©Operative Dentistry, 2020, **45-2,** E77-E90

Efficacy and Adverse Effects of Whitening Dentifrices Compared With Other Products: A Systematic Review and Meta-analysis

A Devila • R Lasta • L Zanella • MA Dall Agnol • SA Rodrigues-Junior

Clinical Relevance

When advising patients, dentists should consider the extrinsic stain removal effect of whitening dentifrices that may ultimately result in color change and yet produce adverse effects more often than regular dentifrices.

SUMMARY

Whitening dentifrices (WDs) are widespread and accessible worldwide, claiming to whiten teeth. Therefore, this systematic review aimed to assess the extrinsic stain removal (ESR), the whitening potential, and the adverse effects of WDs. Randomized controlled trials comparing WDs with regular dentifrices (RDs) and other home-based whitening products were searched at NCBI-PubMed, Cochrane-CENTRAL, EBSCO-Host, and clinicaltrials.gov. The studies were screened and had data extracted by two independent researchers. Eligible studies presented outcomes of ESR, color change, and adverse effects, with no restriction of publication date. Data were meta-analyzed using RevMan 5.3, and the level of evidence was rated according to GRADE criteria. Eleven studies (n=1962) assessed reduction of stain area and intensity through Lobene Stain index, with a mean difference (MD) of –0.33 ([–0.41;–0.25]; p=0.00001) and –0.34 ([–0.44;–0.25]; p=0.00001), respectively. When the modified Lobene Stain index was used (six studies; n=2576), MD was –0.42 ([–0.58;–0.25]; p=0.00001) and –0.30 ([–0.39;–0.21]; p=0.00001), respectively. Mean color change through shade guide tabs (three studies; n=1322) was –1.80 ([–2.33;–1.26]; p=0.00001). All differences were in favor of the WDs, which also produced a risk of adverse effects (RR=1.74; [1.20, 2.52]; p=0.003; four studies; n=1322). The comparison of WDs with paint-on gel (two studies; n=58) yielded similar efficacy and adverse effects (p>0.05), whereas the

Angélica Devila, DDS, private dentist, Chapecó, Santa Catarina, Brazil

Rafaela Lasta, DDS, private dentist, Chapecó, Santa Catarina, Brazil

Luana Zanella, DDS, MsC, private dentist, Chapecó, Santa Catarina, Brazil

Mauro A. Dall Agnol, DDS, MsC, PhD, School of Dentistry, Universidade Comunitária da Região de Chapecó (Unochapecó), Chapecó, Santa Catarina, Brazil

*Sinval A. Rodrigues-Junior, DDS, MS, PhD, Health Sciences Postgraduate Program, Universidade Comunitária da Região de Chapecó (Unochapecó), Chapecó, Santa Catarina, Brazil

*Corresponding author: Servidão Anjo da Guarda, n° 295-D, Bairro Efapi, PO Box 1141, Chapecó, Santa Catarina 89809-000, Brazil; e-mail: rodriguesjunior.sa@unochapeco.edu.br

https://doi.org/10.2341/18-298-L

comparison of WDs with white strips (two studies; n=87) yielded higher efficacy of the latter (p=0.00001) and similar adverse effects (p=0.52). The quality of evidence varied from low to moderate. WDs are more effective in reducing extrinsic stain and producing a whitening-like effect in teeth than RDs, although they also produce more adverse effects. Whitening efficacy of WDs is similar to paint-on gel and lower than white strips. Higher-quality evidence demands larger, well-conducted, independent studies.

INTRODUCTION

Dentrifrices have been a powerful adjunct in dental hygiene, acting as a vehicle for fluoride, among other active ingredients.[1] Their cosmetic effect is inherent to their cleansing effect through biofilm and extrinsic stain removal and relies on the presence of abrasives.[2] Throughout the last two decades, dentifrices have also become a means of responding to the strong esthetic appeal as over-the-counter (OTC) whitening products for at-home tooth whitening, without professional supervision.[3,4]

Dentifrices that claim to whiten teeth have represented more than 50% of the OTC tooth whitening products[5] and their supposedly whitening properties depend on mechanical biofilm removal with a high quantity of abrasives.[3,5,6] Additionally, they may contain chemicals that break down organic molecules of the biofilm, removing chromogens or preventing their accumulation. Surfactants, enzymes, citrates, pyrophosphates, and hexametaphosphates are components of whitening dentifrices (WDs) and help degrade stained biofilms, aiding its mechanical removal.[7] However, the presence of peroxides in dentifrices is less common and is challenging, mainly due to formulation aspects.[7] Therefore, the limited amount of whitening constituents and the short contact time with the tooth surface have raised questions about the real whitening potential of WDs.[8]

Even so, WDs have been recently shown as more effective than regular dentifrices (RDs) in removing extrinsic staining at six weeks, regardless of whether adjunctive chemical antidiscoloration agents were present.[9] This suggests a potential esthetic effect resulting from removal of tooth surface discoloration by using WDs, although it may not translate into significant color improvement.[5] It also has been shown that, even in the absence of a real objective whitening effect, WDs may generate a subjective patient perception of an improved, whiter smile.[10]

However, time required for WDs to reach a whitening-like effect demands further clarification. For instance, although the ADA Acceptance Program Guidelines for Home-Use Tooth Stain Removal Products[11] recommends a minimum six-week assessment time for studies involving WDs, studies have shown significant effect at earlier periods[12] and improved effect with increasing treatment time.[13]

The basis for the widespread recommendation of any therapeutic agent involves the production of clinically proven effects,[2] regardless of the mechanism of action involved. In this sense, how WDs compare with other home-whitening products, including those that contain whitening substances and those that require professional supervision,[5] is paramount to recommend its clinical use. Additionally, safety issues such as allergic responses, abrasion of teeth and restorations, and other undesirable responses should be crystal clear, because these whitening products require no prescription or professional supervision.[4]

Therefore, this systematic review aimed to verify whether WDs are as effective and safe as RDs and as other home-based tooth whitening products and to verify the effect of application time on whitening efficacy. The hypotheses were that 1) WDs are more effective than RDs and produce more adverse effects; 2) the whitening effect improves as application time increases; and 3) WDs are as effective and safe as other home-based tooth whitening products.

METHODS

This systematic review was built based on the recommendations of the *Cochrane Handbook for Systematic Reviews of Interventions* and the *Transparent Reporting of Systematic Reviews and Meta-analyses*[14,15] and focused on answering the questions that follow: are WDs as effective and as safe as 1) RDs and 2) other home-based whitening products; and what is the effect of application time on tooth whitening efficacy?

Search Strategy and PICOS Criteria

PICOS criteria involved the following:

Problem: tooth whitening
Intervention: whitening dentifrices
Comparison: regular dentifrices or other home-based whitening methods
Outcomes: extrinsic stain removal (ESR), color change, and adverse effects

Studies were randomized controlled clinical trials written in English, with no restriction of application

time and outcome measure. Exclusion criteria involved the following: studies that compared WD with associated methods or protocols of tooth whitening and that compared WD with WD, studies with induced staining, studies without baseline data, studies that did not assess the desired outcomes, studies focusing on stain prevention, and studies with immediate color assessment.

