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Vital Bleaching with Whitening Strips: Summary of Clinical Research on Effectiveness and Tolerability

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Abstract

Rapid innovation in vital bleaching has increased the popularity of tooth whitening among dental professionals and patients. A broad range of peroxide-based treatments are currently available including those that are professionally-administered (in-office), professionally-dispensed (custom-tray-based systems), and self-directed (over-the-counter). Recently, a novel, flexible polyethylene bleaching strip was introduced that delivers a hydrogen peroxide bleaching gel to the anterior dentition. This "trayless" system, available in professional-strength and over-the-counter versions, reportedly offers advantages with respect to overall peroxide dose, contact time, and ease-of-use compared to other delivery systems. This paper reviews the relevant published clinical research on whitening strips tested among a broad range of patients commonly encountered in contemporary dental practices.

Keywords: Tooth whitening, tooth bleaching, whitestrips, polyethylene bleaching strip, trayless toothbleaching, peroxide dose, carbamide peroxide, hydrogen peroxide

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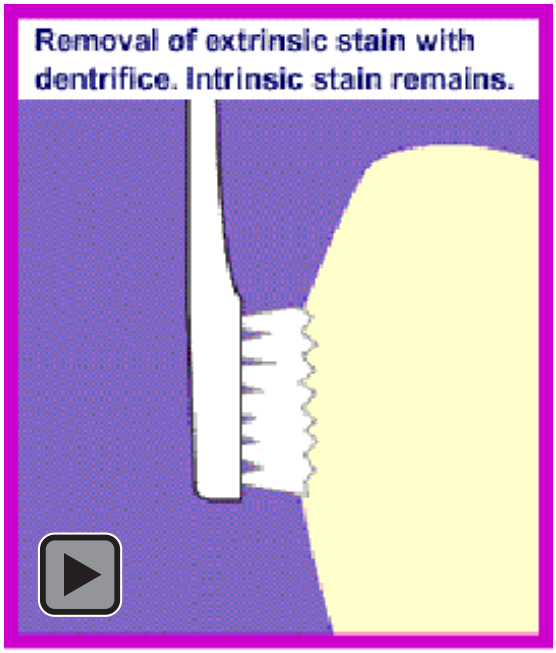


Introduction

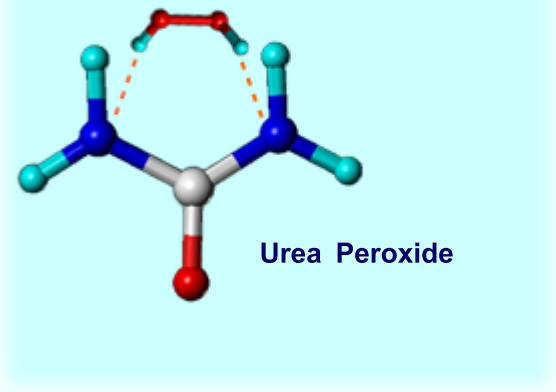
Tooth discoloration has a multi-causal etiology resulting from behaviors, disease, injury, and a host of other exposures along with various physiological processes.[1] Superficial discoloration due to extrinsic stain buildup is typically managed through some combination of in-office treatment (dental prophylaxis) and home care (as with the recent popularity of the whitening dentifrices).[2] Deeper, intrinsic discoloration, such as with the yellowing that occurs as teeth age, can often be ameliorated only via esthetic or restorative care.

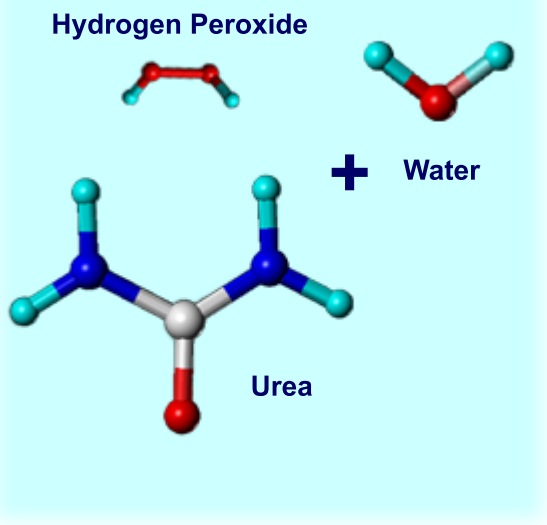
The most common treatment for intrinsic discoloration is bleaching with peroxide. Because of its antimicrobial activity, peroxide has been used extensively in dentistry to treat various oral conditions.[3] Use of peroxide in vital bleaching gained popularity after development of the at-home vital bleaching systems in the late 1980s.[4] Subsequent research demonstrating the safety and efficacy of these agents, along with expanding treatment indications, contributed to explosive growth in vital bleaching with peroxide.[5,6]

Vital bleaching systems may be classified into three categories based upon usage. Treatment may be professionally-administered (in-office care), professionally-dispensed (as with the popular at-home systems), or self-directed (using the various direct-to-consumer bleaching products). Of these, the at-home, custom-tray-based systems represent one of the best-described approaches for whitening in the dental literature. Trade publications describe at least 16 different suppliers of at-home, tray-based bleaching systems.[7] Many of these systems have variants with differing peroxide concentrations, flavors, desensitizing agents, or other modifications.

