follow-up shorter than eight weeks, and (h) articles published in languages other than English.

RESULTS

A total of 537 records were identified through database searching (PubMed, n = 47; Scopus, n = 83; Google Scholar, n = 407). After removal of duplicates (n = 80), 457 records underwent title/abstract screening; 422 were excluded according to predefined eligibility criteria. Thirty-five studies were included in this narrative literature review (Figure 1).

PHOTOBIOMODULATION THERAPY IN MEDICATION-RELATED OSTEONECROSIS OF THE JAWS

Photobiomodulation therapy (PBM) is defined as the therapeutic application of low-power light (typically low-intensity lasers or LEDs) to living tissues in order to modulate biological processes (4). It commonly employs wavelengths in the visible red spectrum (600-700 nm) or near-infrared spectrum (780-980 nm), which are capable of penetrating tissues and being absorbed by cellular chromophores (9). The primary mechanism of PBM is attributed to the absorption of photons by mitochondrial enzymes, mainly cytochrome c oxidase, and other chromophores, triggering a photochemical cascade that results in a transient increase in ATP production, the release of growth factors, and the modulation of reactive oxygen species and signaling molecules (4, 9, 10). As a result, PBM may induce cellular proliferation and differentiation (e.g., fibroblasts, endothelial cells, and osteoblasts), enhance extracellular matrix synthesis, and promote angiogenesis at the treated site (9, 10). It also exerts anti-inflammatory effects by reducing the production of pro-inflammatory cytokines and provides analgesic benefits by decreasing the excitability of nociceptive nerve fibers (9, 10). In experimental models of osteonecrosis, PBM has been shown to preserve osteocyte viability and stimulate new bone formation (11, 12). Additionally, a study in rats with zoledronate-induced MRONJ demonstrated that PBM using an 808 nm diode laser (5 J/cm², 500 mW, 120 s; sessions on days 1, 3, 5, 7, and 10) significantly reduced wound size (11). When combined with platelet-rich fibrin (A-PRF or L-PRF) following surgical resection, the best outcomes in bone regeneration and mucosal healing were achieved (11). These findings support the notion of a synergistic effect, where photochemical activation of factors released from the PRF matrix enhances bone remodeling and soft tissue repair, positioning PBM as a key adjunct when used alongside autologous biomaterials in the management of MRONJ (11).

In the clinical context of MRONJ, PBM has been employed for various purposes: (a) to prevent the onset of osteonecrosis following invasive procedures in at-risk patients (e.g., applying PBM immediately after dental extractions to promote alveolar healing), and (b) to treat established lesions, particularly in early stages, with the aim of promoting mucosal coverage of exposed bone, relieving pain, and potentially reversing limited necrosis (13, 14). Photobiomodulation therapy (PBM) does not directly eliminate necrotic bone; however, it can facilitate soft tissue reepithelialization over the exposed areas, promoting a transition to an inactive disease state (15, 16). Its usefulness has been documented as an adjunct to minimally invasive surgery, contributing to mucosal healing and pain relief in patients with early-stage MRONJ (15). The devices used are primarily low-power diode lasers (660–808 nm) and near-infrared (NIR) emitters at 1064 nm; some authors also report the use of LEDs (14). Output power typically ranges from 0.25 to 1.25 W; energy delivered per point varies between 1.4 and 2.5 J, with exposure times ranging from 3 to 60 seconds (14). These settings usually generate energy densities between 2 and 14 J/cm², although higher values have been reported in isolated studies (14). Clinical studies consistently show that the combination of PRF with PBM after surgery improves MRONJ healing outcomes: in a retrospective study of 34 patients, the use of L-PRF and PBM increased the mucosal healing rate at six months (17). Other studies have reported stage II cases treated with A-PRF and PBM achieving stable mucosal closure and complete bone remodeling within 3 to 6 months, without recurrence (18). Overall, PBM represents a non-invasive, painless, and low-risk intervention, with no significant adverse effects reported, making it an attractive therapeutic support option for patients susceptible to maxillary osteonecrosis (16).

