Nonfluoride caries–preventive agents

Executive summary of evidence–based clinical recommendations

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Because of its high prevalence,[1] dental caries is the focus of many interventions targeted toward prevention and control. The use of fluoridated toothpastes,[2] other topically applied fluorides,[3] fluoridated municipal water[4] and pit-and-fissure sealants,[5-7] along with dietary improvement, remain mainstays of caries management. These modalities, which are based on high-quality evidence, are the first choice for prevention and control of dental caries.

Nonfluoride agents may serve as adjunctive therapeutics for preventing, arresting or even reversing dental caries. This article presents a summary of the evidence-based clinical recommendations developed by a multidisciplinary panel of experts convened by the American Dental Association (ADA) Council on Scientific Affairs (CSA). The report addresses nonfluoride caries-preventive agents including sucrose-free polyol chewing gums, xylitol dentifrices, chlorhexidine, chlorhexidine in combination with

ABSTRACT

Background. In this article, the authors present evidence-based clinical recommendations regarding the use of nonfluoride caries-preventive agents. The recommendations were developed by an expert panel convened by the American Dental Association (ADA) Council on Scientific Affairs. The panel addressed several questions regarding the efficacy of nonfluoride agents in reducing the incidence of caries and arresting or reversing the progression of caries.

Types of Studies Reviewed. A panel of experts convened by the ADA Council on Scientific Affairs, in collaboration with ADA Division of Science staff, conducted a MEDLINE search to identify all randomized and nonrandomized clinical studies regarding the use of nonfluoride caries-preventive agents.

Results. The panel reviewed evidence from 50 randomized controlled trials and 15 nonrandomized studies to assess the efficacy of various nonfluoride caries-preventive agents.

Clinical Implications. The panel concluded that certain nonfluoride agents may provide some benefit as adjunctive therapies in children and adults at higher risk of developing caries. These recommendations are presented as a resource for dentists to consider in the clinical decision-making process. As part of the evidence-based approach to care, these clinical recommendations should be integrated with the practitioner's professional judgment and the patient's needs and preferences. (The full report can be accessed at "http://ebd.ada.org/ClinicalRecommendations.aspx".)

Key Words. Caries; xylitol; chlorhexidine; acidulated phosphate fluoride; evidence-based dentistry; clinical recommendations.

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TABLE 1

Definitions for levels of certainty.*

LEVEL OF CERTAINTY	DEFINITION
High	Strongly established by the best available evidence; conclusion is unlikely to be strongly affected by the results of future studies
Moderate	Based on preliminary determination from the current best available evidence; as more information becomes available, the magnitude or direction of the observed effect could change, and this change may be large enough to alter the conclusion
Low	Available evidence is insufficient to support the statement; more information may allow a reliable estimation of effects

* For more details, visit "http://ebd.ada.org/contentdocs/FINAL_2011_Revised__ADA_Clinical_Recommendations_Handbook.pdf".

thymol, calcium-containing agents, phosphate-containing agents, casein derivatives, sialogogues, iodine and triclosan. (The full report can be accessed online at "http://ebd.ada.org/ClinicalRecommendations.aspx".) The Centers for Disease Control and Prevention partly funded this project.

This report is intended to assist practitioners with decision making about the use of nonfluoride caries-preventive agents to arrest, prevent or reverse caries. The recommendations in this article are not intended to define a standard of care and rather should be integrated with a practitioner's professional judgment and a patient's needs and preferences.

METHODS

The panel conducted a systematic review of the literature (the complete version of which is available at "http://ebd.ada.org/ClinicalRecommendations.aspx"). The panel developed evidence statements based on the body of evidence and graded the level of certainty of the evidence as high, moderate or low on the basis of a standardized grading system (Table 1). Then the panel developed clinical recommendations and graded the strength of each recommendation (Table 2[3,6,8,9]). When the panel found evidence supporting efficacy, the panel members assessed adverse events reported in the trials and discussed any potential adverse events that could be associated with the intervention based on their knowledge of the existing literature. (Note that the panel did not conduct a review of the data specifically for adverse effects). When the panel was unable to reach a consensus in interpreting evidence into clinically relevant recommendations or when it made recommendations based largely on expert consensus, it used a simple majority vote to make final determinations.

RESULTS

Summary of evidence. The panel included 71 published articles whose authors described 50 randomized controlled trials (RCTs) and 15 nonrandomized studies to assess the efficacy of various nonfluoride caries-preventive agents. (Some clinical studies were published as multiple articles.) Only six of these studies were conducted in the United States. Although most studies were conducted in communities with low levels of fluoride in the water supply, participants often used fluoridated toothpaste, received regular dental care that included in-office fluoride therapies or both. Table 3[10-45] (page 1068) presents the evidence statements for each agent. Table 2 presents the recommendations from the expert panel.