Other options for home-use include the numerous, marketed self-directed bleaching systems which have been available for some time.[8] Delivery is via a standard, "one-size fits all" mouthguard or preformed tray that carries self-dispensed bleaching gel to the tooth surfaces. Occasionally, these self-directed bleaching systems include specific toothpastes or rinses as part of the regimen.

Most bleaching systems use either hydrogen peroxide or carbamide peroxide (or more recently, both in combination). The chemistry is similar, since carbamide peroxide, or urea peroxide, degrades into urea and hydrogen peroxide in the





presence of water. By weight, carbamide peroxide contains 33% hydrogen peroxide, so a bleaching gel with 10% carbamide peroxide contains a similar level of active as one containing 3.3% hydrogen peroxide.

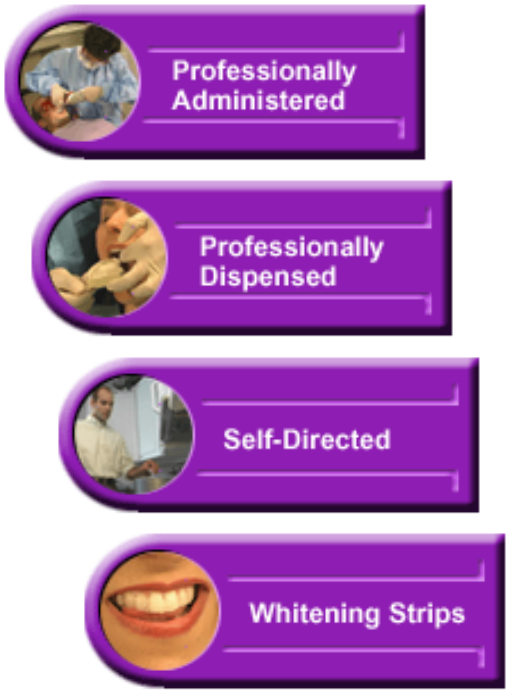
Other factors being equal, higher concentration systems are generally reported as delivering faster, though not necessarily better, whitening.[9] However, response may be impacted by formulation issues that affect peroxide kinetics and its availability at the tooth surface as well as local conditions relating to salivary washout, enzymatic degradation, and others. Increasing concentration is not the only approach to increase whitening. Various agents, especially heat and light, have been used to increase whitening, ostensibly by accelerating peroxide diffusion.[10,11] Other forms of activation have been reported which include use of citric acid in the gel or in a pre-rinse to increase acidity. Whether these function as accelerators or etching agents is unclear, since the latter may contribute to transient whitening. Nonetheless, acidic formulations may pose a significant risk with respect to hard tissue integrity, and there are case reports linking such systems to irreversible hard tissue damage.[12]

Tooth sensitivity and gingival irritation are widely recognized as the most common side effects, with up to two-thirds of individuals affected sometime during the period of active bleaching.[13] These events are typically mild in severity, transient in nature, and often resolve during active treatment.[14] While these effects have been reported for virtually all delivery systems and concentrations, professionally-administered, in-office treatments may have increased tooth sensitivity.[15] The etiology is complex, since tray insertion alone is reported to contribute to some sensitivity.[16] Some systems use fluoride or potassium nitrate alone or in combination in whitening gels, and recent clinical observations suggest that some patients may obtain some degree of pain relief following supplemental treatment of this nature.[17]

While most treatments are short-term, there is a growing body of clinical evidence supporting chronic bleaching regimens. Typically, these are conducted in populations having severe dental staining, especially that attributable to early tetracycline exposure where extended treatment may be necessary to secure a reasonable outcome. Recent clinical research demonstrates significant color improvement and acceptable tolerability following daily bleaching with 10-20% carbamide peroxide gels over a period of several months.[18,19]

Vital bleaching is undergoing rapid change. Some of the changes challenge the basic precepts of the 1980-90s research. The past months have been characterized by rapid innovation in vital bleaching, especially with the advent of new in-office options for immediate care and the emerging popularity of the direct-to-consumer systems. Such is the case with the recently

developed whitening strip – a novel bleaching system that uses a flexible polyethylene strip to deliver a hydrogen peroxide bleaching gel to the anterior dentition.[20] This "trayless" delivery system is reported to offer advantages with respect to overall peroxide dose, contact time, and ease-of-use compared to other delivery systems.[21] The wearing regimen for bleaching strips and other key treatment systems is shown in the corresponding video vignettes which may



serve as educational tools for patient counseling. Ever expanding popularity of bleaching for both dentists and patients, new options for care, glamorous case studies, new (and more egregious) benefits, claims and advertising – what does it all mean for the dental professional? What information is relevant? What are the implications? This paper reviews the relevant published clinical research on one system – whitening strips – with specific reference to its implications with respect to contemporary dental practice.