ANTIMICROBIAL PHOTODYNAMIC THERAPY IN MEDICATION-RELATED OSTEONECROSIS OF THE JAWS

Antimicrobial photodynamic therapy (aPDT) is based on the light activation of a photosensitizing agent to generate reactive oxygen species capable of locally destroying microorganisms (5). Unlike conventional photodynamic therapy used in oncology, which targets tumor cells, aPDT is primarily aimed at bacteria and other pathogens present in the affected tissues (19). The essential components of aPDT include: a photosensitizer (typically a dye that preferentially binds to bacteria, such as methylene blue or toluidine blue), a light source with a wavelength appropriate for exciting the photosensitizer (usually in the red spectrum around 630-660 nm for phenothiazine-type dyes), and the presence of molecular oxygen in the tissue (20, 21, 10). The mechanism of action involves the photosensitizer becoming excited upon light exposure and transferring energy to nearby oxygen molecules, thereby generating free radicals and cytotoxic species (such as singlet oxygen and oxygen radicals) that damage critical microbial structures (e.g., membranes, nucleic acids), ultimately leading to pathogen death (5, 22).

In MRONJ, where polymicrobial infection of necrotic bone is frequently observed (with isolated pathogens including Actinomyces, oral Streptococcus species, Fusobacterium, among others) (23, 24), aPDT offers the advantage of achieving deep local disinfection, even in the presence of microbial biofilms that are resistant to systemic antibiotics (23, 24). Additionally, the photochemical reaction induced by aPDT exerts tissue-level effects that may partially overlap with those of photobiomodulation, stimulating wound healing responses (23, 24). Indeed, aPDT has been described as combining two actions: a direct antimicrobial effect resulting from the cytotoxic activity of the activated photosensitizer, and a biostimulatory effect derived from the delivered light energy, similar to PBM (5, 6, 24, 25). In an experimental study using a rat model of zoledronate-induced MRONJ, the addition of aPDT, 660 nm red light, 50 mW, 2 J (66.7 J/cm²) once per week for four weeks after irrigation with 0.3% methylene blue, produced the best histomorphometric outcomes: significant reduction in necrotic bone area, increased extracellular matrix deposition, and enhanced osteocyte viability (26). These outcomes surpassed those observed in groups treated with PBM alone or with the photosensitizer without irradiation ($p<0.05$) (26). The superior performance of aPDT is attributed to the synergy between laser-induced biostimulation and the generation of reactive oxygen species, which effectively eliminate biofilms, downregulate NF-κB expression and its associated proinflammatory cytokines, and restore the reparative cascade (including angiogenesis, cell migration, and differentiation) within the bone defect (26).

In clinical practice, aPDT has been applied in MRONJ primarily for two purposes: (a) prophylaxis in high-risk patients (e.g., irrigating post-extraction sockets with a photosensitizer followed by laser application to prevent the onset of osteonecrosis), and (b) adjuvant treatment of active lesions, usually in combination with minor surgical procedures (6, 24, 27, 28). A representative prophylactic aPDT protocol described by Tartaroti *et al*. (6) involved applying 0.01% methylene blue directly into the socket immediately after tooth extraction and allowing it to act for 5 minutes. This was followed by irradiation using a red diode laser (660 nm, 0.1 W, 0.028 cm²) for 90 seconds per point, delivering approximately 9 J per point; at least three points were treated (total of 27 J). The procedure was repeated weekly until complete healing was achieved. In their series of 18 patients, none developed MRONJ after a minimum follow-up of six months (6). For the treatment of established MRONJ, aPDT is commonly applied both before and after surgical interventions: preoperative sessions are used to reduce the infectious and inflammatory burden in the affected area, thereby facilitating a more conservative surgery, and postoperative aPDT is applied directly to the surgical bed after resection of necrotic bone to decontaminate the area, with further periodic sessions during the healing phase (29, 30, 31). This sequential approach has demonstrated high success rates in resolving early-stage lesions (29, 30, 31).

It is important to note that the clinical parameters of aPDT may vary across studies (6, 28-31). The most commonly used photosensitizers in dentistry are methylene blue and toluidine blue, typically at concentrations ranging from 0.01% to 0.1% (5, 21, 22). The light source is usually a red diode laser (630-670 nm), although low-power infrared lasers may also be used with certain specialized photosensitizers (5, 21, 22). The energy density per session generally ranges between 10 and 50 J/cm², depending on the mode of application (multiple focused points versus a diffuse beam over the lesion) (6, 28-31). Since aPDT acts locally, it largely avoids the systemic side effects associated with prolonged antibiotic use, making it an attractive alternative or complement for infection control in MRONJ (24). Table 2 provides a comparative summary of the mechanisms of action, biological effects, and clinical indications of both therapies.