Searches for articles were conducted in March 2017 and June 2018 at NCBI-PubMed, Cochrane-CENTRAL, EBSCO-Host, and clinicaltrials.gov. The following search strategy was customized to each database searched: Dentifrices[MeSH Terms] OR Toothpastes[MeSH Terms] OR whitening dentifrice OR whitening toothpaste OR bleaching toothpaste AND Tooth bleaching[MeSH Terms] OR tooth whitening OR bleaching, teeth OR tooth stain removal OR extrinsic stain removal OR pigment removal. The studies were screened by two independent reviewers (AD and RL) in the databases and in the references of the included studies. Disagreements were solved by two other reviewers (LZ and SARJ). Additionally, other potentially relevant studies were searched in the references of the included studies.

Data Extraction

Data were collected independently by AD and RL into previously prepared extraction worksheets with information relative to the published article and characteristics of the study, participants, interventions, and outcomes in each experimental group. Authors of the studies were contacted by email to solve methodologic concerns or to obtain outcome data. Studies in which the data variability was expressed using SE had it converted to SD using the following equation: $SD = SE\sqrt{n}$, where n is the number of participants in each group.

Outcome Measures

Efficacy of the interventions was expressed as the capacity of ESR or color change. The former was assessed using the Lobene stain index,[16] the Lobene stain index modified by Macpherson,[17] and the Shaw and Murray index.[18] The first two indexes generate ordinal measures of stain intensity and area and may also merge both into a composite index. The Shaw and Murray index sums the number of stained squares from a standard grid superposed to the tooth surface. Color variation was assessed through the yellowing change summary measure Δb^*, the lightness change summary measure ΔL^*, and the nondirectional color change summary measure ΔE^* resulting from the tridimensional color space CIE-L*a*b*[19] and by the score difference of shade tabs in Vita Classical and Vita 3D Master shade guides. All efficacy measures generated continuous variables.

Safety was assessed as the occurrence of adverse effects resulting from either using the WD or the RD/other whitening intervention and was analyzed as a dichotomous variable.

Methodologic Quality of the Studies

The Risk of Bias tool 2.0 from the Cochrane Collaboration[20] was applied to each individual study to determine the presence of bias resulting from 1) the randomization process, 2) deviations from intended interventions, 3) missing outcome data, 4) measurement of the outcome, and 5) selection of the reported result. Each study was classified as low risk, high risk, or some concerns for these domains, and an overall risk of bias was designated.

Data Analysis

ESR was expressed as change in staining area, intensity, or in the composite mean score after the interventions. The mean difference was calculated as follows:

$$D = \mu_1 - \mu_2$$

where μ_1 and μ_2 are the mean area, intensity, or composite score before and after the interventions, respectively.[21] Because the composite score appeared to have been calculated differently in different studies, and considering that it derives from original data of stain area and intensity, it is described in the tables; however, it was not meta-analyzed.

The SD of the difference between before and after the interventions was determined through the following equation:

$$S_{\text{diff}} = \sqrt{S_1^2 + S_2^2 - 2 \times r \times S_1 \times S_2},$$

where S_1 and S_2 are the SDs of before and after the interventions, respectively, and r is the coefficient of correlation between before and after scores.[14,21] Because no study provided data of the difference to calculate r, sensitivity analysis was undertaken involving the comparisons at six weeks and simulating r=0, r=0.5, and r=0.9. Because no difference in the pooled effect size measured or in the 95% confidence interval (95% CI) was detected, one adopted the r value that generated the lowest heterogeneity between data (r=0). Heterogeneity

Table 1: *Results of the Comparison Between WD and RD*

Outcome	Comparison (n)	Number of Studies and Comparisons	Effect Size Measure [95% CI]	*p*	Heterogeneity (I^2)
Reduction of stained area (LSI)	WD (n=992) × RD (n=970)	11 studies; 17 comparisons	−0.33 [−0.41; −0.25][a]	0.00001	72%
Reduction of stained area (MLSI)	WD (n=1300) × RD (n=1276)	6 studies; 8 comparisons	−0.42 [−0.58; −0.25][a]	0.00001	91%
Reduction of stain intensity (LSI)	WD (n=992) × RD (n=970)	11 studies; 17 comparisons	−0.34 [−0.44; −0.25][a]	0.00001	78%
Reduction of stain intensity (MLSI)	WD (n=1300) × RD (n=1276)	6 studies; 8 comparisons	−0.30 [−0.39; −0.21][a]	0.00001	78%
Vita Classic shade guide	WD (n=674) × RD (n=648)	3 studies; 4 comparisons	−1.80 [−2.33; −1.26][a]	0.00001	96%
Adverse effects	WD (n=664) × RD (n=658)	4 studies; 5 comparisons	1.74 [1.20;2.52][b]	0.003	0%

Abbreviations: LSI, Lobene stain index; MLSI, Macpherson modified Lobene stain index; RD, regular dentifrice; WD, whitening dentifrice.
[a] *Mean difference [95% CI]: negative results favor the WD.*
[b] *Risk ratio [95% CI]: results above 1 favor the RD.*

was verified using the I^2 test with a significance level <0.10. Data were meta-analyzed with the inverse variance method and random effects model. To meta-analyze data generated using the Vita Classical shade guide, the SD data of Ghassemi and others[22] was used to calculate r to obtain the SD of the difference for Ghassemi and others.[13]

In the presence of high heterogeneity, sensitivity analysis was undertaken using the "leave-one-out" method to identify the role of each individual study on the final effect size measure. Subgroup meta-analyses were undertaken to analyze the hypothesis that whitening efficacy of the WD would rely on application time.

Adverse effects data were meta-analyzed using Mantel-Haenszel with 95% CI and a random effects model. Studies with no adverse effects reported in either group were not included in the meta-analysis. All meta-analyses were performed in RevMan 5.3.[23] The quality of evidence generated for each outcome was analyzed using *The Grading of Recommendations Assessment, Development and Evaluation* (GRADE), considering as parameters the study design, risk of bias, inconsistency, indirect evidence, imprecision, and publication bias.[14,24] Publication bias was assessed by analyzing the symmetry of distribution of the studies around the effect size measure in funnel plots when at least 10 studies were present.

RESULTS

One hundred forty-four potential studies were identified out of 8329 references. Another 15 studies were found by hand search in the references of the included studies (Figure 1). Full-text reading of 76 studies led to exclusion of 36 studies. The remaining 40 studies were included in the qualitative analysis. The Online Appendix file contains complementary information on sensitivity analysis adopted to calculate the SD of studies that did not provide this data; the reasons for exclusion of studies; qualitative description of study design, participants, interventions and results; details on decisions related to risk of bias; publication bias; and grading of evidence.

Comparison WD × RD

Twelve studies qualitatively expressed ESR assessed through Lobene, Lobene modified by Macpherson (composite index), and the Shaw and Murray index.[13,25–35] All 12 studies revealed higher stain removal with the WD than with the RD, behavior that was confirmed by the meta-analysis of stain area and intensity using either Lobene (11 studies[12,36–45] with 1962 participants) or Lobene modified by Macpherson (6 studies[13,22,46–49] with 2576 participants) indexes (Table 1). For either outcome, the heterogeneity level was considered high (72%-91%). The risk of bias was rated serious, because most studies had raised concerns about the randomization process, with possible deviations from intended interventions that could include allocation concealment and about blinding of outcome assessors, leading to concerns in the overall bias. Indirectness and imprecision were not relevant issues; publication bias was not considered an issue, because the distribution of the studies in the funnel plots of the Lobene stain index was fairly symmetrical. The level of evidence was rated low.