DISCUSSION

Clinical considerations. Overall, the published literature on these topics lacks clinical trials that follow the Consolidated Standards of Reporting Trials guidelines,[46] especially with regard to appropriate methods of randomization, sample allocation concealment, accounting for losses to follow-up and intention-to-treat analyses. Most trials included in this systematic review involved assessment of the efficacy of nonfluoride agents. In efficacy trials (explanatory trials), researchers aim to determine whether an intervention produces the expected result under ideal circumstances. In effectiveness trials (pragmatic trials), researchers measure the degree of beneficial effect in real-world clinical settings.[47] The panel noted that effectiveness trials have greater clinical relevance. The panel found that available study findings provided limited information about the caries risk status of participants. The lack of uniformity in description of the background fluoride exposure of study samples, in part, led the panel to conclude that the nonfluoride preventive agents should be considered as adjunctive to a regular caries-prevention program. The evidence does not indicate that these agents are effective in patients whose condition is refractory to proven methods of caries prevention.

Sucrose-free polyol chewing gums. With

ABBREVIATION KEY. ADA: American Dental Association. **CSA:** Council on Scientific Affairs. **NIDCR:** National Institute of Dental and Craniofacial Research. **RCT:** Randomized controlled trial.

TABLE 2

Recommendations from the American Dental Association Council on Scientific Affairs Nonfluoride Caries-Preventive Agents Expert Panel.

Strength of Recommendations: Each recommendation is based on the best available evidence. The level of evidence available to support each recommendation may differ.

STRONG	IN FAVOR	WEAK	AGAINST	EXPERT OPINION
Evidence strongly supports providing this intervention	Evidence favors providing this intervention	Evidence suggests implementing this intervention only after alternatives have been considered	Evidence suggests not implementing this intervention	Evidence is lacking; any recommendation for or against is based on expert opinion

The panel acknowledges the oral and systemic benefits of lowering the quantity and frequency of sugar consumption and encourages practitioners to provide dietary counseling.* The panel also strongly recommends that practitioners first implement evidence-based recommendations regarding topical fluorides† and sealants‡ before attempting to use any nonfluoride therapies. The following recommendations may be considered adjuncts to dietary counseling and a regular caries-preventive program§ offered to patients at higher risk of developing caries.

Polyol (Coronal Caries)	Advise parents and caregivers of children 5 years or older that use of sucrose-free polyol (xylitol only or polyol combinations) chewing gum for 10 to 20 minutes after meals may reduce incidence of coronal caries	WEAK
	Advise adults that use of sucrose-free polyol (xylitol only or polyol combinations) chewing gum for 10 to 20 minutes after meals may reduce incidence of coronal caries	EXPERT OPINION
	Advise parents and caregivers of children 5 years or older that the daily use of xylitol-containing lozenges or hard candies that are dissolved slowly in the mouth after meals may reduce incidence of coronal caries (5-8 grams/day divided into two to three doses)	EXPERT OPINION
Chlorhexidine (Root Caries)	Apply 1:1 mixture of chlorhexidine-thymol varnish every three months to reduce the incidence of root caries	IN FAVOR
	Applying 0.5 to 1.0 percent chlorhexidine gel alone or in combination with fluoride for prevention of root caries is not recommended	EXPERT OPINION
	Using 0.12 percent chlorhexidine rinse alone or in combination with fluoride for prevention of root caries is not recommended	AGAINST
Chlorhexidine (Coronal Caries)	Applying 1:1 mixture of chlorhexidine-thymol varnish alone or in combination with fluoride for prevention of coronal caries is not recommended	EXPERT OPINION
	Applying 10 to 40 percent chlorhexidine varnish alone or in combination with fluoride for prevention of coronal caries is not recommended	AGAINST
	Applying 0.5 to 1.0 percent chlorhexidine gel alone or in combination with fluoride for prevention of coronal caries is not recommended	EXPERT OPINION
	Using 0.12 percent chlorhexidine rinse alone or in combination with fluoride for prevention of coronal caries is not recommended	AGAINST

* Sources: Tinanoff and Palmer[8] and Johnson and colleagues.[9]
† Source: American Dental Association Council on Scientific Affairs.[3]
‡ Source: Beauchamp and colleagues.[6]
§ A regular caries-preventive program includes routine and periodic examination by a dentist, patient education, dietary advice from a health care professional and appropriate use of professional and home fluoride products and dental sealants.