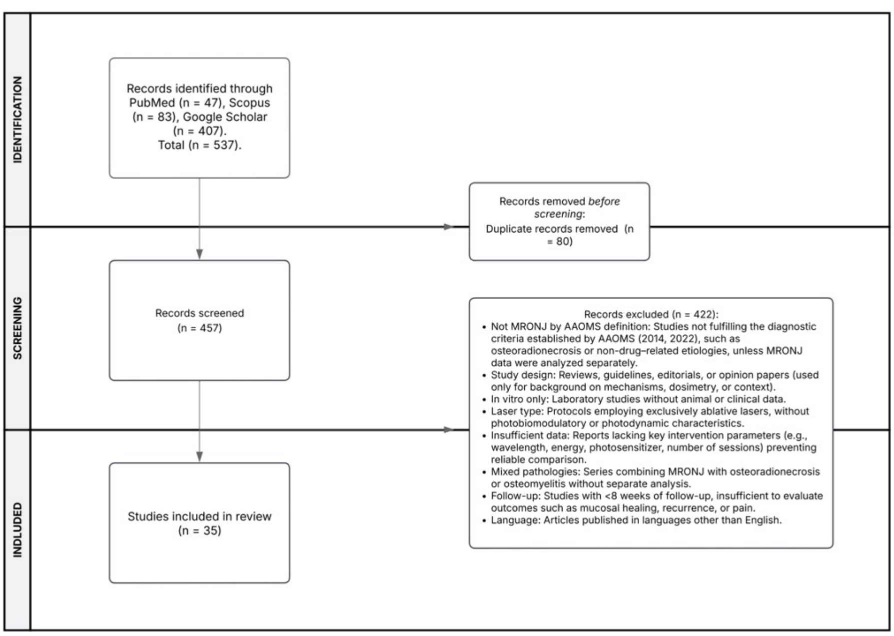

Figure 1. Flowchart illustrating the selection process of the articles identified through the databases and those included in the literature review.

Table 2. Comparison of Photobiomodulation Therapy and Antimicrobial Photodynamic Therapy in Medication-Related Osteonecrosis of the Jaws.

Aspect	Photobiomodulation Therapy (PBM)	Antimicrobial Photodynamic Therapy (aPDT)
Mechanism of action	Photostimulation of tissues using low-power light (4). Increases cellular activity and modulates the inflammatory response via photon absorption by endogenous chromophores (4).	Photoactivation of a photosensitizer in the presence of oxygen (5). Generates free radicals that destroy microorganisms and induces local biostimulatory effects (5, 22).
Primary target	Host tissue cells (osteoblasts, fibroblasts, endothelium, neurons) (32). Aims to enhance the organism's regenerative response (32).	Microbial flora at the lesion site (bacteria in biofilms) (5, 22). Aims to locally disinfect the necrotic bone wound (5, 22).
Biological effects	Stimulates cell proliferation and matrix synthesis (osteogenesis, angiogenesis) (32). Reduces pro-inflammatory mediators (↓NF-κB, ↓IL-1, ↓TNF-α) and edema (33). Improves microcirculation and accelerates epithelialization, with analgesic effect (32, 33).	Destroys bacteria and reduces microbial load in infected bone and soft tissues (23, 24). Decreases the release of bacterial toxins and the inflammation associated with infection (23, 34). May indirectly enhance angiogenesis and wound healing by removing the septic factor (35).
Indications in MRONJ	Prevention in high-risk patients post-extraction (to promote proper bone and mucosal healing) (6). Conservative treatment of early-stage lesions (Stages I–II) to promote mucosal coverage of exposed bone and relieve pain (6, 14). Adjuvant to resective surgery to accelerate regeneration of remaining tissues (36).	Prevention of post-extraction MRONJ in high-risk patients through alveolar decontamination (6). Treatment of lesions with active infection (presence of suppuration or significant bacterial colonization), before and after surgical debridement (29, 31). Cases where extensive surgery is not feasible; repeated aPDT may control infection and stabilize the lesion (30).

DISCUSSION

The biological plausibility for photobiomodulation (PBM) and antimicrobial photodynamic therapy (aPDT) in medication-related osteonecrosis of the jaws (MRONJ) is established; the central question is the strength and applicability of the clinical evidence (4, 9, 20, 23, 32). Signals of benefit are reported mainly in early-stage disease and perioperative settings, commonly alongside conservative surgery and autologous platelet concentrates, but derive predominantly from small, uncontrolled datasets (6, 7, 11, 15, 17, 18, 24, 27, 31).