Methods and Materials

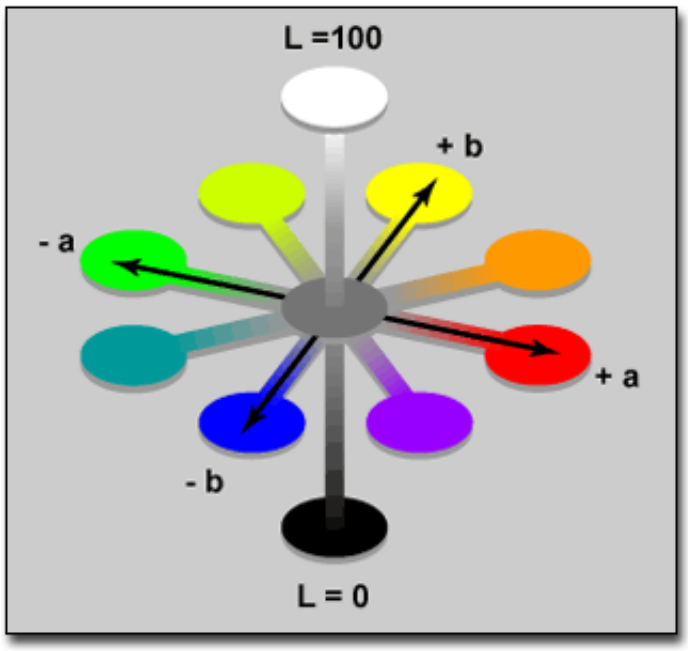
This is an integrated summary of published clinical research on vital bleaching with whitening strips. The summary includes peer-reviewed manuscripts and reviewed and published abstracts from the major dental research meetings since the introduction of whitening strips in mid-year 2000.

There are two strip-based systems described in the literature and currently marketed (Crest Whitestrips™ and Crest Professional Whitestrips™, The Procter & Gamble Company, Cincinnati, OH, USA).

Both of these whitening systems use a flexible, polyethylene strip that is coated with an adhesive hydrogen peroxide bleaching gel. The strips carry 150-200 milligrams of whitening gel distributed uniformly across the strip surface. (Strip size and surface area varies based on arch form, hence the differences in total dose.) The hydrogen peroxide concentration on whitening strips has ranged from 5.3% up to 6.5% in the professionally-dispensed system. Wearing time has been for 30 minutes twice daily for 14 days or longer. The published clinical research has compared whitening strips to various positive and negative controls. Some research used true-placebo strips for comparison, which may be particularly relevant because of the degree of blinding it affords. The published research also includes a variety of marketed bleaching controls, ranging in concentration from 10-20% carbamide peroxide, and others, under varying usage conditions depending on the control.

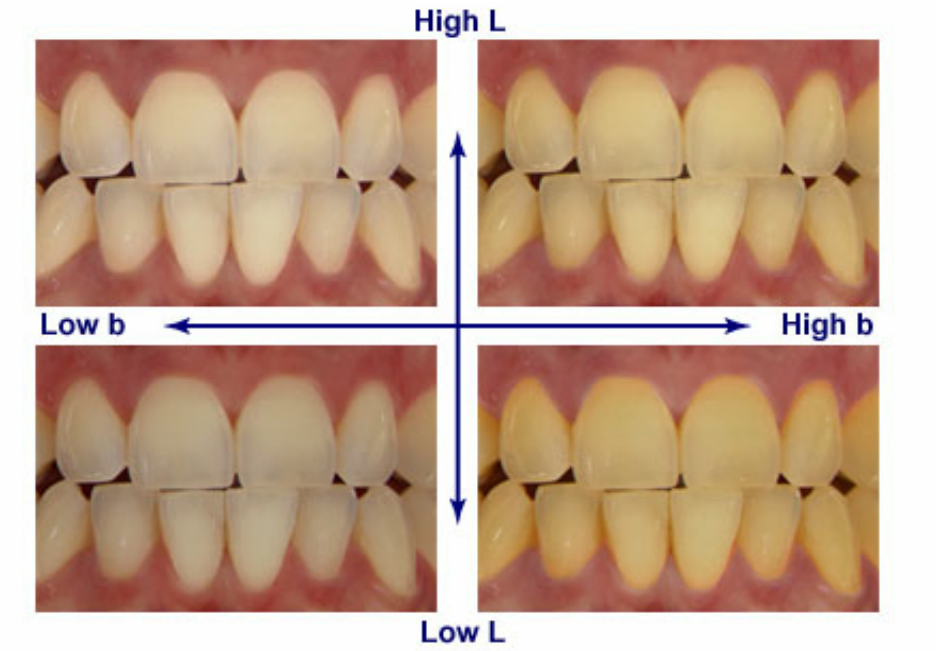
Efficacy and safety outcomes were both reported in the published whitening strip research. Two