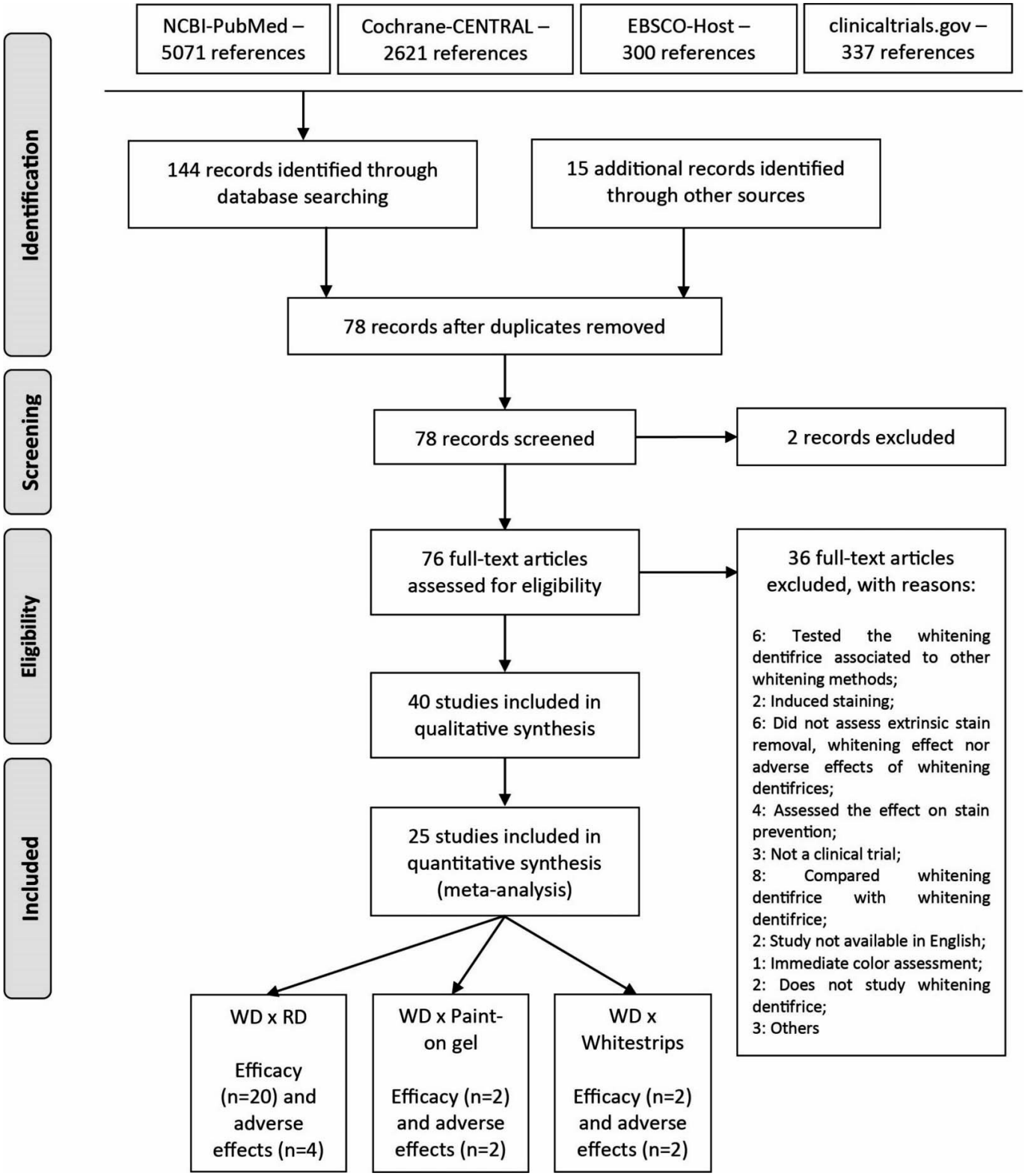

Figure 1. *Flow diagram of the study.*

Table 2: *Difference in Area of ESR (MD [95% CI]) With Either WD or RD in LSI or MLSI Considering Application Time*

Time	LSI				
	Comparison (n)	Number of Studies and Comparisons	Effect Size Measure [95% CI]	*p*	Heterogeneity (I^2)
5 days	—	—	—	—	—
1 week	WD (n=74) × RD (n=70)	1 study; 1 comparison	−0.12 [−0.29;0.05]	0.17	—
2 weeks	WD (n=74) × RD (n=70)	1 study; 1 comparison	−0.24 [−0.41; −0.07]	0.006	—
3 weeks	—	—	—	—	—
4 weeks	WD (n=46) × RD (n=46)	1 study; 1 comparison	−0.28 [−0.58;0.02]	0.07	0%
6 weeks	WD (n=666) × RD (n=652)	9 studies; 15 comparisons	−0.34 [−0.45; −0.24]	0.00001	78%
8 weeks	WD (n=46) × RD (n=46)	1 study; 1 comparison	−0.42 [−0.74; −0.10]	0.010	—
12 weeks	WD (n=43) × RD (n=43)	1 study; 1 comparison	−0.35 [−0.51;−0.19]	0.00001	—
24 weeks	WD (n=43) × RD (n=43)	1 study; 1 comparison	−0.38 [−0.53; −0.23]	0.00001	—

Abbreviations: ESR, extrinsic stain removal; LSI, Lobene stain index; MD, mean difference; MLSI, Macpherson modified Lobene stain index; RD, regular dentifrice; WD, whitening dentifrice.

One study assessed color change using the Vita 3D Master shade guide and found no significant influence of the type of dentifrice.[10] On the other hand, color change assessed using the Vita Classical shade guide, when meta-analyzed (three studies[13,22,50] involving 1322 participants), generated a mean 1.80 whiter shade tab, favoring the WD (Table 1). Heterogeneity was rated high, and risk of bias was rated serious due to concerns regarding the randomization process and potential deviations from intended interventions. Again, indirectness and imprecision were not serious; publication bias was not assessed due to the limited number of studies. The level of evidence was rated low.

Three studies assessed color change through Δs (which represented the before-after color change in each CIEL*a*b* axis and the overall color change).[8,25,51] Koertge and others[25] observed a higher Δb* (reduction of yellowness) with the whitening dentifrices. Horn and others,[8] comparing three WD with a RD, noticed that only one WD produced significantly higher ΔE* than the RD. Pintado-Palomino and others[51] observed no significant difference in ΔE* comparing two WD and a RD.

Eleven studies assessed the occurrence of adverse effects associated with the treatment.[13,25–31,35,51,52] In nine studies, no adverse effect was identified throughout the study.[13,25–28,30,31,35,51] The other two studies reported similar adverse events associated to either treatment group.[29,52] On the other hand, when meta-analyzed, the adverse effects of four other studies[53–56] involving five comparisons were lower with the RD (Table 1). No heterogeneity between studies was identified. Risk of bias was rated serious due to concerns regarding the randomization process and potential deviations from intended interventions that led to concerns in overall risk of bias. Indirectness and imprecision were not relevant issues; however, publication bias was not assessed due to the limited number of studies. The level of evidence was rated moderate. Gingivitis, gingival hyperplasia, gingival ulcer, lip ulcer, desquamation, tooth sensitivity, pain, and stomatitis were adverse effects reported as a consequence of dentifrice use.