The certainty of evidence is limited by study design and risk of bias. The literature is dominated by case reports, small case series, and retrospective cohorts, with a scarcity of adequately powered randomized controlled trials (RCTs) (6, 7, 15, 17, 18, 27-31, 38). Concomitant interventions (minor surgery, platelet-rich fibrin, short antibiotic courses, meticulous local care) complicate attribution of incremental effects to PBM or aPDT and heighten confounding (11, 15, 17, 18, 24). Outcome assessment is frequently unblinded, definitions of “clinical improvement” vary, and follow-up is short, limiting comparability and raising concerns about publication bias (13, 14, 24, 38).

Protocol heterogeneity further undermines external validity. For PBM, studies vary in wavelength, irradiance, fluence, emission mode, number and spacing of sessions, and target tissues, with inconsistent dosimetric reporting (14, 32, 37). For aPDT, variability spans photosensitizer type and concentration, pre-irradiation times, illumination parameters, and treatment frequency (5, 21, 22, 23, 35). These dispersions suggest parameter-dependent effects within narrow biostimulatory/photochemical "windows," impeding robust quantitative synthesis (4, 14, 24).

Clinically, PBM and aPDT should be considered adjuncts rather than alternatives to surgery in advanced disease. In AAOMS stage III, surgery remains foundational, while light-based modalities may serve perioperatively to reduce microbial burden and support healing at viable margins (2, 24, 38). Safety signals appear favorable, but adverse events are inconsistently reported; practical issues include transient mucosal staining and protective measures for aPDT, and adherence to laser safety standards for PBM, particularly in oncology populations (4, 5, 9, 20, 23, 25, 32, 35).

A clear research agenda emerges. Priorities include stage-stratified, sham-controlled, assessor-blinded RCTs with preregistered protocols (14, 38); a harmonized core outcome set; evaluation of durable mucosal closure and ≥6-12-month recurrence; assessment of pain, function, and the need for rescue antibiotics or surgery; incorporation of radiographic and histomorphometric endpoints; and, for aPDT, microbiological biofilm measures, alongside systematic adverse-event reporting (5, 14, 24, 25, 38). Reproducibility requires standardized reporting of PBM dosimetry and aPDT parameters (wavelength, irradiance, fluence, energy per point, number and timing of sessions, target tissues, photosensitizer type and concentration, and pre-irradiation time) (14, 21-23, 35).

PBM and aPDT are feasible adjuncts with potential value in early-stage MRONJ and around conservative surgery, but small, uncontrolled studies, protocol heterogeneity, and the paucity of rigorous trials constrain certainty of benefit (13, 14, 24, 38). Until higher-quality evidence accrues, use should be individualized, transparently discussed with patients, and integrated into multimodal, stage-appropriate care aligned with AAOMS guidance (2, 24, 38).

CONCLUSION

Within the limitations of this narrative review, photobiomodulation and antimicrobial photodynamic therapy should be considered adjunctive, not stand-alone, options for MRONJ. Clinically, their most defensible use is in early-stage disease and as perioperative support (aPDT for localized infection control; PBM for symptom relief and mucosal healing), while surgery remains standard for advanced stages. Consistent adoption requires standardized, stage-specific protocols (defined PBM dosimetry and aPDT parameters) and a core outcome set. Robust, multicenter, sham-controlled randomized trials with adequate follow-up are essential to establish effectiveness, safety, and cost-effectiveness and to inform clinical guidelines.

CONFLICT OF INTEREST: The author reports that there is no conflict of interest.

FUNDING: This research received no external funding.

DATA AVAILABILITY: Data sharing not applicable to this article as no datasets were generated.

ETHICAL STATEMENT FOR HUMAN PARTICIPANT: Not applicable for this research.

AUTHOR CONTRIBUTION STATEMENT: Conceptualization and design: R.B.P.S., M.F.C.V. and M.D.A.; Literature review: R.B.P.S. and M.F.C.V.; Methodology and validation: R.B.P.S., M.F.C.V. and M.D.A.; Formal analysis: R.B.P.S. and M.F.C.V.; Investigation and data collection: R.B.P.S. and M.F.C.V.; Resources: R.B.P.S., M.F.C.V. and M.D.A.; Writing-original draft preparation: R.B.P.S. and M.F.C.V.; Writing-review & editing: R.B.P.S., M.F.C.V. and M.D.A.; Supervision: R.B.P.S., M.F.C.V. and M.D.A.; Project administration: R.B.P.S., M.F.C.V. and M.D.A.

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