effectiveness measures were used. Most often, tooth color was measured objectively from standardized digital images of the anterior dentition that were captured using a high resolution digital camera and motorized zoom lens under standard polarized lighting conditions. The imaged data were transformed to derive numerical values for tooth color in terms of L*a*b*, an international standard for measuring three-dimensional color space.[23] With this method, whitening benefit was defined as decreased b* (reduction in yellow), increased L* (increased lightness), and decreased a* (reduction in redness). In addition, some studies measured whitening subjectively with value-oriented tooth shade tabs (Vita® Zahnfabrik, Vident™, Brea, CA, USA) that have been commonly used in restorative and prosthetic dentistry. Effectiveness was determined, after assigning a numerical shade score ranging from 1-16 based on the sequence recommended by the manufacturer. Tolerability was assessed from oral examination and subject report, as well as clinical examination.



L*a*b* Color Model

This integrated summary pools data from published clinical trials on whitening strip effectiveness to determine absolute effectiveness and to understand factors that influence clinical response. Whitening change from baseline measured by shade or color (L*, a*, b*, and E*) was assessed at day 14 for the twice-daily whitening strip group only (a common regimen across trials) using two sample T-tests. Relationships between age, baseline color, gender, behavioral factors, and treatment on the day 14 whitening strip response were explored using analysis of covariance. All statistical tests were performed at a 0.05 level of significance.



L*b* color as applied to teeth. Colors digitally manipulated to illustrate L*b* values.

Table 1
Summary of Published Clinical Research on Whitening Strips

Reference	Color Endpoint	Target Population Entrance Criteria	N	Whitening Strips Concentration and Regimen	Controls	Duration (Days)
Part 1. Effectiveness Studies Using Whitening Strips						
25,26	Shade	Adults Shade A2+	70	5.3% H_2O_2 Strips 30 minutes BID for 14 days	Placebo strips	14
27	Color ($L^*a^*b^*$)	Adults	36	5.3% H_2O_2 Strips 30 minutes BID for 14 days	10% CP tray 2 hours 15% CP tray 2 hours 20% CP tray 2 hours	14
28	Shade	Adults Shade A3+	36	5.3% H_2O_2 Strips 30 minutes BID for 14 days	10% CP tray overnight 20% CP tray overnight	21
29	Color ($L^*a^*b^*$)	Adults	50	5.3% H_2O_2 Strips 30 minutes BID for 14 days Regular dentifrice	Placebo + whitening dentifrice	49
30	Color ($L^*a^*b^*$)	Adults	20	6.5% H_2O_2 Strips 30 minutes BID for 14 days	10% CP tray 2 hours	14
Part 2. Studies on Factors Affecting Clinical Response with Whitening Strips						
31	Shade	Adults Shade A2+	93	5.3% H_2O_2 Strips 30 minutes BID for 14 days 5.3% H_2O_2 Strips 30 minutes BID for 28 days	Placebo (14 day) Placebo (28 day)	180
32	Color ($L^*a^*b^*$)	Adults	41	5.3% H_2O_2 Strips 30 minutes BID for 14 days	Prebrushing with regular dentifrice No prebrushing	14
33	Color ($L^*a^*b^*$)	Adults	22	5.3% H_2O_2 Strips 30 minutes BID for 14 days 6.5% H_2O_2 Strips 30 minutes BID for 14 days		14
34	Color ($L^*a^*b^*$)	Adults	27	5.3% H_2O_2 Strips 30 minutes BID for 14 days 5.3% H_2O_2 Strips 30 minutes QD for 14 days		180
35	Color ($L^*a^*b^*$)	Adults	36	5.3% H_2O_2 Strips 30 minutes BID for 14 days 6.5% H_2O_2 Strips 30 minutes BID for 14 days	Prebrushing with regular dentifrice No prebrushing	14
Part 3. Use of Whitening Strips in Special Populations						
36	Color ($L^*a^*b^*$)	Children10-18 Post-orthdontia	30	5.3% H_2O_2 Strips 30 minutes BID for 14 days	10% CP tray overnight	56
37	Color ($L^*a^*b^*$)	Children 11-18	106	6.5% H_2O_2 Strips 30 minutes BID for 14 days	10% CP tray overnight	56
38	Shade	Adult Tetracycline	40	6.5% H_2O_2 Strips 30 minutes BID for 14 days	10% CP tray 2 hours	180

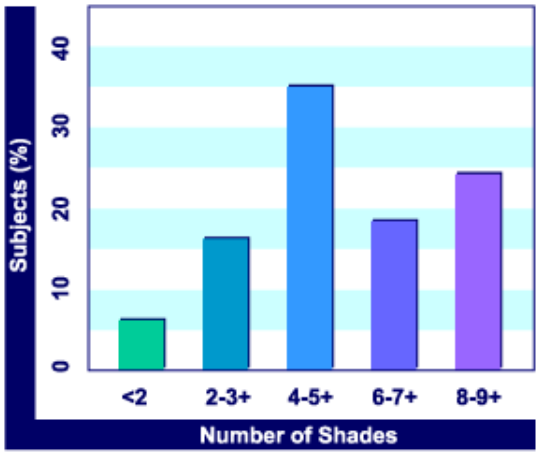
Results

Use of whitening strips for vital bleaching was first reported by case study in mid-year 2000.24 Subsequently, there have been a total of 7 peer reviewed clinical studies and 7 published abstracts involving whitening strips of different concentrations or treatment regimens. Table 1 summarizes this research involving over 600 subjects.

