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Clinical decision-making in tooth bleaching based on current evidence: A narrative review

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ABSTRACT

Objective: This review consolidates current knowledge on dentist-supervised tooth bleaching for vital teeth, drawing from systematic reviews, meta-analyses, and randomized clinical trials (RCTs) that followed CONSORT guidelines.

Data resources: MeSH and free terms like "tooth bleaching," "tooth whitening," "randomized clinical trial," and "systematic review" were used in PubMed, Scopus, and Web of Science databases

Study selection: Out of 839 articles, 444 were selected for full-text review, excluding case reports, non-randomized trials, literature reviews and those not directly related to tooth bleaching or RCTs not following CONSORT 2010. The remaining 203 studies were used to compare the dentist-supervised at-home and in-office clinical protocols, assessing factors such as color change, tooth sensitivity, and gingival irritation. In vitro studies were cited to support and explain basic concepts of different clinical decisions

Conclusions: Daily at-home bleaching with 10 % carbamide peroxide or lower-concentration hydrogen peroxide over three to four weeks is effective. In-office bleaching with high-concentration hydrogen peroxide exhibits variations in protocols based on the HP concentration and gel's pH. Emerging technologies like violet LEDs and photobiomodulation with infrared lasers show promise in enhancing efficacy and reducing sensitivity, respectively, though more research is needed. The review underscores the importance of ongoing research into desensitization strategies to manage sensitivity related to bleaching.

Clinical significance: Tooth bleaching is central to dental aesthetics, offering a range of options that can challenge clinicians. Adverse effects, particularly sensitivity, highlight the need for practice supported in protocols clinically tested and effective desensitization approaches

1. Introduction

The current pervasive emphasis on aesthetics has significantly influenced the pursuit of tooth bleaching [1]. Since the introduction of the nightguard vital bleaching technique using 10 % carbamide peroxide (CP) thirty-five years ago [2], various formulations of bleaching agents, application times, and protocols have been explored by practitioners and extensively studied by researchers [3–5]. Currently, vital bleaching is performed using CP or hydrogen peroxide (HP) gels, available in various concentrations, and administered through at-home or in-office treatments. [6–8].

The mechanism of tooth bleaching is well understood, although there are slight differences between treatments using HP and those using CP-based gels. The hydrogen peroxide molecule primarily acts through the decomposition and release of reactive oxygen species (ROS), which penetrates the interprismatic spaces of the enamel, oxidizing chromophores in dentin, breaking them down into smaller and less pigmented molecules [3]. By decomposing pigments into smaller particles, dental structure acquires greater brightness [9]. The mechanism of action of CP is similar because the CP molecule is decomposed in HP and urea when in contact with water, thus being a precursor of HP. However, carbamide peroxide gel presents only one-third of its concentration of HP and

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exhibits a slower rate of decomposition [3,4]. In this sense, it is important to note that in this process, the success of tooth bleaching is related to the concentration, frequency, and duration of exposure to the whitening agent [7]. Top of FormBottom of Form

Attempts to expedite bleaching efficacy have extensively been reported such as combination of in-office and at-home regimens [10] or light activation of in-office gels [11]. Nevertheless, this excess of options poses challenges for clinicians in determining the most suitable technique for each patient, possibly leading them away from adhering evidence-based protocols. Furthermore, adverse effects associated with peroxide gels, such as their impact on enamel, dentin, pulp and periodontal tissues, have been documented over recent decades [12–14]. The primary clinical implication is tooth sensitivity, which may lead to discontinuation of the bleaching procedure [12]. Consequently, various desensitizing agents and drugs [15], as well as adjustments in gel concentration and application times [16], have emerged as strategies to mitigate this issue. Similarly to the various bleaching protocols, the different possibilities for desensitization protocols can lead to confusion among dentists when selecting a clinical approach.

Therefore, to consolidate the current knowledge and guide practitioners in selecting the most appropriate dentist-supervised at-home and/or in-office bleaching protocols in vital teeth, this narrative review aims to synthesize the most up-to-dated findings from systematic reviews with meta-analysis and/or randomized clinical trials (RCTs) adhering to the 2010 CONSORT (CONsolidated Standards of Reporting Trials) guidelines. With the current data, researchers and clinicians have access to a concise and easy-to-use guide that summarizes all clinically relevant findings from the past 15 years, aiding in the selection of the most appropriate approach for different cases.

2. Methods

Despite not performed a systematic search based on the principles of a systematic review, MeSH and free terms were carefully chosen to identify relevant literature about the tooth bleaching protocols. "*Tooth Bleaching*", "*Tooth Bleaching Agents*", "*Tooth Whitening*", "*Tooth Whitening Agents*" were defined for the treatment. "*Randomized clinical trial*", "*controlled clinical trials randomized*", and "systematic review" terms were selected for the types of study. The search was conducted in three different databases: PubMed, Scopus, and Web of Science.

Initially, 1816 manuscripts were identified and imported into reference management software (EndNote 20.3, Thomson Reuters, Toronto, Canada). After the removal of duplicates and triplicates, a total of 839 articles remained. Initially, titles and abstracts were screened to exclude studies not primarily related to tooth bleaching techniques. Additionally, studies that were not directly focused on tooth bleaching were excluded. Additionally, to provide stronger and more accurate information on the different protocols, only studies published after 2010 were included, as they adhere to the CONSORT 2010 guidelines for reporting randomized clinical trials, which are essential for ensuring transparency, reproducibility, and reliability of trial findings.

Subsequently, 444 articles underwent full-text review, initially to determine whether they were randomized clinical trials or systematic reviews. For the randomized clinical trials, each study was individually assessed for adherence to the CONSORT 2010 guidelines. Specifically, the selected papers were evaluated for the inclusion of sample size calculation, allocation concealment, inclusion/exclusion criteria, randomization, blinding, and the presence of a flow chart. Systematic reviews and/or meta-analysis were required to include a PICO question that compares different protocols or other aspects, for example, the efficacy of at-home versus in-office bleaching through clinical trials.

Selected studies also focused on comparisons of dentist-supervised clinical protocols for vital teeth that examined variables such as color change, tooth sensitivity, and gingival irritation. Since the aim of this narrative review was based on only dentist-supervised at-home or in-office bleaching, articles investigating non-vital bleaching, fluorosis management, or those focusing solely on over-the-counter bleaching agents, which are used without dentist supervision, were not considered for suggestions of clinical decision-making. After finishing the search process, 159 randomized clinical trials and 44 systematic reviews with or without meta-analysis were included in the present review. *In vitro* research papers and some previous literature reviews were later read and used herein to contextualize and justify important aspects of tooth bleaching agents' characteristics or their cytotoxic effects.

3. Results

3.1. At-home bleaching

3.1.1. Which are the CP agents' concentration and usage time recommended?

Traditionally, at-home bleaching has been performed using low concentrations of CP, and evidence suggests that such protocols can lead to stable tooth color changes for up to 2 years [17,18]. Meireles et al. (2010) showed that 10 % or 16 % CP resulted in similar color change outcomes [18]. More recently, Sutil et al. (2020) demonstrated that 10 % CP (4 h a day) reached the same esthetic efficacy as a 37 % CP regimen (30 min a day) over a 3-week period. In a systematic review with meta-analysis, de Geus et al. (2018) demonstrated that at-home bleaching with 10 % CP achieves comparable efficacy to higher concentrations of CP gels, but with a reduced risk and intensity of tooth sensitivity [7]. However, it is important to note that there were high variations in protocols in terms of CP concentration, commercial gels composition, and application time among the included studies, and future studies with rigorous methodologies are crucial to increase the certainty of these findings.

Regarding usage time, Dariba et al. (2017) pointed out that 10 % CP regimen used overnight was more effective for bleaching when compared to a daily 1-hour regimen [19]. Also, another study showed that extending a 2-hour daily use of 10 % CP from 2 to 3 weeks improved bleaching efficacy without increasing tooth sensitivity [20]. In patients with tetracycline-stained teeth, a 15 % CP gel was effective with daily 2-hour at-home bleaching over 3 months [21]. Interestingly, in tetracycline-affected teeth, a clinical trial has shown that at-home bleaching with high-concentration CP (daily 1 h for 20 days) was more effective than in-office bleaching with 40 % HP (three sessions), likely due to the extended application time allowed in at-home bleaching [22].

On the other hand, a recent RCT reported that reducing the usage time of 10 % CP from 8 h to 2 h or 4 h per day over 3 weeks did not significantly reduce color change under the evaluation using a digital spectrophotometer and, more importantly, significantly reduced tooth sensitivity levels [16]. In addition, a microsensor set in the customized acetate trays detected those shorter times of CP improved patient compliance with the daily use of CP. However, subjective evaluations using a visual shade guide, which is also important on evaluation efficacy of bleaching protocols, revealed a significantly decrease in the color change by the 2-hour regimen, suggesting that a more effective approach would be to reduce the time of CP use only by half (from daily 8–4 h) [16].