Sensitivity analysis revealed no significant shift of effect size using the leave-one-out method with each individual study. Subgroup meta-analyses of ESR considering application time varied from five days to 24 months, and revealed that, for extrinsic stain area, with the exception of the one-week assessment, the other time periods favored the WD in at least one stain index ($p<0.05$; Table 2). The same behavior was observed regarding the extrinsic stain intensity ($p<0.05$; Table 3). Color change measured by means of shade tab position was assessed from five days to six weeks and also favored the WD ($p<0.05$; Table 4). Heterogeneity, when measurable, varied from 0% to 81% for ESR and from 0% to 98% for color change based on shade guide measures.

Comparison WD × Paint-on Gel

Two studies[57,58] involving 58 participants assessed color change through ΔE* and adverse effects comparing the WD with the paint-on gel. The meta-analysis revealed no significant difference in color change or adverse effects measures ($p>0.05$). There was no serious concern about heterogeneity (Table 5). On the other hand, the risk of bias was

Table 2: *Difference in Area of ESR (MD [95% CI]) With Either WD or RD in LSI or MLSI Considering Application Time (ext.)*

Time	MLSI				
	Comparison (n)	Number of Studies and Comparisons	Effect Size Measure [95% CI]	*p*	Heterogeneity (I^2)
5 days	WD (n=143) × RD (n=152)	2 studies; 3 comparisons	−0.18 [−0.32; −0.03]	0.02	0%
1 week	—	—	—	—	–
2 weeks	WD (n=115) × RD (n=126)	1 study; 2 comparisons	−0.33 [−0.48; −0.17]	0.0001	0%
3 weeks	WD (n=59) × RD (n=60)	1 study; 1 comparison	−1.36 [−1.59; −1.13]	0.00001	–
4 weeks	WD (n=662) × RD (n=639)	4 studies; 6 comparisons	−0.26 [−0.42; −0.10]	0.001	79%
6 weeks	WD (n=260) × RD (n=235)	3 studies; 4 comparisons	−0.69 [−0.88; −0.51]	0.00001	70%
8 weeks	WD (n=61) × RD (n=64)	1 study; 1 comparison	−0.10 [−0.25; 0.05]	0.19	–
12 weeks	—	—	—	—	—
24 weeks	—	—	—	—	—

rated serious, because both studies raised concerns about the randomization process, with possible deviations from the intended interventions that could include allocation concealment and missing outcome data, leading to concerns in the overall bias. Indirectness and imprecision were not relevant issues; publication bias was not assessed due to the limited number of studies. The level of evidence was rated low.

Comparison WD × Whitening Strips

Two studies[57,59] involving 87 participants assessed color change through Δb* and ΔL* and also assessed adverse effects comparing the WD with whitening strips. Reduction of yellowness (Δb*) and increase of lightness (ΔL*) were significantly higher using the whitening strips ($p<0.00001$; Table 5). The occurrence of adverse effects was not significantly different in either group; heterogeneity was a concern only for adverse effects ($I^2=59\%$). On the other hand, the risk of bias was rated serious, because both studies raised concerns about the randomization process and possible deviations from intended interventions that could include allocation concealment; one of them also generated concerns about missing outcome data, leading to concerns in the overall bias. Indirectness and imprecision were not relevant issues; however, publication bias was not assessed due to the limited number of studies. The level of evidence was rated moderate for color change and low for adverse effects.

Comparison WD × Custom Tray

One study[58] involving 29 participants analyzed the influence of 1% hydrogen peroxide containing activated WD × the tray system containing 5% carbamide peroxide gel. The ΔE* was 1.49 higher with the tray system than with the WD ($p<0.0014$). Ten participants of the tray system group manifested oral irritation or tooth sensitivity (66.7%) vs three in the WD group (21.4%).

DISCUSSION

Whitening dentifrices have been largely commercialized, claiming to contribute to the whitening effect of teeth. This study proved this claim to be true, either by ESR or color change. Therefore, the hypothesis that a whitening-like effect would be better provided by WDs compared with RDs was accepted. Also, compared with RDs, WDs induced more adverse effects. The study also showed that the whitening effect is not time dependent, with results showing up as early as five days of dentifrice use, leading to the rejection of the second hypothesis. Finally, the whitening efficacy and the potential of producing adverse effects of the WDs were similar to most of the other home-based whitening products, leading to the acceptance of the third hypothesis.

Efficacy was expressed in this study as the capacity of ESR and color change. Extrinsic dental staining differs from the intrinsic stain by being a discolored pellicle adhered to the tooth surface, as opposed to the inner discoloring caused by medicines, such as tetracycline, dental traumatism, or aging.[60] ESR requires cleansing and polishing actions produced by abrasive-containing dentifrices or professional prophylaxis products. Also, the presence of agents responsible for releasing the adherent stain or for bleaching chromogens has been suggested.[7]

ESR was analyzed using predefined standard stain indexes. The Lobene stain index[16] provides

Table 3: *Difference in Intensity Reduction of Extrinsic Stain (MD [95% CI]) With Either WD or RD in LSI or MLSI Considering Application Time*

Time	LSI				
	Comparison (n)	Number of Studies and Comparisons	Effect Size Measure [95% CI]	*p*	Heterogeneity (I^2)
5 days	—	—	—	—	—
1 week	WD (n=74) × RD (n=70)	1 study; 1 comparison	−0.26 [−0.42; −0.10]	0.001	—
2 weeks	WD (n=74) × RD (n=70)	1 study; 1 comparison	−0.63 [−0.79; −0.47]	0.00001	—
3 weeks	—	—	—	—	—
4 weeks	WD (n=46) × RD (n=46)	1 study; 1 comparisons	−0.16 [−0.45; 0.13]	0.29	0%
6 weeks	WD (n=666) × RD (n=652)	9 studies; 15 comparisons	−0.34 [−0.46; −0.22]	0.00001	81%
8 weeks	WD (n=46) × RD (n=46)	1 study; 1 comparison	−0.26 [−0.54; 0.02]	0.07	—
12 weeks	WD (n=43) × RD (n=43)	1 study; 1 comparison	−0.35 [−0.53; −0.17]	0.0001	—
24 weeks	WD (n=43) × RD (n=43)	1 study; 1 comparison	−0.36 [−0.54; −0.18]	0.0001	—

Abbreviations: LSI, Lobene stain index; MD, mean difference; MLSI, Macpherson modified Lobene stain index; RD, regular dentifrice; WD, whitening dentifrice.

an ordinal scale that varies from 0 (no stain) to 3 (heavy stain) for stain intensity and 0 (no stain) to stain over one third, two thirds, or more than two thirds of the region (scores 1, 2, and 3, respectively) for stain area. This is assessed in the gingival region and the body region of the tooth. Its modification in 2000 by Macpherson and others[17] differs by including the proximal surfaces of the tooth in the index and by considering different distributions of stain in buccal/labial surfaces and lingual/palatal surfaces. In this sense, the buccal/labial surfaces are categorized as follows: 1 (stain limited to pits/grooves), 2 (stain outside pits/grooves, up to 10% of the area), and 3 (more than 10% of the area affected), and the lingual/palatal surfaces are categorized similarly to the original index. A total of 97% of the studies that assessed ESR used the Lobene stain index or its modification. The meta-analysis of stain area and intensity results favored the WD, regardless of the stain index used. Area and intensity results varied 0.09 and 0.04 between indexes, respectively, and this variation was not significant, as revealed by the overlapping CIs (Table 1). The only study that assessed ESR with the Shaw and Murray index[33] confirmed the higher ESR capacity with the WDs, proving this significant effect regardless of the measurement instrument used. The composite index assessed by Lobene and Macpherson-modified Lobene is a product of the stain area and intensity scores and was reported by a sufficient number of studies to provide a meta-analysis. However, the lack of information about a standardized procedure for calculation and the evidence of a different scaling for this index between studies led to the decision for qualitative presentation of these results only.