This research focused on 3 different areas: effectiveness, factors that influence clinical response, and use in "so-called" special populations or special settings. Four of these trials used tooth shade and nine used tooth color to measure effectiveness. The population exhibited considerable diversity with respect to age, with study subjects ranging from 10-74 years. (Table 2) Because two of the 9 color trials targeted children, the mean age for those studies was much lower than the four shade trials (27 years versus 40 years).

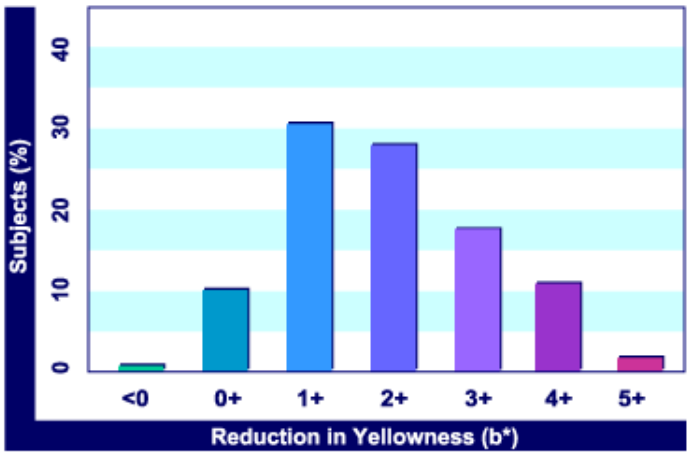
In the pooled sample, use of whitening strips for 30 minutes twice daily resulted in a mean shade change of 5.5 units, which differed significantly from baseline ($p < 0.0001$). There was a considerable range in response, with approximately 24% of individuals averaging over 8.0 shades improvement. (Figure 1) Similar results were observed for tooth color where use of whitening strips for 30 minutes twice daily resulted in a mean Δb^* and ΔL^* of -2.4 and 2.0, respectively. This represented highly statistically significant ($p < 0.0001$) improvements in tooth color including reductions in yellowness and increased lightness. Approximately 13% of subjects had more than a 4.0 unit reduction in yellowness with only two weeks treatment. (Figure 2)

Table 2 Summary of Demographic and Behavioral Parameters and Beginning Tooth Color/Shade		
Parameter	Effectiveness Measure	
	Tooth Shade (4 Trials)	Tooth Color (9 Trials)
Sample Size	239	368
Demographic Parameters		
Age (Years)		
Mean (SD)	40.0 (11.5)	27.0 (12.2)
Range	18-74	10-61
Gender		
Female	59.3%	61.5%
Ethnicity		
Non-White	11.6%	30.2%
Behavioral Parameters[a]		
Tobacco Use	15.0%	4.7%
Coffee/Tea/Cola Consumption	95.0%	58.5%
Baseline Color/Shade		
Mean Shade (SD)	10.3 (3.0)	
Mean Color (SD)		
L* (lightness)		76.0 (2.4)
a* (Red-green)		8.0 (1.3)
b* (blue-yellow)		17.6 (1.9)



Distribution of Mean Shade Improvement
Twice-Daily Use of Whitening Strips for 14 days
4 Randomized Clinical Trials

Figure 1



Distribution of Mean Color Improvement (Δb*)
Twice-Daily Use of Whitening Strips for 14 Days
9 Randomized Clinical Trials