Indeed, Melo et al. (2024), through a systematic review with meta-analyses, concluded that although shortening to the lowest usage time of at-home bleaching agents significantly reduces reports of tooth sensitivity, it does not maintain color change compared to the longer duration recommended by manufacturers. However, the included studies remain heterogeneous, resulting in a low certainty of the evidence [23]. A subsequent and recently published RCT [24] with a rigorous methodology demonstrated that both 2-hour and 4-hour daily applications of 10 % CP over a 2-week protocol resulted in the same color change and sensitivity levels as the 8-hour regimen, regardless of the observation method (spectrophotometer x visual guide units). However, the Whiteness Index for Dentistry changes after treatments

were inconclusive, which can be addressed to the reduced sample size, as discussed by the authors [24]. In recent years, the Whiteness Index for Dentistry [25] has become a crucial tool for evaluating bleaching efficacy, alongside color change outcomes, highlighting the need for further RCTs on this topic.

Based on the cited studies, recent evidence supports the use of 10 % CP over higher-concentrated carbamide peroxide due to its similar efficacy and lower risk of sensitivity compared to higher-concentrated CP gels. However, a critical evaluation of available evidence suggests that a 2-hour daily application of 10 % CP may not consistently achieve the highly acceptable esthetic outcomes associated with carbamide peroxide gels. Up to this moment, a 4-hour daily application of 10 % CP for three weeks would be an optimal approach to maintain efficacy, reduce the risk of tooth sensitivity, and improve patient compliance with tray use at home compared to overnight application [16]. If a reduced duration (2 hours) is chosen, the clinician should be aware that a longer period of use could be required to achieve the optimal bleaching result. Still, Table 1 depicts successful at-home bleaching protocols already tested under RCTs, taking into consideration the shortest time of use without negative effects to the esthetic efficacy within each clinical trial.

Table 1
Summary of the current clinical at-home bleaching protocols in terms of peroxide agent concentrations, time of use and type of trays.

Authors (Year)	Agent	Time of Use*	Type of Tray	Findings
Pavani et al. (2023) [16]	10 % CP	4 hours a day for 3 weeks	Customized	No color differences seen when reducing twice as much (from 8 h to 4 h) the gel's exposure time
Dariba et al. (2019) [20]	10 % CP	2 hours a day for 3 weeks	Customized	Prolonging daily 2-hour use of 10 % CP for 7 days was more effective than a 2-week regimen
Botelho et al. (2017) [21]	15 % CP	2 hours a day for 3 months	Customized	Effective protocol for resolving **tetracycline-stained** teeth
Terra et al. (2025) [24]	10 % CP	2 or 4 hours a day for 2 weeks	Customized	No color differences when reducing gel's application time from 8 to 2 or 4 hours
Carlos et al. (2017) [26]	10 % HP	30 minutes a day for 2 weeks	Prefilled	HP-prefilled tray exhibited similar outcomes to overnight use of 10 % CP in a customized tray
Chemin et al. (2018) [27]	4 % HP	30 minutes a day for 2 weeks	Customized	Reducing the HP concentration maintained the efficacy of 10 % HP with lower sensitivity
Terra et al. (2021) [28]	4 % HP	30 minutes a day for 4 weeks	Customized	Prolonging 4 % HP bleaching for 7 days was more effective than a 3-week long regimen
Paula et al. (2023) [29]	4 % HP	30 minutes a day for 3 weeks	Customized	Use of 4 % HP for 30 min reached similar results to 1-hour long gel application
Cordeiro et al. (2019) [30]	10 % HP	30 minutes a day for 2 weeks	Prefilled	Prefilled tray reduced sensitivity and gingival irritation, maintaining the efficacy of customized one
Monteiro et al. (2019) [31]	10 % HP	30 minutes a day for 2 weeks	Prefilled and Customized	Similar efficacy and sensitivity outcomes rendered by both methods without genotoxicity

* Other application time and number of weeks or agents were tested, as denoted in the *Findings* collum, but the *Time of Use* collum represents the shortest time of gel's exposure with maintenance of the esthetic efficacy.

Even though 15 and 16 % CP are available in the market, only one RCT following 2010 CONSORT compared 10 % and 16 % CP [18], showing no differences among the techniques. However, a meta-analysis by de Geus et al. (2018) already indicated that concentrations exceeding 10 % CP increase the risk and severity of tooth sensitivity [7]. Future RCTs with rigorous methodology should explore whether a 16 % CP gel used for a shorter duration (1–2 hours) can maintain the efficacy of at-home bleaching with reduced sensitivity. However, as of now, there is no clinical evidence to support this approach.

3.1.2. Which are the HP delivery methods, concentration, and usage time recommended?

In recent years, low-concentration HP has also been studied for at-home bleaching using customized trays, prefilled disposable trays, or whitening strips. Bleaching upper and lower arches separately or simultaneously using 10 % HP (30 min daily/2 weeks) did not influence final outcomes [32]. Carlos et al. (2017) concluded that using 10 % HP (prefilled trays – Opalescence Go, Ultradent, Salt Lake City, UT, United States) or 9.5 % HP (customized trays) led to similar bleaching outcomes, without differences in sensitivity or gingival irritation. Although patients classified prefilled trays as comfortable, these trays exhibited higher gel overflow and lower comfort compared to customized trays [26]. Mailart et al. (2021) detected that prefilled 10 % HP (Opalescence Go, Ultradent) caused mild intensitiy of sensitivity and gingival irritation, but these effects were more pronounced than those observed when using 10 % HP loaded in a customized tray [33].

Monteiro et al. (2019) reported no differences in clinical color change and genotoxicity with 10 % HP used in three different systems (customized trays, prefilled disposable trays, or whitening strips) [31]. Similarly, Cordeiro et al. (2019) showed not only that prefilled disposable trays loaded with 10 % HP promoted lower sensitivity and gingival irritation, but also that 10 % HP whitening strips were equally similar to HP used in customized trays with reduced sensitivity [30]. Even though evidence is conflicting regarding the delivery methods for HP, the most up-to-date protocols for at-home bleaching with HP are illustrated in Table 1. Since prefilled trays and strips with HP and can be sold over-the-counter, it is important to emphasize the necessity of dentist supervision and that RCTs have evaluated their use only up to 2 weeks (30 min daily).

When it comes to HP concentrations, a RCT showed that 4 % HP in a customized tray achieved similar color change to 10 % HP in a 2-week regimen, but with reduced tooth sensitivity [27]. Paula et al. (2023) found that reducing usage time of 4 % HP from 2 h to 30 min did not reduce bleaching efficacy after 3 weeks of bleaching [29]. However, Terra et al. (2022) showed that extending the total bleaching time from 3 to 4 weeks was necessary to maintain bleaching esthetic outcomes reducing the usage time of 4 % HP from 2 h to 30 min [28]. Given this scenario, daily at-home bleaching using low concentrations of HP (less than 10 %) in a customized tray for 30 min up to a 4-week regimen could be an effective approach to reduce tooth sensitivity without jeopardizing bleaching results.

3.1.3. Are there outcomes differences between CP and HP at-home agents?

According to Mailart et al. (2017), using 10 % HP daily for 30 min (either in prefilled or customized trays) resulted in a color change similar to that achieved with 10 % CP used daily for 2 h, even during a one-year clinical follow-up. Nevertheless, it is important to note that prefilled 10 % HP caused a slightly higher incidence of sensitivity in such RCT [33]. In contrast, one RCT concluded that 10 % CP used overnight produced significantly better color change and lower sensitivity compared to 10 % HP used either for 1 h or overnight [19]. Another clinical trial found that a 1-hour use of 6 % HP and overnight application of 10 % CP led to similar sensitivity prevalence, but the

latter resulted in higher efficacy and greater satisfaction among the participants [34].

Indeed, a systematic review with meta-analyses indicated that tray-delivered CP agents exhibited a slightly improved objective color change (measured using digital spectrophotometers) compared to HP-based products. However, the review also found no significant differences in sensitivity, gingival irritation, or subjective color change (measured using visual shade guide units) [35]. Therefore, the choice between HP and CP still should be based on the patient's profile and time availability for tray use rather than solely on which agent provides the highest efficacy. It is imperative, however, to follow protocols already tested under a randomized clinical design to ensure that the appropriate use of HP and CP time will guarantee the satisfactory efficacy and safety of tooth bleaching.

3.1.4. Are there ideal designs for customized acetate trays?

Regarding the specifics of customized acetate trays used by patients, a systematic review with meta-analyses concluded that gel reservoirs in customized trays would not be necessary to ensure at-home bleaching efficacy. However, the authors indicated the necessity of further RCT with higher quality [36]. Subsequent clinical studies confirmed that the presence or absence 1-mm reservoirs in acetate trays did not influence bleaching efficacy, even after one year of follow-up [37,38]. Evidence also suggests that the tray's cut-out style (scalloped or nonscalloped in the gingival margin) [39] does not significantly affect bleaching efficacy or sensitivity levels. Therefore, the cut-out design could be chosen according to the dentist's preference, but presence of reservoir is not necessary. However, clinical evidence suggests that a nonscalloped tray extending 3 mm over the soft tissue causes significantly greater gingival irritation and sensitivity intensity compared to a tray trimmed 1 mm apically to the gingival margin [40]. Thus, nonscalloped tray limit should not exceed 1 mm from gingival margin.