TABLE 3

Level of certainty of evidence statements for each nonfluoride agent reviewed in this report.*

AGENT	EVIDENCE STATEMENT	LEVEL OF CERTAINTY
Sucrose-Free Polyol Chewing Gums	In children aged 5 to 16 years, supervised consumption of chewing gum sweetened with sucrose-free polyol (xylitol only or polyol combinations) for 10 to 20 minutes after meals marginally reduces incidence of caries†	Moderate
Xylitol Candy and Lozenges	In children reporting caries experience, consumption of xylitol-containing lozenges or hard candy reduces incidence of coronal caries‡	Low
Chlorhexidine Varnish for Coronal Caries	In children aged 4 to 18 years, professionally applied 10 to 40 percent chlorhexidine varnish does not reduce the incidence of caries§	Moderate
Chlorhexidine-Thymol Varnish for Coronal Caries	In children up to 15 years, application of a 1:1 mixture of chlorhexidine-thymol varnish does not reduce the incidence of caries¶	Low
Chlorhexidine-Thymol Varnish for Root Caries	In adults and elderly people, application of a 1:1 mixture of chlorhexidine-thymol varnish reduces the incidence of root caries#	Moderate
Chlorhexidine Rinse for Coronal Caries	In children and adults, use of 0.05 to 0.12 percent chlorhexidine rinse does not reduce the incidence of coronal caries**	High
Chlorhexidine Rinse for Root Caries	In adults and elderly people, use of 0.12 percent chlorhexidine rinse does not reduce the incidence of root caries††	Moderate

* There is insufficient evidence to support any statement regarding the caries-preventive effects of xylitol syrup, xylitol in dentifrices, chlorhexidine varnish for root caries, chlorhexidine gels, triclosan, iodine, sialogogues, calcium phosphate products and use of nonfluoride agents in pregnant women. A conclusion of "insufficient" evidence does not mean that the intervention is ineffective but rather that the panel did not find enough evidence to support a recommendation.

† Sources: Finn and colleagues,[10] Richardson and colleagues,[11] Szoke and colleagues,[12] Beiswanger and colleagues,[13] Glass,[14] Machiulskiene and colleagues,[15] Alanen and colleagues,[16] Alanen and colleagues,[17] Kovari and colleagues,[18] Peng and colleagues,[19] Makinen and colleagues,[20] Makinen and colleagues,[21] Kandelman and Gagnon,[22] Petersen and Razanamihaja[23] and Isokangas and colleagues.[24]

‡ Sources: Alanen and colleagues,[17] Oscarson and colleagues[25] and Honkala and colleagues.[26]

§ Sources: Du and colleagues,[27] de Soet and colleagues,[28] Jenatschke and colleagues,[29] Fennis-le and colleagues[30] and Forgie and colleagues.[31]

¶ Sources: Petersson and colleagues,[32] Splieth and colleagues,[33] Ogaard and colleagues,[34] Baca and colleagues,[35] Twetman and Petersson[36] and Plotzitza and colleagues.[37]

Sources: Baca and colleagues,[38] Brailsford and colleagues[39] and Tan and colleagues.[40]

** Sources: Wyatt and colleagues,[41] Wyatt and MacEntee,[42] Spets-Happonen and colleagues,[43] Luoma and colleagues[44] and Duarte and colleagues.[45]

†† Sources: Wyatt and colleagues[41] and Wyatt and MacEntee.[42]

regard to sucrose-free polyol chewing gums, the panel noted that it is biologically plausible that the act of chewing itself increases the rate of food clearance from the mouth, increases saliva production and more quickly neutralizes plaque acids, thereby potentially lowering the incidence and progression of caries. Unfortunately, study participants in the control arms of the reviewed studies did not chew gum, making it impossible to distinguish between possible benefits associated with chewing itself versus those associated with the effects of the polyol.

In balancing the benefits and the potential adverse effects of use of these chewing gums, the majority of the panel believed that the benefits of supervised gum chewing added to a caries-prevention regimen, especially in children at high risk of experiencing caries, could outweigh the potential adverse effects (for example, choking hazard for children younger than 4 years[48] and adverse health effects[49-54]). Therefore, the panelists agreed with the recommendation that practitioners advise parents and caregivers of healthy children older than 5 years and at high risk of experiencing caries that the children use sucrose-free polyol chewing gum (containing either xylitol only or polyol combinations) after meals. Chewing gum use should be reserved for neurologically healthy children 5 years and older who are willing and able to chew for an extended period (the investigators in most of the studies included in this review reported that the participants chewed for at least 10 minutes). The panel extrapolated the evidence to adults who are at higher risk of developing caries and recommended chewing sucrose-free polyol gum (containing either xylitol only or polyol combinations) after meals. In balancing the benefits and risks of a chewing gum regimen, some panel members thought that the evidence for efficacy was not

strong enough to make a recommendation in favor of instituting gum chewing after meals.