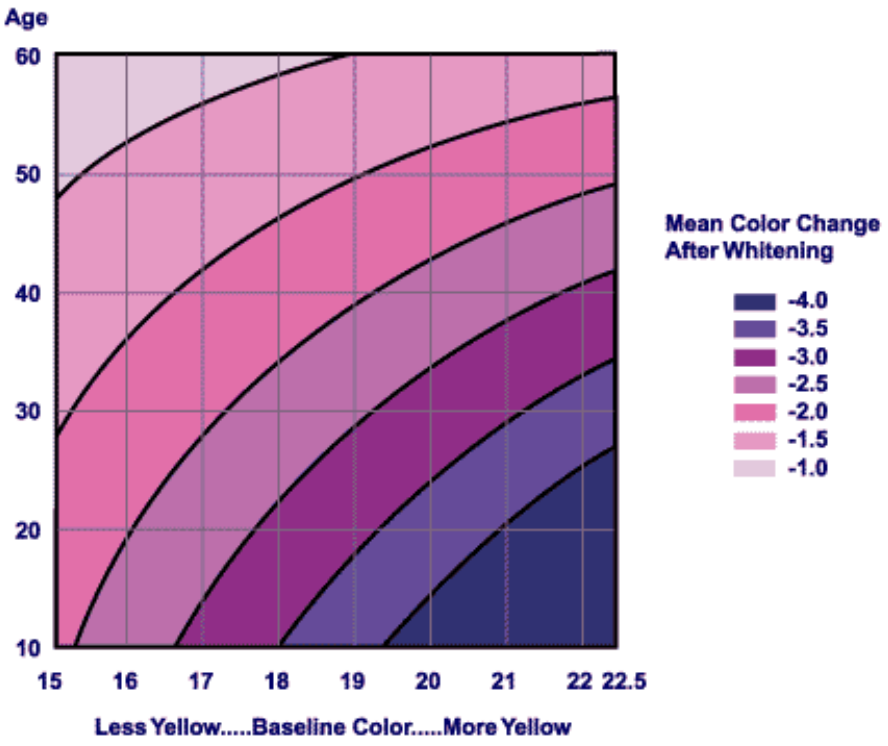
Figure 2

Table 3
Effect of Age or Starting Color on Whitening Response (Δb*)Adjusted for Treatment Only

Effect	Estimate	Standard Error	p-Value
Age (years)	0.0326	0.0069	< 0.0001
Starting Color (b*)	-0.1858	0.0397	< 0.0001
Gender (F-M)	0.2079	0.1565	0.1856
Coffee/tea (Yes-No)	0.2172	0.1719	0.2086

The various demographic, behavioral, and clinical parameters were evaluated to determine significant contributors to the primary response variable, reduction in yellowness (Δb*). Only age, baseline color, and treatment were significant effects in the model. (Tobacco use was excluded from the analysis due to the small number of positive responses.) In general, the magnitude of the whitening response decreased with age. The pooled data suggested that, on average, for every 10 years of aging individuals should expect approximately 0.3 units less whitening benefit. Baseline color affected response as well with the greatest average whitening occurring seen in individuals with more yellow teeth. (Table 3) Importantly, there was a significant (p=0.04) age by baseline interaction effect on Δb*. The relationship between age and starting color and the magnitude of the whitening response is illustrated using a contour plot. (Figure 3) Given age and starting color, the plot predicts the average whitening response. The pooled data on whitening strips demonstrate that the whitening response would be similar between a 21-year old with a starting b* of approximately 16.0 (less yellow) and a 40-year old with a starting b* of about 19.0 (more yellow).

Figure 3.



Gender

Bleaching treatment should not require modification based on gender. Clinical data indicates that males and females experience a similar whitening response, other factors considered equal.

Coffee/Tea Consumption

Bleaching treatment should not require modification based on coffee/tea consumption. Based on clinical results, coffee/tea drinkers and non-drinkers experience a similar whitening benefit, other factors considered equal. (Note: coffee/tea drinkers may require a different post-bleaching maintenance plan since coffee/tea can promote extrinsic stain.)

Initial Tooth Color

Bleaching time may need to be adjusted based on initial tooth color. Clinical results indicate more yellow teeth show a greater magnitude of response.

Age

Bleaching time may need to be adjusted based on age. Clinical data indicates that younger patients show a greater magnitude of response.

Age and Initial Tooth Color

Bleaching schedule may need to be adjusted based on age and initial tooth color. Younger patients with more yellow teeth show the greatest whitening benefit. Older patients with less yellow initial tooth color show the smallest response. Set appropriate expectations.

Factors Affecting Tooth Color and their Implications

The overall adverse event profile showed tooth sensitivity and oral irritation to be the most common side effects associated with whitening strip use. This response was highly variable, depending on the treatment. In virtually all instances, the response was minor and transient and did not contribute to treatment interruption. Across all published research, there were only 3 dropouts "for cause" – that is – individuals who discontinued treatment due to whitening strip-related tooth sensitivity or oral irritation.

Discussion

Unlike most self-directed systems and many of the professionally-administered or dispensed systems, whitening strips have been evaluated and reported in a series of controlled clinical trials. Evidence of the safe and efficacious use of the strip bleaching systems has been established in a series of randomized clinical trials relative to placebo,[26,31] professionally-administered bleaching systems,[27,28,30,36-38] and whitening dentifrices[29] in studies involving different populations and time points. Related research has demonstrated similarities between participants in multiple whitening strips clinical trials and the general population.[39,40] This assures the response seen in the whitening strips clinical trials carries the broadest possible inference to the general population.