3.2. In-office bleaching

3.2.1. Which is the ideal bleaching gel concentration to be used in-office?

Conventionally, in-office tooth bleaching utilizes 35–40 % HP gels over 2–4 sessions spaced at 7-day intervals. However, a multi regression with logistic analysis has revealed that in-office bleaching could lead to four times higher tooth sensitivity compared to at-home bleaching [41]. In this direction, many RCTs have compared high- and low-concentration HP bleaching gels or exploring reductions in gel application time [42–44].

Reducing HP concentration from 35 or 40 % to 6 % or 15 % did not maintain the same high esthetic outcomes achieved with higher concentrations in four selected RCTs, although tooth sensitivity was significantly attenuated [45–48]. Remarkably, two systematic reviews published in the same year highlighted that sensitivity caused by in-office low- to medium-concentration (6–20 %) HP gels is lower than that caused by high-concentration (35–40 %) HP gels. However, while Pontes et al. (2020) concluded that HP gels ranging from 6 % to 20 % significantly enhanced objective color change [49], Maran et al. (2020) reported low-certainty of the evidence which showed no differences in the efficacy reached among different HP concentrations [6]. Therefore, there remains a need for standardized protocols in future RCTs to definitively determine whether using lower concentrations of HP gels can maintain the optimal esthetic outcomes achieved through in-office bleaching.

Another protocol tested the use of 37 % CP gels in-office, but RCTs have indicated significant reduction in the bleaching effectiveness when using CP gels compared to high-concentrated HP gels [50–53]. Even though a recently published systematic review concluded that high-concentrated CP might not compromise the efficacy of in-office bleaching in comparison to HP-based protocols, the certainty of evidence was low or moderate due to inconsistencies across the studies. Indeed, only three studies were selected in their review, preventing the performance of a meta-analysis [54]. A subsequent RCT reported that a 37 % CP gel resulted in color and whiteness changes similar to those of a 35 % HP gel immediately after the second in-office session with reduced sensitivity [55]. However, a long-term follow-up remains necessary. Based on all these findings, although use of CP could be encouraged mostly because of its positive effect on tooth sensitivity, in-office bleaching with concentrations of HP lower than 35 % HP would not guarantee highly acceptable bleaching outcomes. Therefore, up to this moment, use of in-office 35–40 % HP gels is still preconized in adults.

However, low-concentrated bleaching gels appear as an alternative in adolescents since some RCTs showed that 6 % or 20 % HP were capable of promoting self-perception of color change in these patients with low prevalence of tooth sensitivity, which is the major counter-indication reason for bleaching in adolescent patients [56–58]. On this note, it is important to emphasize that according to the American Academy of Pediatric Dentistry, tooth bleaching must be avoid in primary and mixed dentitions [59]. Carneiro et al. (2024) have also detected that an additional session of 6 % HP is necessary to reach the high-concentration HP efficacy. Even though this protocol for adolescents would increase the number of in-office sessions, it holds the advantage of discarding the necessity of gingival barrier, as the gingival irritation levels reported by the volunteers were low [56]. In adults, a recent RCT has concluded that pricier gingival barriers promoted lower levels of sensitivity during bleaching with 37 % CP and were preferred by the operators in terms of handling features [60].

3.2.2. Is it necessary to replenish and reduce application time of in-office bleaching gels?

The in-office technique involves applying bleaching gel to the teeth for a short duration to achieve the desired whitening effect. However, the optimal exposure time and the need to replace the gel within the same clinical session remain subjects of discussion. Meireles et al. (2021) attested that reducing the application time of a 37.5 % HP gel from 24 min (3 ×8 min) to 16 min (2 ×8 min) did not affect both clinical efficacy and tooth sensitivity [61]. Also, there is evidence showing that in-office bleaching efficacy of 35 % HP is maintained only if the instructed application time is reduced by up to one-third [61,62]. In other words, the standard time recommended by some manufacturers of 45–50 minutes could be reduced up to at least a 30-min long session. Paula et al. (2015) have detected that a 2-day interval between two in-office sessions using 35 % HP did not impact the efficacy and sensitivity compared to the standard 7-day interval [63].

Martins et al. (2018) indicated that a simplified in-office protocol with 40 % HP (1 ×40 min) rendered the same esthetic outcomes and sensitivity levels as for the manufacturer's recommendation (2 ×20 min) [64]. This study also verified that the commercial gel tested (Opalescence Boost, Ultradent) presents stable neutral pH over the entire gel application. *In vitro* studies have evaluated the diffusion of reactive oxygen species (ROS) from bleaching agents with different pH levels (neutral and acidic) and their penetration into the pulp space, aiming to explain the reduced sensitivity associated with neutral pH bleaching agents. The studies demonstrated that ROS diffusion to the pulp is lower with neutral gels compared to acidic gels, which likely accounts for the differences in post-bleaching sensitivity between these products [65,66]. Reduced diffusion can lead to a diminished reaction in the pulp tissue, thereby minimizing sensitivity.

Besides this, systematic reviews have attested the non-necessity of gel's renewal during the same bleaching session, but the low number of studies and variations in the protocols of the studies led to a very low certainty of evidence [67,68]. A subsequent study confirmed the non-necessity for replenishing a 35 % HP gel, showing that a single 30-min application maintained the highly acceptable bleaching indexes and, more importantly, reduced tooth sensitivity [69]. More recently, Favoreto et al. (2024) demonstrated that applying a 35 % HP gel for 1 × 30 min rendered similar color change outcomes with reduced tooth sensitivity when compared to 2 × 20 min or 1 × 40 min protocols [69].

Based on this evidence, it is possible to recommend a single application of 35–40 % HP gels for at least 30 minutes in a minimum of 2 sessions at a minimum of 2 days of interval.

However, a recent RCT stated that two commercial 35 % or 38 % HP gels (Potenza Bianco Pro SS, PHS, Joinville, SC, Brazil and Whiteness HP Automixx, FGM, Joinville, SC, Brazil) presented pH lower than 5.5 throughout or at least during half of a 50-min application. Therefore, caution is essential regarding the pH of the chosen gel, especially if not replenishing, to avoid adverse effects on the enamel or increased tooth sensitivity. Table 2 compiles the lowest and highest pH values recorded over the course of a single application of current in-office commercial bleaching gels. These values were not necessarily extracted from randomized clinical trials.

3.2.3. *Does in-office gels' pH, agitation, volume, and storage temperature influence the bleaching outcomes?*

Even though decomposition of HP into reactive oxygen species are favored in an alkaline environment, Loguercio et al. (2017) showed that gels from the same manufacturer presenting different pH (2.5 and 7.0) resulted in similar clinical color change, even after one year from the end of bleaching. However, the neutral in-office gel was proven to cause less painful sensation when compared to the acidic one [72,73]. Similar color findings were reported by Gumy et al. (2024), who also showed that after a single 50-min applications of gels with pH ranging from 5.4 to 8.0, there were still 70 % of HP available in the gel [71].

Clinical evidence displayed that the gel could remain on the surface without agitation, showing no gains to efficacy and sensitivity when sonic activation was performed using a 20 % HP gel [74]. Nonetheless, recent RCTs showed that attaching a brushing tip into the gel applicator significantly diminished tooth sensitivity caused by 6 % [57] and 35 % [75] HP gels. In this scenario, gel volume also influences in the sensitivity levels, being suggested to use a reasonable volume to cover the buccal enamel surface (approximately 0.05 mL of the gel) without negatively implicating efficacy [76,77].

Finally, the gel temperature storage does not affect the efficacy and sensitivity results but does impact in the viscosity of the 35 % HP gel [78]. However, it is indicated to avoid storage temperatures higher than 25 °C. As a result, it could be suggested the commercialization of neutral/alkaline gels with a brushing tip application system that regulates the appropriate gel's volume. Overall, the most updated directions in terms of in-office bleaching are synthesized in Fig. 1.

Table 2
Summary of the highest and lowest pH of gels reported in the literature during a single application in the same in-office session.