The Δs from the tridimensional color space CIEL*a*b*, widely used in tooth color change assessments,[51,61] revealed significant color change toward a lighter tooth using some WDs in comparison to the baseline color.[8,25,51] In one study, color change was significant from baseline and similar with the WDs and the RD,[51] whereas in another study, no color change was observed with either dentifrice through a four-week assessment period.[8] It has been suggested that any overall color change resulting from WD use implies ESR and should not be confounded with a real bleaching effect.[51] This effect relies more on the amount and type of abrasive in the dentifrice[51] than on the presence of additional antidiscoloration chemical agents.[9]

When color change was assessed by the difference of shade tab score of the Vita Classical shade guide, meta-analysis revealed that WDs produced almost two shade tabs lighter than the RDs (Table 1). Although the difference of shade tab score was lower than the difference produced by peroxide-containing whitening products,[61] it was significant toward a higher color change effect by the WD. In summary, most studies that assessed color change as a relevant outcome presented some whitening-like effect as consequence of WD use.

Considerable heterogeneity, as measured by the I^2, was identified between studies regarding the efficacy outcomes of the comparison between WD and RD (Table 1). The presence of significant heterogeneity indicated that variability higher than the expected in the effect size measure existed between studies. This variability should be incorporated to the model adopting the random effects

Table 3: *Difference in Intensity Reduction of Extrinsic Stain (MD [95% CI]) With Either WD or RD in LSI or MLSI Considering Application Time (ext.)*

Time	MLSI				
	Comparison (n)	Number of Studies and Comparisons	Effect Size Measure [95% CI]	*p*	Heterogeneity (I^2)
5 days	WD (n=143) × RD (n=152)	2 studies; 3 comparisons	−0.15 [−0.27; −0.03]	0.01	0%
1 week	—	—	—	—	—
2 weeks	WD (n=115) × RD (n=126)	1 study; 2 comparisons	−0.29 [−0.41; −0.16]	0.00001	0%
3 weeks	WD (n=59) × RD (n=60)	1 study; 1 comparison	−0.38 [−0.51; −0.25]	0.00001	—
4 weeks	WD (n=662) × RD (n=639)	4 studies; 6 comparisons	−0.21 [−0.35; −0.08]	0.001	75%
6 weeks	WD (n=260) × RD (n=235)	3 studies; 4 comparisons	−0.49 [−0.58; −0.40]	0.00001	0%
8 weeks	WD (n=61) × RD (n=64)	1 study; 1 comparison	−0.30 [−0.41; −0.28]	0.00001	41%
12 weeks	—	—	—	—	—
24 weeks	—	—	—	—	—

model, which assumes that the true effect size varies from one study to another.[14] Also, in the presence of considerable heterogeneity, sensitivity analysis and subgroup meta-analysis are recommended to aid in the identification of possible sources of heterogeneity, either clinical or methodologic. Demographic and behavioral characteristics of the participants represent important sources of heterogeneity,[61] as well as the constitution of the WDs and RDs studied. As to the latter, it has been previously shown that the presence of antidiscoloring chemical adjuncts in the WD does not interfere in the effect size measure.[9] The other information, as presented by the primary studies, does not allow subgroup meta-analysis that could explain clinical heterogeneity.

A subgroup meta-analysis was set *a priori* based on the hypothesis that the total study time and, as a consequence, the cumulative treatment time, could improve color change produced by the WDs, as previously observed.[13] Treatment time did not influence significantly the ESR analyzed using either Lobene or Macpherson modified Lobene stain indexes, because in all times tested, starting at five days and throughout 24 weeks, at least one index revealed significant results in favor of the WD (Tables 2 and 3). Similar behavior was observed when color change was analyzed using the shade tabs of Vita Classical shade guide (Table 4). From five days to four weeks, an increasing effect size was observed toward the WD, stabilizing from four to six weeks. This suggests that a whitening-like effect based on superficial abrasion and removal of surface pigmentation may be observed short term, earlier than the six-week period recommended by the ADA guidelines.[11]

Adverse effects were almost twice more likely to occur when using the WD (Table 1), with emphasis on tooth sensitivity and soft tissues repercussions. Compositional differences of WDs compared with RDs mainly involve the amount, shape, size, acuteness, and hardness of abrasives[3] and are probably related to the occurrence of adverse effects that may affect quality of life of users, such as pain or discomfort, and eventually lead to discontinuation of the treatment. Other adverse effects were not identified in the primary studies, because they require other detection approaches. Wear of the tooth and of restorations, for instance, are seldom identified by patient report or visual examination, but they may affect long-term biofilm retention due

Table 4: Difference in Color Change (MD [95% CI]) With Either WD or RD Considering Application Time

Outcome	Time	Comparison (n)	Number of Studies and Comparisons	Effect Size Measure [95% CI]	*p*	Heterogeneity (I^2)
Shade position	5 days	WD (n=115) × RD (n=126)	1 study; 2 comparisons	−0.47 [−0.77; −0.17]	0.002	0%
Shade position	2 weeks	WD (n=136) × RD (n=149)	2 studies; 3 comparisons	−1.83 [−3.30; −0.35]	0.02	96%
Shade position	4 weeks	WD (n=222) × RD (n=198)	3 studies; 4 comparisons	−2.28 [−3.30; −1.25]	0.0001	98%
Shade position	6 weeks	WD (n=201) × RD (n=175)	2 studies; 3 comparisons	−2.03 [−2.73; −1.34]	0.00001	92%

Abbreviations: MD, mean difference; RD, regular dentifrice; WD, whitening dentifrice.

Table 5: *Comparison Between the WD and Other Home-Based Whitening Products*

Comparison (n)	Outcome	Number of Studies and Comparisons	Effect Size Measure [95% CI]	*p*	Heterogeneity (I^2)
WD (n=28) × paint-on gel (n=29)	ΔE*	2 studies; 2 comparisons	0.15 [−1.87;2.18][a]	0.88	0%
WD (n=28) × paint-on gel (n=30)	Adverse effects	2 studies; 2 comparisons	3.74 [0.31;44.98][b]	0.30	40%
WD (n=45) × white strips (n=42)	Δb*	2 studies; 3 comparisons	2.37 [2.07;2.66][a,c]	0.00001	0%
WD (n=45) × white strips (n=42)	ΔL*	2 studies; 3 comparisons	2.14 [1.78;2.49][a,c]	0.00001	0%
WD (n=45) × white strips (n=42)	Adverse effects	2 studies; 3 comparisons	0.60 [0.13;2.80][b]	0.52	59%

Abbreviation: WD, whitening dentifrice.
[a] Mean difference [95% CI].
[b] Risk ratio [95% CI].
[c] Favored the white strips.

to increased roughness, and even affect the cosmetic aspect of the smile.[3,62]