These whitening strip studies confirm previous reports of the relationship between concentration and effectiveness. For both strip and tray systems, increasing peroxide concentration was observed to improve whitening response.[27,28,35] Other studies examined the effect of extending treatment duration. In these studies, twice daily treatment with whitening strips over a 28-day period resulted in up to 29% additional whitening versus 14-day treatment[31,36,37] In addition, one study evaluated whitening strip usage over a longer period. This study of patients with tetracycline staining compared twice daily use of 6.5% whitening strips to two hour daily use of a 10% carbamide peroxide gel in a custom bleaching tray.[38] After two months continuous use, both treatments were effective averaging a 4-6.5

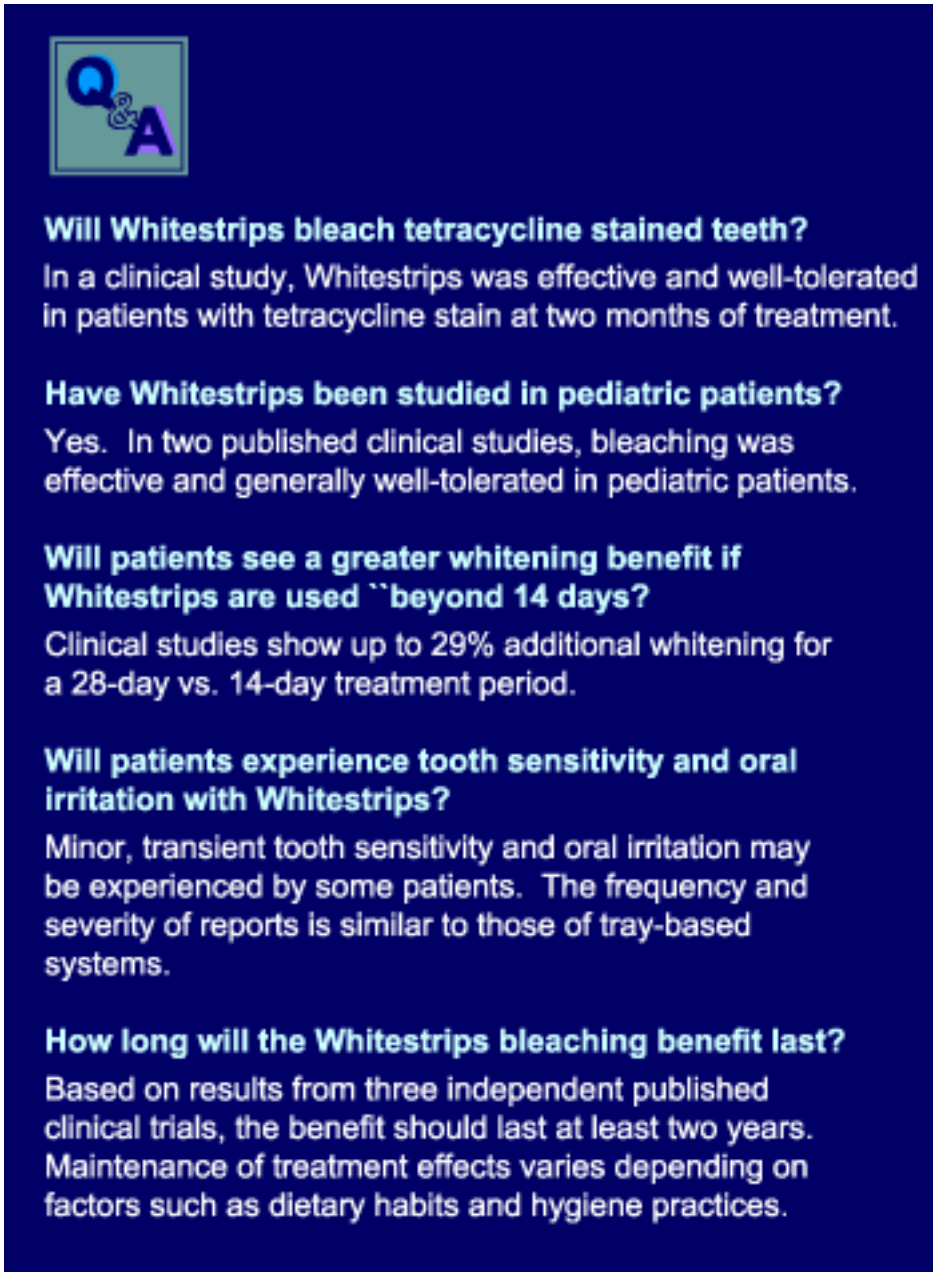
Whitening strips use on tetracycline staining. Only the maxillary arch was treated. (Courtesy of Dr. Gerard Kugel).

shade improvement. Response in the whitening strip group was superior to the active control at both the one and two month time points. While it may take several months of treatment, clinical response in this population can be impressive.