Study (Year)	Application Time	HP (%)	Commercial Name	Highest pH	Lowest pH
Cavalli et al. 2019 [70]	1 × 40 min	35 % HP	Whiteness HP Maxx (FGM, Joinville, SC, Brazil)	5.5	5.8
		35 % HP	Whiteness HP Blue (FGM)	7.0	7.0
		35 % HP	Pola Office (SDI, Bayswater, Victoria, Melbourne)	3.0	3.2
Silva et al. 2023 [66]	1 × 30 min	35 % HP	DSP White Clinic Calcium (DSP Biomedical Group, Campo Largo, PR, Brazil)	8.2	8.0
		35 % HP	Nano White (DMC, São Paulo, SP, Brazil)	7.2	7.0
		40 % HP	Opalescence Xtra Boost (Ultradent, Salt Lake City, UT, USA)	7.8	7.5
		38 % HP	Potenza Bianco Pro SS (PHS Group, Joinville, SC, Brazil)	5.5	5.0
		37.5 % HP	Pola Office + (SDI)	6.9	6.5
		35 % HP	Total Blanc (DFL, Rio de Janeiro, RJ, Brazi)	6.7	5.8
		35 % HP	Total Blanc One-Step (DFL)	7.2	6.2
		35 % HP	Whiteness Automixx (FGM)	6.6	5.5
		35 % HP	Whiteness Automixx Plus (FGM)	7.5	7.0
		35 % HP	Whiteness HP Blue (FGM)	8.2	8.0
Gumy et al. (2024) [71]	1 × 50 min	38 % HP	Potenza Bianco Pro SS (PHS Group)	5.5	5.2
		35 % HP	Whiteness Automixx (FGM)	7.0	5.0
		35 % HP	Whiteness Automixx Plus (FGM)	7.7	7.5
		35 % HP	Whiteness HP Blue (FGM)	8.5	8.0

3.2.4. *Is in-office bleaching more effective and invasive than at-home therapy?*

There is clinical evidence suggesting that both at-home and in-office bleaching modalities promote similar efficacy even up to 2 years after treatment completion [79]. A meta-analysis found no significant differences in bleaching efficacy or tooth sensitivity between both modalities [80]. However, the studies included in these reviews were highly heterogeneous in terms of bleaching protocols, and only those with low risk of bias were included in the meta-analysis, indicating a need for more RCTs to strengthen the evidence base.

Two subsequent RCTs demonstrated that at-home bleaching with 10 % CP (either 2 or 8 hours per day every 14 days) achieved greater objective color change than in-office bleaching with 35 % HP (two sessions), with no significant difference in tooth sensitivity risks between them [43,81]. Conversely, Sever et al. (2018) concluded that a single in-office session with 40 % HP resulted in higher clinical efficacy and sensitivity levels compared to at-home bleaching with 6 % HP (1 h a day during 6 consecutive days) [82]. A recently published umbrella review on this topic reported no significant differences between at-home and in-office bleaching in terms of efficacy and tooth sensitivity [83]. However, the authors reiterated the concern raised by de Geus et al. [80] regarding the considerable variation in bleaching protocols and concentrations across the included studies. Therefore, it still remains an open question whether one modality overcomes the other.

In the past, it was demonstrated by *in vitro* studies that high-concentrated bleaching gels compromise the enamel surface more significantly than lower-concentration formulations, leading to increased surface roughness and decreased microhardness, tensile strength, and mineral content of enamel [84–87]. More recently, advancements such as pH stabilization and the incorporation of sodium fluoride and calcium into bleaching gels appear to have mitigated these effects, regardless of the gel's concentration [13,88]. Nevertheless, it is still recommended to wait between 7 and 21 days before restoring bleached teeth, regardless of the modality, to allow for enamel bond strength recovery and color stabilization [89]. Although the use of antioxidants to restore immediate enamel bond strength has shown effectiveness in *in vitro* studies, no RCTs have validated the long-term success of restorations in bleached teeth following the application of sodium ascorbate, alpha-tocopherol, grape seed extract, or green tea [90].

Based on a multi-regression, in-office bleaching can increase four times the risk of sensitivity [41], thereby being a factor to be considered

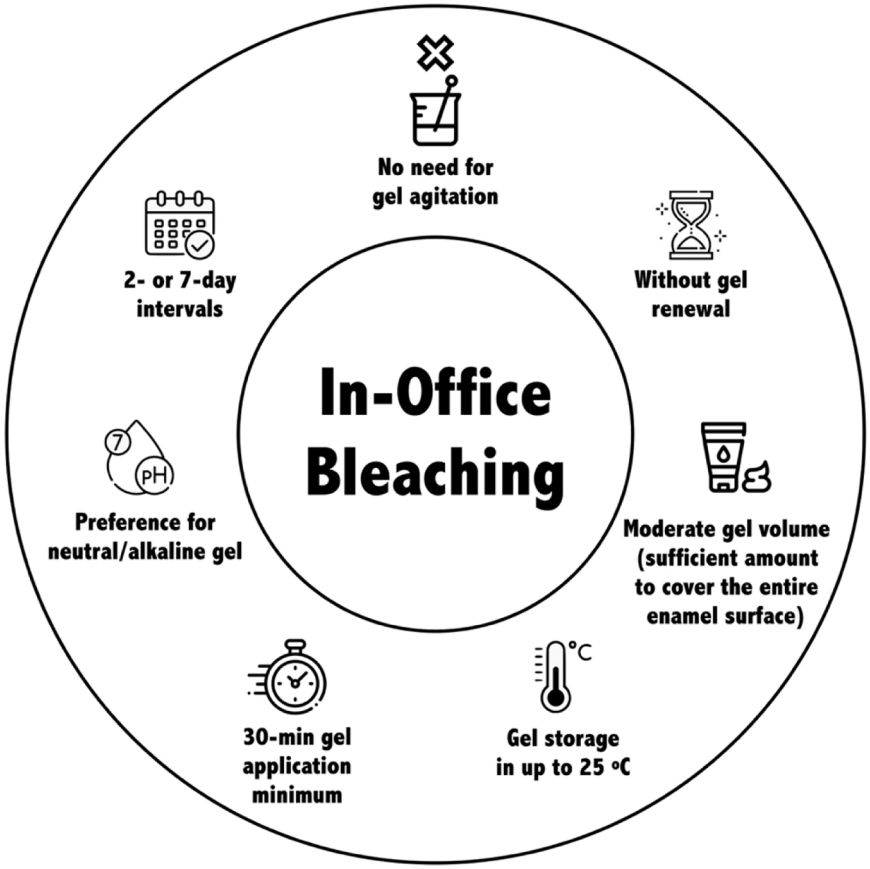

Fig. 1. Most relevant aspects about the bleaching gels for in-office techniques.

when planning bleaching in patients reporting previous sensitivity. Also, several *in vitro* studies demonstrated that higher HP concentrations could incite higher cytotoxicity effects i.e., decrease in viability, increase in oxidative stress and morphology changes of odontoblast-like cells [91–93], which highlights the importance of reducing the concentration of peroxides used for bleaching teeth. However, the long-term clinical impact of tooth bleaching to pulp tissue, regardless of its modality, remains unknown. Additionally, although *in vitro* research has shown that HP penetration into the pulp chamber is significantly higher in teeth with enamel cracks [94], no RCTs have investigated the effect of sealing enamel cracks with fluid resins—such as those used as gingival barriers—prior to bleaching. This highlights a gap in the literature regarding the potential benefits of sealing enamel cracks to reduce HP penetration and improve the safety of bleaching treatments.

Given that supervised at-home bleaching with low-concentration CP or HP remains the safest option for patients and current evidence aforementioned reveal no color change differences between at-home and in-office bleaching, we encourage clinicians to prioritize at-home protocols. However, in certain cases, in-office bleaching may be necessary. Patients with time constraints who seek immediate results or those with compromised compliance—who may struggle to consistently follow at-home treatment protocols—can benefit from the professional supervision and immediate outcomes of in-office bleaching. If an individualized treatment plan necessitates in-office approaches, ~~we believe that~~ following the present guidelines could help minimizing potential damage during in-office sessions.

3.2.5. Is combined bleaching more effective than solely in-office or at-home therapies?

Regarding combined bleaching therapies (at-home and in-office), a systematic review with meta-analysis found no significant differences in color change compared to isolated at-home or in-office bleaching [95]. Nonetheless, combined bleaching was associated with increased tooth sensitivity, despite including studies with a high risk of bias. Recent studies have investigated combinations of low- or high-concentration HP with 10 % CP [96,97]. Interestingly, Rezende et al. found that decreasing the gel concentration (from 35 % to 20 % HP) in the preliminary in-office session maintains esthetic efficacy as well as reducing tooth sensitivity. Thus, it is possible to infer that adding a preliminary exposure with higher HP concentrations is responsible to increase report of sensitivity in the combined bleaching.

Vaez et al. (2019) suggested that a single preliminary in-office session with 35 % HP before starting at-home bleaching with 10 % CP significantly reduced the time to achieve satisfactory aesthetic results by 3.7 days [98]. However, a one-day interval between in-office and at-home bleaching commencement was necessary, and combined bleaching was found to increase sensitivity risk without enhancing final aesthetic results or patient satisfaction. Daily at-home bleaching was found to be more effective than alternating days (2 every days) for combined bleaching [99]. A recent RCT also indicated that the order of bleaching modalities did not affect the efficacy of combined bleaching [42]. Therefore, using a preliminary in-office session as a "jump start" for bleaching may not be the only effective protocol for combining techniques, enabling starting with at-home bleaching instead. Current evidence suggests that a second in-office bleaching session is unnecessary to achieve the efficacy of combined bleaching, though it may reduce the number of days required for at-home bleaching. However, the authors did not assess the impact of this second in-office session on tooth sensitivity [100], thereby the second in-office session should be discouraged in combined bleaching.