The comparisons of the WD with other home-based whitening products revealed higher efficacy of the hydrogen peroxide–containing white strips and a carbamide peroxide–based tray system. The 18% carbamide peroxide paint-on gel and the WD produced similar color change (Table 5). All tooth whitening systems, including the WD compared here, had their whitening mechanism based on liberation of oxygen free radicals through the tooth structure from peroxide-containing substances.[63] These systems have been shown to rely on the concentration of oxygen-releasing substances and on time of contact with the tooth structure for their whitening capacity.[61] In this sense, the higher whitening performance of the white strips and the tray system is explained by the prolonged contact time of the whitening peroxides with the tooth structure, given each whitening regimen (twice a day for 30 minutes and once a day for six to eight hours, respectively).[57,58] Interestingly, the similar performance of the paint-on gel in comparison with the WD may be due to the short application time regimen (twice a day for 15-30 minutes), regardless of the substantial difference of hydrogen peroxide content between them. No significant difference in occurrence of adverse effects was observed between the WD and the other whitening methods, excepting the tray system, which presented a 40% higher occurrence of oral irritation or tooth sensitivity,[58] also possibly associated with the concentration of peroxide.

Overall risk of bias generated concerns in 85% of the primary studies. Risk of bias is related to whether key aspects of the randomized controlled trial designs were taken into consideration and how, and these may influence methodologic heterogeneity.[61] Frequent concerns in primary studies were related to random sequence generation and deviations from the intended interventions. The latter is related to allocation concealment to participants, care providers, and trial personnel and the likelihood of unbalanced interventions between groups due to lack of allocation concealment.[20] Risk of bias was considered serious in both comparisons because of concerns generated in key methodologic issues of the randomized controlled trials.

Imprecision relates to the sample size required to correctly reject the null hypothesis[21] and was rated serious for the comparison between the WD and the paint-on gel. Rating took into consideration the small sample size based on two studies and the 95% CI that failed to exclude the threshold of no effect for both efficacy and adverse effects measurement. For the other comparisons, imprecision was not an issue, considering that the pooled number of participants in the meta-analyses reached the minimum required by the Acceptance Program Guidelines for Home-Use Tooth Stain Removal Products,[11] and the 95% CI of the estimate of treatment effect excluded the no effect threshold. However, only 7.5% of the included studies presented a sample size calculation or a rationale to justify the sample size.

Publication bias is present when the dataset of the literature misrepresents the true body of evidence because of a biased sample of relevant studies.[21,64] It may be caused by various reasons, including the difficulty of publication of negative results, and may lead to conclusions of significant effects due to nonidentification of studies with nonsignificant results.[64] Funnel plots display the relationship between the study size and effect size and represent absence of publication bias through symmetric distribution of studies around the mean effect size.[21] Funnel plots were generated for ESR analyzed by the Lobene stain index, because it included more

than 10 studies and revealed a symmetric distribution of study sizes around the mean effect size. For the other outcomes, publication bias was not assessable due to the limited number of studies. Caution during interpretation of results is recommended, because approximately 80% of the studies were conducted or sponsored by the manufacturers of the WDs.

The quality of evidence generated was rated based on GRADE criteria[65] for the recommendation of WD compared with RD, paint-on gel, and white strips. The level of evidence for efficacy and adverse effects produced by the WD in comparison with the RD was low and moderate, respectively. Risk of bias and inconsistency was responsible for downgrading evidence of efficacy. The comparison with the paint-on gel generated a low level of evidence for recommendation of the WD, based on a serious risk of bias and imprecision. Compared with the white strips, a moderate level of evidence of efficacy and low level of adverse effects favored the white strips. The risk of bias and inconsistency downgraded the level of evidence for adverse effects. Noteworthy, previous studies called attention to the low-quality evidence base of home-based tooth whitening procedures, highlighting the preponderance of industry-conducted studies.[61,66]

This review presented evidence of a whitening-like effect produced by WDs, taking into consideration all possible outcome measures and follow-up times reported. It confirmed the higher ESR capacity of WDs reported elsewhere[9] and revealed greater adverse effects in comparison to RDs. Finally, it highlights the demand for high-quality, high-sample, independent studies to further improve the quality of the existing evidence.

CONCLUSION

Whitening dentifrices are more effective in reducing extrinsic stain and producing a whitening-like effect in teeth than regular dentifrices. Also, they do produce more adverse effects. The efficacy of the whitening dentifrice does not seem to rely on application time. Both, whitening efficacy and production of adverse effects of whitening dentifrices are similar to most of the other whitening products.

Caution is recommended when interpreting these conclusions, because they are impacted by the low quality of the primary studies, most of which are sponsored by industry. The limited number of studies and limited sample size hinder statistically sound comparisons between whitening dentifrices and other home-based whitening products. High-quality evidence requires larger, well-conducted, independent studies.

Acknowledgements

The authors thank Dr. Stephen Siegel, editor in chief of the *Journal of Clinical Dentistry*, and Daniel Perkins on behalf of AEGIS Communications for retrieval of full-text papers published in the *Journal of Clinical Dentistry* and *Compendium of Continuing Education in Dentistry*. The project was funded by FAPESC Grant 06/2017.

Conflict of Interest

The authors of this manuscript certify that they have no proprietary, financial, or other personal interest of any nature or kind in any product, service, and/or company that is presented in this article.

(Accepted 20 July 2019)

References

1. Clarkson J, Walsh T, & Worthington H (2011) Cochrane reviews on the benefits/risks of fluoride toothpastes *Journal of Dental Research* **90(5)** 573-579.
2. Cury JA & Tenuta LMA (2014) Evidence-based recommendation on toothpaste use *Brazilian Oral Research* **28(Special Issue 1)** 1-7.
3. Barbieri GM, Mota EG, Rodrigues-Junior SA, & Burnett Jr LH (2011) Effect of whitening dentifrices on the surface roughness of commercial composites *Journal of Esthetic and Restorative Dentistry* **23(5)** 338-345.
4. ADA Council on Scientific Affairs (2009) Tooth whitening/bleaching: treatment considerations for dentists and their patients *American Dental Association (Chicago)* 2009(September 2009) 1-12.
5. Demarco FF, Meireles SS, & Masotti AS (2009) Over-the-counter whitening agents: critical assessment of the OTC products for home-use bleaching *Brazilian Oral Research* **23(Special Issue 1)** 64-70.
6. Moran J, Claydon NC, Addy M, & Newcombe R (2005) Clinical studies to determine the effectiveness of a whitening toothpaste at reducing stain (using a forced stain model). *International Journal of Dental Hygiene* **3(1)** 25-30.
7. Joiner A (2010) Whitening toothpastes: a review of the literature *Journal of Dentistry*. **38(Supplement 2)** e17-e24.
8. Horn BA, Bittencourt BF, Maria Mongruel Gomes O, & Farhat PA (2014) Clinical evaluation of the whitening effect of over-the-counter dentifrices on vital teeth *Brazilian Dental Journal* **25(3)** 203-206.
9. Soeteman G, Valkenburg C, Van der Weijden G, Van Loveren C, Bakker E, & Slot DE (2018) Whitening dentifrice and tooth surface discoloration: a systematic review and meta-analysis *International Journal of Dental Hygiene* **16(1)** 24-35.
10. Raoufi S & Birkhed D (2010) Effect of whitening toothpastes on tooth staining using two different colour-

measuring devices: a 12-week clinical trial. *International Dental Journal* **60(6)** 419-423.