In this tetracycline stain study, twice-daily use of the 6.5% hydrogen peroxide whitening strips was well-tolerated over the two month treatment period. The principal side effects were transient tooth sensitivity and gingival irritation, which was generally similar in nature and severity to those reported in other long-term use trials involving tray-based bleaching systems.[18] After 60 hours of treatment over a 2 month period, no subject in the strip group discontinued due to an adverse event. This long-term, daily treatment of tetracycline stain corroborates and expands the safety of strip-based tooth whitening as reported in earlier, shorter duration clinical trials.[25,27] Chronic dosing studies of this nature represent a "torture test" of sorts compared to conventional 2-4 week treatment regimens, and as such, have been identified as providing an additional level of assurance of the safety of shorter-term vital bleaching with peroxide.[41]

While tetracycline stain represented one "special" population for bleaching, two studies examined response in another specialized application – vital bleaching in children.[36,37] A total of 136 teens and preteens with discolored teeth participated in the two independent trials that compared one-hour daily use of whitening strips to overnight use of a 10% carbamide peroxide tray system. One study targeted post-orthodontic patients. The studies demonstrated highly significant color improvements for both systems. Response was generally

Whitening strips use on teenagers with intrinsic staining. Only the maxillary arch was treated. (Courtesy of Dr. Kevin Donly).



similar except for the non-orthodontically treated patients where the 224-hour tray regimen yielded a 29% improvement in the mandibular teeth relative to the 28-hour strip regimen, perhaps attributable to pre-existing malocclusion. In both studies, bleaching was generally well tolerated and none of the preteens or teens discontinued treatment early due to adverse events. The authors concluded that this research demonstrated tooth whitening in teens may be safely accomplished using the short contact time, hydrogen peroxide bleaching strips, or overnight carbamide peroxide tray systems tested in this study. Color improvement was readily visible in most cases.

Three of the published studies evaluated the duration of the whitening after bleaching.[26,31,34] These independent studies, which used different measurement methods (shade and color), reported sustained whitening over a 6-month post-treatment monitoring period. All three studies reported some post-treatment reduction in benefit of approximately 14% for color and 8-42% for shade depending on the treatment regimen and population. In one shorter-term comparative trial, shade retention benefits were similar or better with strip treatment compared to 10% or 20% carbamide peroxide controls.[28] Overall, the treatment effects were estimated to persist at least two years.34.

The research provides important perspective on predicting clinical response. The findings confirm the widely held presumption that darker, more yellow teeth respond better to bleaching. However, new findings from the integrated whitening strip research demonstrate the whitening response is better in younger individuals. The amount of secondary dentin, hard tissue permeability, and other factors may contribute to this observation. In addition, this integrated research demonstrates a significant interaction between age and starting color that influences ultimate response. Accordingly, younger individuals with darker teeth will, on average, see a better clinical response than older individuals.

Importantly, this research shows vital bleaching to be well-tolerated overall, whether using whitening strips or the specific tray-based systems tested in this research. At any of the concentrations tested, the most prominent side effects with either delivery system (strip or tray) were transient tooth sensitivity and minor oral irritation. Two factors contribute to tolerability. The research demonstrates the relationship between peroxide concentration and tolerability.[27] Two studies describes a new factor – pre-bleaching tooth brushing – as contributing to tolerability, especially oral irritation.[32,35] Nonetheless, most reports were minor. In the 13 clinical studies, only 1% of subjects who used whitening strips discontinued treatment early because of tooth sensitivity or oral irritation.

This research demonstrates whitening strip effectiveness across a broad range of populations, formulations, and usage conditions. Outcomes were demonstrated using differing measurement methods at various time points during and after treatment, indicating a robust treatment effect. The majority of studies used a single common method – digital image analysis – to measure effectiveness. Such methods, which assess three-direction (dimension) color space, have been reported to be more objective and linear, and as such, are preferred for clinical trials research.[42] Use of common, and more importantly, consistent methods allows for the pooled comparisons reported herein. However, all color-based measurements are not equal, so care must be taken when comparing outcomes from these trials that used more conservative digital image methods versus other color systems.

The summary is limited to published reports on the clinical response following use of whitening strips and does not include published research relating to other preclinical research relating to enamel and dentin safety, microbiology, or others. In total, the whitening strip clinical research program represents one of our group's most comprehensive undertakings to date. The 13 unique clinical studies already published during the first year of introduction represent less than one-third of already completed clinical research. Other studies, including studies already accepted for publication, will no doubt add further to the literature on vital bleaching.

Conclusion

With the development of bleaching strips, patients and professionals now have a fourth category of whitening treatments from which to choose. Dental professionals may recommend this system to a broad range of patients, including special population groups, with the assurance that its efficacy and safety is supported by a robust clinical program. Response to bleaching should not be affected by gender or coffee/tea consumption. Patients with yellow teeth, particularly younger patients, generally show the greatest whitening benefit. The convenience of the strips system allows patients to bleach during daily activities, thus increasing the potential for compliance, successful outcomes, and patient satisfaction. Bleaching strips also serve to heighten patient awareness of oral health, thereby providing a point-of-entry for professionally administered cosmetic and therapeutic dental procedures.

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