Table 3 synthesizes the most current combination protocols after clinical verification. It is important to emphasize that all the at-home

Table 3
Summary of the current clinical protocols of combined bleaching.

Authors (Year)	In-Office	At-Home	Findings
Rezende et al. (2016) [96]	1 single preliminary session with 20 % HP (1 ×40–50 min)	10 % CP (2 hours a day for 2 weeks) in customized tray	Replacing the 35 % HP session with 20 % HP maintained efficacy with lower sensitivity under combination (1-week interval between techniques)
Rodrigues et al. (2018) [97]	1 single preliminary session with 38 % HP (1 ×45 min)	10 % CP (4 hours a day for 2 weeks)	The preliminary single session did not enhance final esthetic outcomes achieved by at-home bleaching alone
Vaez et al. (2019) [98]	1 single preliminary session with 35 % HP (1 ×45 min)	10 % CP (1 hour a day for 16 days) in customized tray	The combined protocol (1-day interval between techniques) reduced 3.7 in average the number of days to reach at-home bleaching alone's efficacy
Takamizawa et al. (2023) [99]	3 sessions with 35 % HP (1 ×20 min)	6 % HP (90 min a day for 10 days) in prefilled tray	Using at-home bleaching in consecutive days among in-office intervals increased the combined bleaching efficacy compared to alternating days
Zhong et al. (2023) [42]	1 session with 40 % HP (before or after at-home bleaching)	10 % CP (8 hours a day for 2 weeks) in customized tray	The order of in-office bleaching session did not alter the final outcomes of combined bleaching

and/or in-office bleaching protocols presented in this review have been performed each with different commercial products, which may impact the final esthetic outcomes due to variations on composition, viscosity and other factors [101]. Based on all the current evidence, it's feasible to support the use of a preliminary in-office session to motivate the patients but keeping in mind that a low-concentrated HP gel could decrease the risk for sensitivity in the combined regimen. For patients reporting previous sensitivity, at-home bleaching still would be a more appropriate approach.

3.3. Light-Assisted Bleaching

3.3.1. Is there any light source effective to enhance bleaching efficacy?

One of the most researched questions in tooth bleaching over recent decades concerns the impact of light activation on in-office peroxide gels, once it has been hypothesized that light could increase the bleaching gels temperature and, consequently, expedite the decomposition of HP into reactive oxygen species [102]. In the 2010s, there was extensive investigation into the activation of 6 % or 35 % HP using hybrid light sources (blue LEDs and infrared lasers), with findings indicating no significant increase on the final outcomes of bleaching by light [103–106]. It is noteworthy that older light sources like halogen lamps, plasma arc lamps, and metal halide lamps were previously used. A recent RCT demonstrated that the halogen lamp, no longer recommended for activating in-office gels, does not enhance the effect of high-concentration HP on tooth color change [107].

Indeed, He et al. (2012) and Maran et al. (2018) confirmed through systematic reviews and meta-analyses that light-assisted tooth bleaching does not increase efficacy or decrease adverse effects, regardless of the type of light source used in the studies conducted [108,109]. In contrast, SoutoMaior et al. (2010) demonstrated that light activation can reduce tooth sensitivity outcomes [110]. As the light industry has evolved over the years with continuous introduction of new sources, comparing light-assisted bleaching protocols has become increasingly challenging. This has resulted in heterogeneous evidence with low certainty across systematic reviews. Network meta-analysis studies have attempted to address whether specific light sources might excel over others or not. However, due to limited studies for each type of light, these analyses have indicated that no single light source consistently outperforms others or significantly alters the efficacy and sensitivity patterns achieved with high-concentration HP [111,112]. Therefore, use of older lights and, mostly of current blue LEDs [113], is unnecessary during in-office bleaching. Some evidence have shown that the use of ozone did not impair the levels of bleaching efficacy, and managed positively the sensitivity issue [114–116], but it is crucial to take into account that it is a very costly technology.

3.3.2. Are photoactivated titanium dioxide-enriched bleaching gels effective?

Light-activated gels containing commercial titanium dioxide (TiO_2) nanoparticles have been introduced to reduce the HP concentration required for in-office bleaching. TiO_2 is a semi-conductive metal oxide that, when reaching an electronic requirement (ultraviolet light excitation), can generate light, heat, or even reactive oxygen species. For a clinical use, efforts are centered into doping TiO_2 with other chemical elements to shift its absorbance spectrum to visible light [1].

While these formulations have shown a decrease in reported sensitivity, some RCTs have indicated that commercial 6 % HP gels incorporated with titanium dioxide doped with nitrogen and irradiated with hybrid light sources (blue LED/infrared laser), did not achieve the same high aesthetic efficacy as standard 35 % HP in-office bleaching [117–121], probably because of the impairment between the absorbance light spectrum of commercial TiO_2 and blue wavelength or because of its low availability of HP. RCTs have shown that commercial TiO_2-containing 15 % HP gels, when irradiated under the same conditions (blue LED/infrared laser), resulted in more stable tooth color change than 6 % HP or even higher bleaching efficacy than 35 % HP without light [122,123]. On the other hand, other RCTs showed that 6 % with TiO_2 and irradiated with blue wavelength resulted in significantly lower color change than 35 % HP [124,125]. Regardless of these outcomes, it is important to emphasize the low number of evidence on this topic and that use of a blue light source for in-office bleaching is no longer supported by clinical evidence [109,112].

3.3.3. Is the novel generation of violet LEDs effective when used alone or combined with gels?

Since 2020, RCTs have been focusing on studying violet LEDs, which represent the latest generation of light for in-office bleaching. Contrary to manufacturers' claims that violet wavelengths alone could achieve significant tooth color change by a physical breakdown of organic molecules adhered to the surface of enamel, clinical evidence unanimously indicates that this physical bleaching effect is suboptimal [126–130]. Indeed, Kury et al. (2022) demonstrated *in vitro* that violet light with a wavelength matching a commercial violet LED (Bright Max Whitening, MMOptics, São Carlos, SP, Brazil) is 98 % absorbed by a 1-mm thick enamel slice [131].

There is clinical evidence suggesting that combining at-home bleaching with in-office sessions using only violet LED irradiation can enhance overall efficacy, but this study did not follow-up the volunteers over time [132]. Moreover, some RCTs have demonstrated that violet LEDs can increase the effectiveness of in-office bleaching therapies using either 37 % CP or 35 % HP, even after 1 year from end of bleaching, without increasing the incidence of tooth sensitivity [133–135]. In this

instance, likewise when no light is applied, there is no need to exceed a 30-minute application of bleaching gels or renew the gel during treatment [136]. Table 4 shows a protocol of violet LED use in-office tested in at least there RCTs. Since the light's manufacturer indicates use of a single 30-min long bleaching gel application along with the light irradiation, it is imperative to use a neutral/alkaline gel under light cycling (Table 2).

Consequently, this new generation of violet LED light may represent a promising approach to potentially reduce the concentration of in-office bleaching gels permanently, but systematic reviews with meta-analysis are still necessary. Additionally, violet LEDs have been found to significantly enhance the colorimetric changes achieved by commercial TiO_2-enriched 6 % HP gels compared to a blue LED system, achieving efficacy similar to 35 % HP treatments [137]. Such event could be explained by the fact that doped TiO_2 holds higher absorbance spectrum to violet LEDs. To the best of the authors' knowledge, up to this moment, only one brand (DMC Equipment, São Carlos, SP, Brazil) commercialize 6 % hydrogen peroxide with TiO_2, which was demonstrated to decrease tooth sensitivity when combined with violet LED in a recent RCT. However, this approach did not increase efficacy in comparison to 6 % HP gel without TiO_2 [138]. Hence, it is important to expand evidence on this topic before recommending the use of TiO_2-enriched gels combined with violet LED.

3.3.4. The impact of diet and smoking on bleaching efficacy or tooth sensitivity

Few studies complying with CONSORT 2010 have investigated the effect of habits on at-home bleaching efficacy, showing no interference of dietary, including drinking coffee or red wine [142,143]. Only one RCT complying with the CONSORT 2010 guidelines evaluated the impact of coffee and tea on in-office bleaching outcomes, showing that drinking coffee in the subsequent days after finalizing in-office bleaching may promote tooth staining, compromising the bleaching stability over time. However, drinking coffee during bleaching did not influence the efficacy attained [144]. Hence, patients do not need to quit drinking coffee among the intervals of bleaching sessions, but caution should be taken in the first 21 days following the last in-office session. One feasible explanation could be the short-term increase in enamel surface roughness promoted by high-concentrated or acidic HP gels, turning teeth more susceptible to the deposition of extrinsic pigments [145,146]. However, action of human saliva may recover the enamel surface properties in the short-term, reducing the susceptibility to the staining [147]. Overall, two recent systematic reviews with meta-analysis of studies with low risk of bias demonstrated that consumption of dark beverages does not impair the color change promoted by tooth bleaching [148,149].