11. ADA Council on Scientific Affairs (2012) Acceptance program requirements: Home-use tooth stain removal products. ADA Guidelines *American Dental Association (Chicago)* 2012(April 2012) 1-10.
12. Sreenivasan P, DeVizio W, Prasad KVV, Rajesh G, Kalyanpur R, & Rao CB (2009) Clinical stain removal efficacy of two dentifrices after one and two weeks of use *Journal of Clinical Dentistry* **20(7)** 1-4.
13. Ghassemi A, Vorwerk L, Cirigliano A, Hooper W, Co D, & Nathoo S (2015) Clinical effectiveness evaluation of a new whitening dentifrice *Journal of Clinical Dentistry* **26(3)** 66-71.
14. Higgins J & Green S (2011) *Cochrane Handbook for Systematic Reviews of Interventions*. Version 5.1.0 [updated March 2011]. The Cochrane Collaboration, 2011. Available from www.handbook.cochrane.org.
15. Moher D, Liberati A, Tetzlaff J, & Altman DG (2009) Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement *Journal of Clinical Epidemiology* **62(10)** 1006-1012.
16. Lobene R (1968) Effect of dentifrices on tooth stains with controlled brushing *Journal of the American Dental Association* **77(4)** 849-855.
17. Macpherson LMD, Stephen KW, Joiner A, Schafer F, & Huntington E (2000) Comparison of a conventional and modified tooth stain index *Journal of Clinical Periodontology* **27(11)** 854-859.
18. Shaw L & Murray JJ (1977) A new index for measuring extrinsic stain in clinical trials. *Community Dentistry and Oral Epidemiology* **5(3)** 116-120.
19. Commission Internationale d'Eclairage (2004) CIE technical report: colorimetry. CIE Pub No. 15.3, Vienna, Austria: CIE Central Bureau, 2004.
20. Higgins JPT, Sterne JAC, Savovic J, Page MJ, Hróbjartsson A, Boutron I, Reeves B & Eldridge S (2016) A revised tool for assessing risk of bias in randomized trials In: Chandler J, McKenzie J, Boutron I, Welch V (editors). Cochrane Methods. Cochrane Database of Systematic Reviews Suppl 1(10) 1-21.
21. Borenstein M, Rothstein HR, Hedges LV, & Higgins JP (2009) *Introduction to Meta-Analysis*. John Wiley and Sons, Ltd: West Sussex.
22. Ghassemi A, Hooper W, Vorwerk L, Domke T, DeSciscio P, & Nathoo S (2012) Effectiveness of a new dentifrice with baking soda and peroxide in removing extrinsic stain and whitening teeth *Journal of Clinical Dentistry* **23(3)** 86-91.
23. Review Manager (RevMan) [Computer program]. Version 5.3. Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2014. 43.
24. Guyatt G, Oxman AD, Akl EA, Kunz R, Vist G, Brozek J, Norris S, Falck-Ytter Y, Glasziou P, Debeer H, Jaeschke R, Rind D, Meerpohl J, Dahm P, & Schünemann HJ (2011) GRADE guidelines: 1. Introduction: GRADE evidence profiles and summary of findings tables *Journal of Clinical Epidemiology* **64(4)** 383-394.
25. Koertge TE, Brooks CN, Sarbin AG, Powers D, & Gunsolley JC (1998) A longitudinal comparison of tooth whitening resulting from dentifrice use *Journal of Clinical Dentistry* **9(3)** 67-71.
26. Nathoo S, Mateo LR, Delgado E, Zhang YP, & Devizio W (2011) Extrinsic stain removal efficacy of a new dentifrice containing 0.3% triclosan, 2.0% PVM/MA copolymer, 0.243% NaF and specially-designed silica for sensitivity relief and whitening benefits as compared to a dentifrice containing 0.3% triclosan, 2% PVM/MA *American Journal of Dentistry* **24(Special Issue A)** 28A-31A.
27. Buelo A, Ghassemi A, Vorwerk L, Hooper W, & Nathoo S (2016) Clinical study to determine the stain removal effectiveness of a new dentifrice formulation *Journal of Clinical Dentistry* **27(3)** 80-83.
28. Shao Y, Xue J, Peng C, Li C, Zhang S, & Zhou H (2017) Clinical evaluation of a toothpaste containing lysozyme for removal of extrinsic stains on the tooth surface: an 8-week, double-blind, randomized study *American Journal of Dentistry* **30(3)** 147-150.
29. Young S, Mason S, Milleman JL, & Milleman KR (2017) A randomized clinical study to evaluate the effect of an ultra-low abrasivity dentifrice on extrinsic dental stain *American Journal of Dentistry* **30(5)** 255-261.
30. Ayad F, Arcuri H, Brevilieri E, Laffi S, Lemos AM, Yoshioka M, Baines E, Sheth J, & Devizio W (1999) Efficacy of two dentifrices on removal of natural extrinsic stain *American Journal of Dentistry* **12(4)** 164-166.
31. Gerlach RW, Ramsey LL, & White DJ (2002) Extrinsic stain removal with a sodium hexametaphosphate-containing dentifrice: comparisons to marketed controls *Journal of Clinical Dentistry* **13(1)** 10-14.
32. Collins L, Naeeni M, Schäfer F, Brignoli C, Schiavi A, Roberts J, & Colgan P (2005) The effect of a calcium carbonate/perlite toothpaste on the removal of extrinsic tooth stain in two weeks *International Dental Journal* **55(3)** 179-182.
33. Walsh TF, Rawlinson A, Wildgoose D, Marlow I, Haywood J, & Ward JM (2005) Clinical evaluation of the stain removing ability of a whitening dentifrice and stain controlling system *Journal of Dentistry* **33(5)** 413-418.
34. Li YC, He T, Sun L, Zhang Y, Li X, Wang Y, Zhao S, & Tang RY (2007) Extrinsic stain removal efficacy of a dual-phase dentifrice *American Journal of Dentistry* **20(4)** 227-230.
35. Xie P, Lu J, Wan H, & Hao Y (2010) Effect of toothpaste containing d-limonene on natural extrinsic smoking stain: a 4-week clinical trial *American Journal of Dentistry* **23(4)** 196-200.
36. Sharma N, Galustians J, Qaquish J, Rustogi KN, Petrone ME, Chaknis P, Devizio W, Volpe AR, & Proskin HM (1999) A six-week clinical efficacy study of three commercially available dentifrices for the removal of extrinsic tooth stain *Journal of Clinical Dentistry* **10(3)** 111-114.
37. Yin W, Li X, He S, Ma H, Hu D, Zhang YP, Delgado E, Devizio W, & Mateo LR (2010) Extrinsic stain removal efficacy of a new desensitizing dentifrice containing 8.0% arginine, calcium carbonate and 1450 ppm fluoride

American Journal of Dentistry **23(Special Issue A)** 36A-40A.