Xylitol candy, lozenges and syrup. On the basis of results from three studies,[17,25,26] a majority of the panel recommended the use of xylitol lozenges or hard candy after meals for children older than 5 years. The majority of the panel also suggested a dose of 5 to 8 grams per day divided into two or three doses to maximize clinical benefits. As discussed previously, hard candy also should be used under supervised conditions in neurologically healthy children to reduce the risk of choking.[48] The panel did not find sufficient evidence to support recommendations for use of xylitol by children younger than 5 years. Some members of the panel thought that the existing weak evidence was not sufficient to support a recommendation for the use of xylitol delivered through lozenges.

Topical chlorhexidine products. In the United States, chlorhexidine is marketed as a 1:1 mixture of chlorhexidine-thymol varnish (such as Cervitec Gel, Ivoclar Vivadent, Schaan, Liechtenstein) and a 0.12 percent chlorhexidine gluconate mouthrinse (such as Peridex Chlorhexidine Gluconate 0.12% Oral Rinse [3M ESPE, St. Paul, Minn.] and PerioGard [Colgate, New York City]). The U.S. Food and Drug Administration has not approved either of these agents for caries prevention. In Europe, 10 to 40 percent chlorhexidine varnishes (for example, EC40 [Biovent, Nijmegen, Netherlands], BioC [Biovent] and Chlorzoin [Knowell Therapeutic Technologies, Toronto]) are marketed. Chlorhexidine gels also are not available in the United States.

Although chlorhexidine has been shown to reduce *Streptococcus mutans* in the oral cavity temporarily,[55] most of the clinical study investigators who evaluated coronal caries as the outcome did not show a statistically significant reduction in caries with the use of chlorhexidine in any vehicle. On the basis of the results of these studies, the panel recommended against using chlorhexidine products for coronal caries prevention at this time. With respect to root caries, the panel concluded that application of chlorhexidine-thymol varnish may help reduce the incidence of root caries in adults and elderly people and reported insufficient evidence supporting the use of 10 to 40 percent chlorhexidine varnish.

CONCLUSIONS

After conducting a comprehensive review of the literature, the panel concluded that certain nonfluoride agents may provide some benefit as adjunctive therapies in children and adults who are at higher risk of experiencing caries. The panel found at least 10 ongoing clinical trials that may in the future provide additional evidence for or against the effectiveness of many of these modalities. Therefore, on the basis of available evidence, the panel recommended sucrose-free chewing gum (containing either xylitol only or polyol combinations) or xylitol lozenges for caries prevention. In addition, the panel found that a 1:1 mixture of chlorhexidine-thymol varnish may be efficacious in the prevention of root caries.

A clinician must consider a patient's risk of experiencing disease and other factors such as readiness for change, oral health literacy and compliance when developing an optimal caries prevention plan. Patient education, dietary advice and periodic clinical examinations should be part of such a plan. Clinicians should encourage parents and caregivers to limit a child's consumption of sugar-containing foods and drinks and, when possible, to confine consumption to mealtimes.[8,9]

In light of good supportive evidence, the panel reminds clinicians that professional and home-use fluoride products, including fluoridated toothpastes and dental sealants, remain the primary interventions effective in preventing caries[2,3,5-7] and recommends that clinicians follow published evidence-based guidelines for these modalities.[3,6] In contrast, the modalities examined in this review had less evidentiary support, both for and against.

Regarding some studies in which the evidence was lacking, of poor quality or contradictory, and in which the panelists could not reliably estimate the benefits versus harms on the basis of the findings of published studies, the panelists concluded that there was insufficient evidence. In such cases, clinicians and patients alike should understand fully the uncertainty in the underlying evidence, as well as any potential risks of using or not using a particular intervention. The patient's caries risk status, the practitioner's professional judgment and a patient's needs and preferences should guide all decision making.

Use of any adjunctive strategies does not eliminate or change the requirements for proven modalities for caries prevention, including topical fluorides and sealants. The panelists did not compare fluoride with nonfluoride therapies because they strongly recommend using proven caries-prevention modalities—including dietary improvement, fluorides and sealants—before attempting to use other strategies, including those that are the topic of this report. ■

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