Another RCT evaluated the impact of a cola-drink on tooth bleaching outcomes. Even though the darkened beverage did not significantly influence the esthetic outcomes rendered by 35 % HP, it did increase the intensity of tooth sensitivity [150]. Such event could be explained by the very low pH of soft drinks. Therefore, it is important to advise patients who frequently consume acidic beverages about the increased risk of tooth sensitivity.

Regarding smoking during the bleaching treatment, clinical RCTs and a systematic review [151–154] concluded that color change provided by at-home bleaching with carbamide peroxide was not lower in smoker volunteers. As a result, there is no evidence supporting the need to counter indicate bleaching in patients with teeth stained by tobacco. Also, a prospective observational cohort study showed that the smoking habit associated with 22 % carbamide peroxide gel for at-home bleaching does not show genotoxic potential on oral cells [155], corroborating the safety of the bleaching procedure to the human health.

3.3.5. The impact of orthodontic treatment on bleaching outcomes

A recent clinical trial has observed that the presence of orthodontic brackets downgraded the Whiteness index achieved by 35 % HP bleaching, [156]. A systematic review stated that low-quality evidence suggests that the optimal time to perform tooth whitening in patients undergoing conventional orthodontic treatment is after bracket removal, with a recommended waiting period of at least 30 days to allow the enamel, pulp, and periodontal tissues to recover after orthodontic treatment [157]. Currently, there is insufficient evidence to support tooth whitening during active orthodontic treatment.

In recent days, aligners have increasingly become popular based on their ease of use and esthetic appeal. A recent clinical trial showed, that applying carbamide peroxide gel altered the biomechanical properties of the vacuum-formed retainers (aligners), resulting in a decrease in tensile strength and an increase in hardness and internal roughness [158]. Therefore, using the aligners also to load a bleaching gel, during orthodontic treatment, may compromise or at least delay the desired alignment outcomes. No RCT has assessed the impact of resin attachments on the final bleaching results. Brackets or attachments may act as physical barriers to the penetration of bleaching gels into the interprismatic spaces, potentially compromising the results. However, it is important to note that bleaching gels can diffuse through tooth structures, allowing for whitening of the entire tooth, including areas covered by brackets or attachments. [3,159]. Therefore, rigorous and well-designed studies are paramount to address this open question.

Table 4
Current protocols used for light-activating bleaching gels with violet LED and photobiomodulation of teeth with infrared laser.

Authors (Year)	Purpose	Light Source	Parameters	Irradiation Protocols
Santos et al. (2021) [129], Kury et al. (2022) [128], Mayer-dos-Santos et al. (2022) [126]	**Irradiation of bleaching gel**	Violet light-emitting diode (401.82 nm)	Four light emitting diode lamps. Illumination area of the curved acrylic tip = 10.7 cm^2. Total power = 1.2 W. Irradiance at the position corresponding to the right upper incisor = 8.0 mW/cm^2	Twenty 1-min activations with consecutive 30-s intervals (no light irradiation). Light tip must be positioned 8 mm away from the arches. Gels were applied during 30 min without renewal
Silva et al. (2020) [139]	**Teeth photobiomodulation before bleaching gel's application**	Laser diode Arsenic Gallium and Aluminum (ArGaAl) with infrared wavelength (808 nm)	1.7 J at 60 J/cm^2, spot size of 0.028 cm^2	16 s at two perpendicular points both apical and central on the buccal surface of incisors, canines, and premolars
Paula et al. (2019) [140]	**Teeth photobiomodulation after bleaching gel's removal**	Laser diode Arsenic Gallium and Aluminum (ArGaAl) with infrared wavelength (808 nm)	1.7 J at 60 J/cm^2, spot size of 0.028 cm^2	Continuous mode during 16 s per area
Alencar et al. (2018) [141]	**Teeth photobiomodulation combined with NaF application prior to bleaching gel's application**	Laser diode Arsenic Gallium and Aluminum (ArGaAl) with infrared wavelength (808 nm)	3.75 W/cm^2 at 60 J/cm^2, spot size of 0.028 cm^2	Continuous mode during 16 s per area

3.4. The impact of existing restorations on bleaching outcomes

Applying peroxide-based gels on restored anterior teeth or on the lingual surface rather than on buccal surface intact surface resulted in significant decrease in color change [160–162]. Thus, bleaching teeth with multiple restorations remains a challenge, often requiring more invasive rehabilitation approaches to address severe discoloration or the replacement of restorations that no longer match the natural tooth color after bleaching [163,164]. Although a previous *in vitro* study showed that the presence of restorations may increase HP penetration into the pulp chamber following in-office bleaching [165], the available evidence from a recent RCT indicates that the presence of restorations does not lead to higher sensitivity levels during at-home bleaching [162]. This suggests that, under at-home treatment protocols, restorations may not significantly impact the risk of sensitivity, even with the potential for HP exposure [162]. However, it is recommended to clinically evaluate the marginal integrity of restorations before applying bleaching gels.

3.5. Management of Tooth Sensitivity

3.5.1. Do infrared lasers decrease tooth sensitivity due to bleaching?

Various photobiomodulation (PBM) protocols using LEDs or infrared lasers with different parameters have been tested primarily to address tooth sensitivity levels following bleaching treatments. Given the fact that HP and/or ROS can penetrate into pulp, triggering an inflammatory and sensorial reaction, and that lasers can penetrate dental hard tissues, PMB could induce neuropharmacological effects, including the production, release, and metabolism of various endogenous agents. Also, it could influence nerve cell action potentials by altering cell membrane permeability or temporarily affecting sensory axon endings [166].

Although the results from studies using PBM are controversial [141, 167–174], it is worth noting that a systematic review with meta-analysis concluded that PBM using low-level laser significantly reduced sensitivity during in-office bleaching without jeopardizing color outcomes [175]. Paula et al. (2019) showed that use of an infrared laser and a potassium nitrate gel, used separately or together, decreased sensitivity after bleaching, but they did not act synergically [140]. However, such protocols not only reduced sensitivity among volunteers but also decreased the peak sensitivity experienced from 3 days to just 1 day following the application of 35 % HP [140]. Also, Alencar et al. (2018) demonstrated that low-level laser therapy combined with a topical application of 5000 ppm sodium fluoride application for 5 min prior to each in-office bleaching session significantly decrease the occurrence of tooth sensitivity, but the effect of PMB isolated was not conducted [141]. A more recent systematic review also suggested that low-level laser therapy could reduce tooth sensitivity after tooth bleaching [176]. Even though only a small number of RCTs have been conducted on this topic and included in the systematic reviews, the use of PMB could be encouraged by clinicians as a strategy for managing tooth sensitivity. PMB protocols with infrared lasers, before in-office bleaching session or after the gel's removal, are also presented in Table 4, based on support of evidence.

3.5.2. Are nitrate-, fluoride-, and/or calcium-based desensitizer gels effective?

Several desensitizing agents have extensively been evaluated in clinical settings. According to one systematic review with meta-analysis, potassium nitrate- and sodium fluoride-based agents, not incorporated into at-home and in-office bleaching gels, were effective in reducing tooth sensitivity [177]. In other words, using topical desensitizing agents before or after bleaching could minimize patients' symptoms. Potassium nitrate is capable of penetrating into the pulp chamber, wherein could act by prevent nerve repolarization due to the excess of K^+ ions on the external site of nerve membrane [178]. However, a more recent systematic review with meta-analysis suggested that the study [177] might have overestimated the effect size and concluded that the impact of such agents, although significant to reduce sensitivity, is subtle and clinically questionable [179]. Conversely, Pereira-Lores et al. (2024) demonstrated in a subsequent RCT that wearing a customized tray loaded with a commercial gel containing 3 % potassium nitrate and 0.11 % sodium fluoride significantly reduced sensitivity associated with at-home bleaching using 16 % CP applied daily for 6 hours [180].

Recent RCTs testing nitrate-based agents with rigorous methodology have showed that factors such as concentration (5 % vs. 10 % vs. 35 %) [181,182], sonication (with or without agitation) [183], exposure time (10 minutes before bleaching vs. 5 minutes after in-office bleaching) [184], number of applications (before vs. before and after in-office bleaching) [185], and using preloaded trays [186] did not decrease the levels of tooth sensitivity. There is also evidence that incorporation of potassium nitrate agents into 35 % HP [187] and 10 % CP [15,187, 188] gels for in-office and at-home bleaching, respectively, also does not diminish the prevalence nor intensity of tooth sensitivity.