38. Yankell SL, Emling RC, Petrone ME, Rustogi K, Volpe AR, & Proskin HM (1999) A six-week clinical efficacy study of four commercially available dentifrices for the removal of extrinsic tooth stain *Journal of Clinical Dentistry* **10(3)** 115-118.
39. Ayad F, Demarchi B, Khalaf A, Petrone ME, Chaknis P, Devizio W, Volpe AR, & Proskin HM (1999) A six-week clinical efficacy study of a new dentifrice for the removal of extrinsic tooth stain *Journal of Clinical Dentistry* **10(3)** 103-106.
40. Mankodi S, Sowinski J, Davies R, Ellwood R, Bradshaw B, Petrone ME, Devizio W, Chaknis P, Volpe AR, & Proskin HM (1999) A six-week clinical efficacy study of a tooth whitening tartar control dentifrice for the removal of extrinsic tooth stain *Journal of Clinical Dentistry* **10(3)** 99-102.
41. Ayad F, Demarchi B, Khalaf A, Davies R, Ellwood R, Bradshaw B, Petrone ME, Chaknis P, Devizio W, Volpe AR, & Proskin HM (2000) A six-week clinical tooth whitening study of a new calculus-inhibiting dentifrice formulation *Journal of Clinical Dentistry* **11(3)** 84-87.
42. Ayad F, Khalaf A, Chaknis P, Petrone ME, DeVizio W, Volpe AR, & Proskin HM (2002) Clinical efficacy of a new tooth whitening dentifrice *Journal of Clinical Dentistry* **13(2)** 82-85.
43. Nathoo S, Petrone ME, DeVizio W, Chaknis P, & Volpe A (2002) A six-week clinical study to compare the stain removal efficacy of three dentifrices *Journal of Clinical Dentistry* **13(2)** 91-94.
44. Singh S, Mankodi S, Chaknis P, Petrone ME, DeVizio W, Volpe AR, & Proskin HM (2002) The clinical efficacy of a new tooth whitening dentifrice formulation: a six-month study in adults *Journal of Clinical Dentistry* **13(2)** 86-90.
45. Sielski C, Berta RL, Petrone ME, Chaknis P, DeVizio W, Volpe AR, & Proskin HM (2002) A study to assess the tooth whitening efficacy of a new dentifrice formulation variant containing a special grade of silica: a six-week study on adults *Journal of Clinical Dentistry* **13(2)** 77-81.
46. Matheson J, Cox T, Baylor N, Joiner A, Patil R, Karad V, Ketkar V, & Bijlani N (2004) Effect of toothpaste with natural calcium carbonate/perlite on extrinsic tooth stain *International Dental Journal* **54(5)** 321-325.
47. Nathoo S, Singh S, Petrone DM, Wachs GN, Chaknis P, DeVizio W, & Proskin HM (2008) Clinical studies to assess the extrinsic stain prevention and stain removal efficacy of a variant of a commercially available dentifrice containing a new dual silica system *Journal of Clinical Dentistry* **19(3)** 95-101.
48. Prasad KVV, Sreenivasan PK, Rajesh G, Ramya K, Bhasker Rao C, & de Vizio W (2011) The efficacy of dentifrices on extrinsic tooth stains among community dwelling adults in India: a randomised controlled trial *Community Dental Health* **28** 201-205.
49. Ghassemi A, Vonverk L, Hooper W, Cirigliano A, De Sciscio P, & Nathoo S (2015) Extrinsic stain removal effectiveness of a new whitening dentifrice *Journal of Clinical Dentistry* **26(3)** 72-75.
50. Kakar A, Rustogi K, Petrone ME, Yun PZ, DeVizio W, & Proskin HM (2004) A clinical investigation of the tooth whitening efficacy of a new hydrogen peroxide-containing dentifrice *Journal of Clinical Dentistry* **15(2)** 41-45.
51. Pintado-Palomino K, Vasconcelos CVM, da Silva RJ, de Fressatti AL, da Motta BJG, de Pires-de-Souza FCP, & Tirapelli C (2016) Effect of whitening dentifrices: a double-blind randomized controlled trial *Brazilian Oral Research* **30(1)** e82.
52. Volpe AR, Mooney R, Zumbrunnen C, Stahl D, & Goldman HM (1975) A long term clinical study evaluating the effect of two dentifrices on oral tissues *Journal of Periodontology* **46(2)** 113-118.
53. Isaacs RL, Bartizek RD, Owens TS, Walters PA, & Gerlach RW (2001) Maintenance of tooth color after prophylaxis: comparison of three dentifrices *Journal of Clinical Dentistry* **12(2)** 51-55.
54. Gerlach RW & White DJ (2001) Removal of extrinsic stain using a tartar control whitening dentifrice: a randomized clinical trial *Journal of Clinical Dentistry* **12(2)** 42-46.
55. Gerlach RW, Liu H, Prater ME, Ramsey LL, & White DJ (2002) Removal of extrinsic stain using a 7.0% sodium hexametaphosphate dentifrice: a randomized clinical trial *Journal of Clinical Dentistry* **13(1)** 6-9.
56. Young S, Parkinson C, Hall C, Wang N, Milleman JL, & Milleman KR (2015) A randomized clinical study investigating the stain-removal potential of two experimental dentifrices *Journal of Clinical Dentistry* **26(4)** 96-103.
57. Gerlach RW, & Barker ML (2003) Clinical response of three direct-to-consumer whitening products: strips, paint-on gel, and dentifrice *Compendium of Continuing Education in Dentistry* **24(6)** 458-466.
58. Gerlach RW, Barker ML, & Tucker HL (2004) Clinical response of three whitening products having different peroxide delivery: comparison of tray, paint-on gel, and dentifrice *Journal of Clinical Dentistry* **15(4)** 112-117.
59. Yudhira R, Peumans M, Barker ML, & Gerlach RW (2007) Clinical trial of tooth whitening with 6% hydrogen peroxide whitening strips and two whitening dentifrices *American Journal of Dentistry* **20(Special Issue A)** 32A-36A.
60. Volpe AR, Petrone ME, DeVizio W, Emling RC, & Yankell SL (1999) A new perspective on the methodology for clinical efficacy evaluations of tooth whitening dentifrices *Journal of Clinical Dentistry* **10(Special No. 3)** 95-98.
61. Serraglio CR, Zanella L, Dalla-Vecchia KB, & Rodrigues-Junior SA (2016) Efficacy and safety of over-the-counter whitening strips as compared to home-whitening with 10 % carbamide peroxide gel: systematic review of RCTs and metanalysis *Clinical Oral Investigations* **20(1)** 1-14.
62. Da Costa J, Adams-Belusko A, Riley K, & Ferracane JL (2010) The effect of various dentifrices on surface roughness and gloss of resin composites *Journal of Dentistry* **38(Supplement 2)** e123-e128.
63. Kwon SR & Wertz PW (2015) Review of the mechanism of tooth whitening *Journal of Esthetic and Restorative Dentistry* **27(5)** 240-257.

64. Coleman BG, Johnson TM, Erley KJ, Topolski R, Rethman M, & Lancaster DD (2016) Preparing dental students and residents to overcome internal and external barriers to evidence-based practice *Journal of Dental Education* **80(10)** 1161-1169.

65. Guyatt G, Oxman AD, Akl EA, Kunz R, Vist G, Brozek J, Norris S, Falck-ytter Y, Glasziou P, & Jaeschke R (2011) GRADE guidelines: 1. Introduction GRADE evidence profiles and summary of findings tables *Journal of Clinical Epidemiology* **64(4)** 383-394.

66. Hasson H, Ismail AI, & Neiva G (2007) Home-based chemically-induced whitening of teeth in adults *Cochrane Database of Systematic Reviews* **52(1)** 71-72.