Calcium-based agents interact with hard tissues by forming precipitates on the enamel, which helps reducing the detrimental effects of demineralization and alterations in enamel morphology. *In vitro* research has also indicated that calcium significantly decrease the penetration of hydrogen peroxide into the pulp chamber [189]. Although calcium-based desensitizing agents were not capable to clinically interfere with the risk of sensitivity in a RCT [190], one systematic review with meta-analysis has demonstrated that these agents could slightly level off intensity of sensitivity [191]. However, similar to all reviews on desensitizers, the certainty of evidence was considered low or very low, highlighting the need for more high-quality RCTs on this topic. None of the aforementioned studies have found that desensitizing agents jeopardize tooth color change outcomes. Taking this vast number of evidence, it is possible to say that using only one of the above agents will not guarantee the decrease of sensitivity levels, but their use does not negatively affect the efficacy of bleaching treatments.

3.5.3. Are there any effective alternative desensitizing gels?

Glutaraldehyde-containing agents are suggested for reducing dentin hypersensitivity; however, these materials did not clinically reduce tooth sensitivity levels following bleaching[192–194]. One RCT has detected that an experimental gel containing 5 % glutaraldehyde and 5 % potassium nitrate significantly decreased sensitivity when applied prior to in-office 35 % HP bleaching [195], suggesting that the combination of different agents may be promising. According to the authors, glutaraldehyde could have acted as a cross-linker in proteins of both enamel and dentin, thereby hindering the diffusion of hydrogen peroxide. [195].

Topical agents such as Otosporin [196] and nanoencapsulated eugenol [197] as well as systematic administration of ascorbic acid [198] have not been shown to reduce sensitivity, while there is conflicting evidence regarding the effectiveness of potassium oxalate [199, 200] and casein phosphopeptide-amorphous calcium phosphate with fluoride (CPP-ACPF) [201–204] agents. Recently, a systematic review with meta-analyses with moderate certainty of evidence concluded that topical drug application was ineffective in reducing in-office tooth bleaching sensitivity [205]. Few studies have clinically indicated the successful use of other agents i.e., strontium chloride [206], sodium hexametaphosphate [207], tetracalcium phosphate combined with dicalcium phosphate anidrous (TPCP) [208], and vitroceramic particles (45S5 bioglass or biosilicate) [209,210], but more studies are necessary to confirm such findings. Even though evidences are controversial on this topic or systematic reviews show no efficacy in terms of reducing sensitivity, most of the studies showed no compromise on the bleaching efficacy, thereby allowing the clinician to opt for the use or not of such agents. Additionally, continuous monitoring of emerging evidence by dental professionals is essential for informed clinical decision-making. Clinical protocols using desensitizing agents are detailed in Table 5.

Table 5
Desensitizing agents suggesting clinical success on reducing tooth sensitivity according to recent randomized-controlled clinical trials.

Authors (Year)	Bleaching Modality	Desensitizer Agent	Protocol
Paula et al. 2019 [140]	In-office (35 % HP)	5 % potassium nitrate and 2 % sodium fluoride	The agent was applied with a brush applicator previously to bleaching, being left undisturbed for 10 minutes. Combination with low-level laser therapy does not increase its efficacy
Parreiras et al. (2018) [195]	In-office (35 % HP)	5 % glutaraldehyde and 5 % potassium nitrate experimental gel	Experimental gel was left undisturbed for 10 min, and then the gel was slightly agitated with a rubber cup for 10 s, previously to 35 % HP gel
Barros et al. (2020) [200]	At-home (22 % CP)	1.5 % potassium oxalate	Patients were directed to load a small amount of desensitizing gel on the tray and wear it for 10 min after at-home bleaching
Pereira-Lores et al. (2024) [180]	At-home (16 % CP)	3 % potassium nitrate and 0.11 % sodium fluoride	Patients were directed to load a small amount of desensitizing gel on the tray and wear it for 30 min after at-home bleaching
Alexandrino et al. (2017) [203]	In-office (35 % HP)	CPP-ACPF	The paste containing the agent was applied on the enamel surface with a brush applicator during 5 minutes after bleaching gel removal
Pompeu et al. (2021) [206]	In-office (35 % HP)	Strontium chloride	The agent was applied with a brush applicator after bleaching and agitated during 20 seconds before being left undisturbed for 10 minutes. Combination with low-level laser therapy increases its efficacy
Mehta et al. (2018) [208]	In-office (40 % HP)	TPCP	Two 20-second agitations with rubber cup for each tooth prior to in-office bleaching
Alencar et al. (2017) [211]	At-home (22 % CP)	5 % potassium nitrate and 2 % sodium fluoride or 10 % strontium chloride-containing toothpastes	Immediately after the removal of bleaching CP agent, patients received the application of the dentifrices during 5 min and were directed to toothbrush with the same dentifrices twice a day throughout the at-home bleaching treatment

3.5.4. *Are toothpastes effective to reduce tooth sensitivity?*

The use of desensitizing toothpastes has also gained attention in recent years, but results are controversial. An one-week toothbrushing regimen before the start of in-office bleaching did not prevent or reduce tooth sensitivity when using arginine- [212,213] or potassium nitrate-containing [214] dentifrices. Nonetheless, toothpastes containing strontium chloride, potassium nitrate and sodium fluoride, or arginine combined with calcium carbonate have been demonstrated to attenuate tooth sensitivity when used during toothbrushing intermittently to at-home bleaching [211] or in an customized acetate tray worn after in-office bleaching [215]. Cabral et al. (2024) concluded in a systematic review that desensitizing toothpastes were effective for at-home bleaching only when used in conjunction with higher concentrations of carbamide peroxide gels (22 % CP) and for in-office bleaching only when a single session was performed. [216]. Up to this moment, no meta-analysis has been conducted due to the limited number of studies and the variability in products and methodologies among them. However, studies have unanimously shown that, regardless of the agent used, desensitizing toothpastes did not negatively impact the efficacy of tooth bleaching [213,215,216]. Similar to the previous discussion, the clinical decision should be guided by the clinician's preference. However, if the dentist chooses to recommend a toothpaste as a desensitizing agent, the selection of the most appropriate product should be based on the specific needs of each case. As potassium nitrate products hold the ability to penetrate the pulp chamber and influence nerve polarization, we encourage dentists to prescribe toothpastes containing this component, following the protocol described by Alencar et al. (2017) [211] in Table 5. Dentists should also be aware that the concentration of bleaching gel on use could impair the desensitizing effect desired.

3.5.5. *Are analgesics effective on reducing tooth sensitivity following bleaching?*

The administration of analgesic drugs during in-office bleaching has not shown any significant impact on tooth sensitivity [217]. A meta-analysis has demonstrated a slight, yet significant, decrease in pain intensity provoked by high-concentration HP bleaching [218]. However, since this difference may not be clinically relevant, new RCTs with larger sample sizes are needed. A recent RCT indicated that preemptive use of codeine-containing analgesics does not regulate sensitivity levels effectively [219]. One feasible explanation for this scenario could rely on the fact that ROS penetrating into pulp could activate inflammatory mediators, which would not be solved by analgesia [220]. Therefore, the use of analgesics should not be prescribed after in-office bleaching sessions, as the cost-benefit is minimal. This practice exposes the patient to medication that is unlikely to be effective and therefore unnecessary.

3.5.6. *Are anti-inflammatories effective on reducing tooth sensitivity following bleaching?*

Available systematic reviews and meta-analyses consistently indicate that nonsteroidal anti-inflammatory drugs do not effectively reduce reports of tooth sensitivity following high-concentration HP bleaching [205,217,221–223]. Despite this, some of the studies included in the cited reviews exhibited high risk of bias, highlighting the necessity for new and better-designed RCTs. Some follow-on studies have concluded that preemptive administration of ibuprofen (400 mg) and cafein [224], piroxican (200 mg) [225], etodolac (400 mg) [226], naproxen (500 mg) [227], and topical application of dipyrone gel (500 mg) [228] does not influence in the sensitivity outcomes. Regarding the use of dexamethasone, both existing RCTs have shown no improvement in pain levels [229,230]. None of these studies have attested any negative implications of drugs on the esthetic efficacy achieved by high-concentration HP, even when administered perioperatively [231,232], but their use should be discouraged because of lack of efficacy on pain control. Such findings could be a result of the difficulty of an oral drug to be delivered in the pulpal tissue, showing that topical agents could facilitate more effective drug delivery to the pulpal space [233].

3.5.7. Is there any combination of drugs and desensitizers effective on managing tooth sensitivity?

Araújo et al. (2021) concluded that preemptive use of paracetamol-codeine analgesics combined with a 5-minute topical application of a calcium-based desensitizing gel significantly decreased the sensitivity induced by 35 % HP compared to placebo-controlled groups [234]. Likewise, preemptive administration of ibuprofen along with nitrate- and fluoride-based gel application was effective in reducing such adverse effect [235]. Another RCT has shown that application of a gel containing 5 % ibuprofen and 10 % arginine significantly reduced symptoms of pain associated with in-office bleaching [236]. It is noteworthy that combinations of desensitizing agents with drugs appear to be more effective in controlling bleaching-induced tooth sensitivity than their separate use, but further RCT are necessary to justify the clinical application.

4. Discussion and future perspectives

The answers above indicate that numerous RCTs and systematic reviews have investigated various aspects of tooth bleaching. A recent bibliometric detected a growing trend in RCTs on tooth bleaching over the last 30 years [237]. A notable observation is the significant variability in protocols and experimental designs among RCTs within the same modality, which complicates drawing firm conclusions. Indeed, most systematic reviews highlight that this variability—stemming from differences in commercial bleaching and desensitizing gels, application times, and light sources—could contribute to the heterogeneity in results [6,111,191,218]. Despite this, systematic reviews and RCTs still represent the highest levels of evidence in the scientific hierarchy [238]. To date, there is no current comprehensive literature review that synthesizes clinical evidence on all critical aspects of tooth bleaching to guide clinicians in making informed decisions. Since not all questions have been addressed by systematic reviews, and some reviews have called for subsequent well-designed RCTs, we have chosen to also include also RCTs in this review to provide a more complete overview.

Although the primary goal of a literature review is not to assess the risk of bias in included studies, this review exclusively includes randomized clinical trials (RCTs) that adhere to the 2010 CONSORT guidelines. The CONsolidated Standards Of Reporting Trials (CONSORT) Statement, initially introduced in 1996 and updated in 2001 and 2010, aims to standardize the reporting of RCTs [239]. This standardization facilitates critical evaluation of study design, including aspects such as sample size calculation, randomization, allocation concealment, and blinding [240]. Loguercio et al. (2017) demonstrated through a systematic review that only approximately 50 % of RCTs in tooth bleaching adhered to CONSORT guidelines. However, adherence to CONSORT does not guarantee that all reporting standards—particularly those related to protocol, allocation concealment, and sample size—are meticulously followed by authors [241]. Therefore, while this review serves as a practical guide, we recommend that clinicians critically appraise individual RCTs to address specific questions relevant to their practice.

Current clinical evidence suggests that lower concentrations of peroxide gels can maintain bleaching efficacy while minimizing tooth sensitivity [7]. However, factors such as pH and application time remain critical for both the effectiveness and potential adverse effects of bleaching [66]. For at-home bleaching, 10 % CP gel is still the most supported option, balancing efficacy with low levels of sensitivity report [80]. Recent findings indicate that overnight application is no longer necessary, enhancing the compliance with tray use and reducing tooth sensitivity [16]. Additionally, low-concentration HP gels have emerged as viable alternatives, allowing for the use of prefilled or custom trays for just 30 minutes a day over a period of up to 4 weeks, with some RCTs showing no differences in terms of sensitivity compared to 10 % CP [26,28]. Although at-home bleaching protocols are well-established, there is currently no clinical evidence that defines specific frequencies for bleaching treatments, such as whether they should be performed once a year or every two years. While some patients may undergo bleaching treatments at regular intervals, the optimal frequency for maintaining results or minimizing adverse effects remains unclear. The lack of long-term studies and standardized protocols makes it difficult to establish a clear guideline on how often whitening treatments should be performed. Further clinical research is needed to determine the most effective and safe interval between treatments to ensure both aesthetic outcomes and the preservation of oral health.

The efficacy of over-the-counter whitening products was not reviewed herein, as the focus of the present review was on dentist-supervised bleaching protocols. These OTC products contain diverse components, such as blue covarine, low concentrations of hydrogen peroxide, activated charcoal, and abrasives with higher abrasiveness than regular toothpastes. This composition may explain why some systematic reviews have concluded that whitening toothpastes have a greater impact on tooth color change compared to regular toothpastes [242,243]. However, current RCTs on this topic confirm that so-called whitening toothpastes or mouthrinses do not achieve bleaching outcomes comparable to those observed with carbamide peroxide gels [244–246]. Over the past five years, the introduction of activated charcoal-containing products has gained expressive attention from the scientific community. A substantial number of *in vitro* studies has shown that charcoal-containing toothpastes or powders produce significantly lower color change than supervised at-home bleaching and may negatively affect surface roughness, topography, and wear of both teeth and composites [247–250]. Clinical evidence further discourages the use of charcoal-based products, as they provide minimal whitening effects and result in low comfort, ease-of-use, and whitening satisfaction among users [251,252]. Therefore, dentist-supervised bleaching remains the most effective and safest treatment option for patients seeking at-home bleaching.

In-office bleaching remains challenging, as higher concentrations of hydrogen peroxide (HP) are still necessary to achieve satisfactory results [6]. Higher HP concentrations lead to increased intrapulp HP penetration, which can cause inflammatory and sensory reactions [12,91]. While neutral or alkaline high-concentration HP gels can reduce tooth permeability [66], not needing replenishment in the same in-office session, efforts continue to find ways to lower the in-office HP concentration for adults. However, a systematic review showed a low certainty of evidence that low-concentrated bleaching gels uphold the color change promoted by high-concentrated HP and that further RCTs are necessary to determine which is the best concentration of HP and extent of protocol is necessary to maintain in-office bleaching efficacy [6].

Currently, novel violet LED technology is being explored for its potential synergistic effects with photocatalytic particles or nanoparticles. Recent *in vitro* research showed that experimental bleaching gels with 6 % or 10 % HP, combined with co-doped titanium dioxide nanoparticles[1,253], titanium dioxide nanotubes [254], niobium pentoxide [255], or manganese oxide [93], can achieve similar color and whiteness index changes as commercial 35 % HP. Nevertheless, further randomized clinical trials (RCTs) are needed to validate these findings. While these emerging technologies show promise, future research should also focus on developing nanoparticles that react spontaneously, eliminating the need for an expensive bleaching light source. In this sense, Kury et al. (2022) found that a commercial violet LED for in-office bleaching displayed a very heterogenous beam profile and unstable irradiance over the 30-min long protocol indicated by the manufacturer [131], suggesting that quality of the light sources must be upgraded.

Also, given that dentists utilize blue or blue/violet LED units to cure composite resins [256], there is potential for confusion in selecting the appropriate light source. This confusion could arise if polywave lights, which are capable of emitting a range of wavelengths, inadvertently activate bleaching gels. Such misapplication could result in an unintended increase in pulp temperature [257,258] if the light is used for the duration (approximately 20 min-long light activation) recommended by

manufacturers of lights specifics for bleaching [128]. Additionally, clinicians must be aware that infrared lasers are not suitable for activating bleaching gels. Instead, their use is specifically indicated for biomodulating teeth response either prior to the application of in-office bleaching gels or following their removal. As previously demonstrated, RCTs and systematic reviews concluded that infrared lasers may reduce sensitivity [140,141,175]. However, the protocols adopted by dentists should be grounded in successful results of some clinical studies, subject to change with the growing evidence on the topic (see Table 4).

As shown during the review, desensitizing topical agents raise controverse, but their use will not affect the esthetic outcomes achieved by bleaching gels [179,191]. Combination of two types of agents seem promising, but more RCTs are necessary to draw a conclusion in terms of the most effective combination and protocols. In recent days, *in vitro* studies are exploring bleaching gels with remineralizing agents beyond calcium or sodium fluoride. Given the high prevalence of patients with early-stage erosion or abrasion —often difficult for clinicians to detect— [259] experimental gels incorporating Biosilicate [92,260] or 45S5® bioglass [261,262] have been shown *in vitro* to maintain enamel mineral levels or reduce intrapulp HP penetration in sound or early-stage eroded teeth. This could serve as a protective factor for patients with undetected early-stage erosion undergoing at-home or in-office bleaching and that could potentially be more prone to tooth sensitivity [92]. As society evolves and research advances, the quest to find optimal solutions for addressing patient needs intensifies. This has been clearly observed in the field of teeth bleaching since the classical nightguard vital bleaching study by Haywood & Heymann [2], and it appears likely to continue in the years to come.

5. Conclusion

Since different modalities (at-home and in-office) and agents (hydrogen and carbamide peroxides) are available for tooth bleaching, clinical decision-making based on current evidence might aid the dentist on choosing the most appropriate bleaching protocol to achieve efficacy and safety for their patients. Both at-home and in-office bleaching are effective, but their combination can incite higher levels of tooth sensitivity. At-home bleaching can be performed using either 10 % CP or 10 % or lower-concentrated HP gels for 3 or 4 weeks-long, respectively. Recent evidence show that in-office bleaching with high-concentrated HP gels still may promote more effective esthetic outcomes compared to lower concentrations of HP gels used in-office, but with higher levels of tooth sensitivity. Neutral or alkaline gels may remain unchanged for at least 30 min in a minimum of 2 sessions. Violet LEDs and photobiomodulation with infrared lasers are promising to increase the efficacy of low-concentrated gels or decrease tooth sensitivity, respectively, but more studies are paramount to confirm their necessity or the most adequate protocols. While topical desentizing agents, dentifrices, or drugs are overall not effective separately on controlling tooth sensitivity, alternative protocols combining more than one desensitizer should be further explored to provide effective desensitization approaches in the future.

Declaration of Competing Interest

The authors declare no potential conflicts of interest concerning the authorship or publication of this work.

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