



Nonfluoride Caries-preventive Agents: New Guidelines

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ABSTRACT

Nonfluoride caries-prevention agents have been developed and promoted to the dental profession in the recent past. The oral healthcare professional is encouraged to use evidence-based information when making clinical decisions. Recently, a systematic review was completed by a panel of experts convened by the American Dental Association Council on Scientific Affairs and recommendations were developed to address efficacy of nonfluoride agents in reducing the incidence of caries and arresting or reversing the progression of caries. The panel found that all nonfluoride agents should be used as adjuncts, following initial use of primary caries prevention strategies (fluoride, sealants, anticaries diet). This paper discusses the levels of certainty for evidence statements and clinical applications of these recommendations.

Clinical significance: The panel concluded that certain nonfluoride agents may provide some benefits as adjunctive therapies in children and adults at higher risk of developing caries.

Keywords: Anticaries, Nonfluoride, Caries prevention, Caries risk.

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INTRODUCTION

It is common to leave the exhibit hall at national dental meetings with a sackful of brochures for dental products. Questioning of the industry representatives may result in receiving copies of published studies describing the efficacy of products. Dental professionals are advised to review the scientific evidence for any product used in practice or for products recommended to patients. One problem with this experience is finding the time to read the information and knowing enough about biostatistics to interpret the strength of the study data. Large sums of money are invested by the

dental industry to identify products which solve clinical problems and develop effective agents which are easy to use. Separating the 'wheat from the chaff' requires effort and understanding of study design and statistical test strengths.

Identification of 'Best Evidence'

Professional organizations have in the recent past begun to base clinical practice recommendations on study designs representing the best evidence, namely systematic reviews (SR). Systematic reviews include trials with rigorous designs to minimize bias, namely the randomized controlled trial (RCT) and when appropriate, combine study data into a meta-analysis (MA) to increase the power. This research provides direction to clinicians, in a nonbiased manner, for product usefulness and efficacy. Recently, the American Dental Association, Council on Scientific Affairs formed an expert panel of researchers and clinicians to conduct a SR to evaluate the evidence regarding nonfluoride products available in the United States which have been promoted to have an anticaries effect. The authors evaluated studies of sucrose-free polyol chewing gums, xylitol dentifrices, chlorhexidine, chlorhexidine in combination with thymol, calcium-containing agents, phosphate-containing agents, casein derivatives, sialogogues, iodine and triclosan. This panel presented evidence-based clinical recommendations for products but stipulated them to be used as adjuncts to primary anticaries strategies (Box 1).¹ The report summarized findings regarding the efficacy of nonfluoride agents in reducing the incidence of caries and arresting or reversing the progression of caries (<http://ebd.ada.org/ClinicalRecommendations.aspx>).¹ The resource is for dentists and team members to consider in the clinical decision-making process. At the same site, a color-coded chairside guide is available to guide clinicians in making clinical decisions for in-office use of products as well as

for patient recommendations. The full report can be freely accessed at http://ebd.ada.org/contentdocs/clinical_recommendations_non_fluoride_caries_preventive_agents_full_report.pdf.

Box 1**Primary Anticaries Strategies**

- Fluoride dentifrice, topically applied fluoride, fluoridated municipal water (0.7 ppm)
- Pit and Fissure sealants
- Diet which eliminates between meal sugar consumption (reduces frequency of sugar consumption) and, if sugar is consumed, encourages nonretentive sugar consumption at mealtimes

METHODS**Clinical Questions**

The authors addressed two clinical questions as follows:

1. In the general population, does the use of a nonfluoride caries preventive agent reduce incidence, arrest or reverse caries?
2. In individuals at higher caries risk, does the use of a nonfluoride caries preventive agent reduce incidence, arrest or reverse caries?

The literature was searched using various MESH terms in MEDLINE, PubMed and the Cochrane Library for studies. The search of MEDLINE and the Cochrane Library from 1966 through April 9, 2010 identified 2,697 articles, and some additional studies were identified by manual search. 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. Exclusion and inclusion criteria were established and papers were screened by two reviewers using the criteria. Two members of the expert panel resolved differences between the reviewers. Following the initial search, three additional studies were found and included. Trials were appraised for five separate domains, including reporting, external validity, bias, confounding and statistical power. Trials were appraised by two independent reviewers and a standardized application of the appraisal instrument was used by all reviewers. A composite score was developed for each study based on a standardized rating scale as follows:

Reporting (range 1 - 10) > 9 = good; 8 to 7 = fair; <6 = poor; Internal validity including bias, confounding and power (range 1 - 14) >12 = good; 11 -10 = fair; < 9 = poor.

The number of new decayed, missing or filled surfaces or teeth (DMF) experienced by each treatment group in a study was the defined outcome measure. DMFS data was used over defs data. When studies with the same outcome measures and data reporting allowed, meta-analysis was

used to synthesize the results, if multiple studies were included in the review. A random-effects model was used to overcome some of the limitations of heterogeneous data and the level of certainty grading was based on these considerations.

Process for Developing Clinical Recommendations

Evidence statements were based on the body of evidence and the level of certainty of the evidence was graded as high, moderate or low on the basis of a standardized grading system. Clinical recommendations were developed from this information. When evidence supporting efficacy was found, adverse events reported in the trials were assessed and members discussed any potential adverse events that could be associated with the intervention based on knowledge of the existing literature. When a consensus was unable to be reached in interpreting evidence for clinically relevant recommendations or when recommendations were made, based largely on expert consensus, a simple majority vote was used to make final determinations. Definitions for the various levels of evidence are included in the clinical guideline.

Primary (Mainstay) Anticaries Strategies

The expert panel explained, at the beginning of the executive summary of recommendations, that 'the use of fluoridated toothpastes, other topically applied fluorides, fluoridated municipal water and pit and fissure sealants, along with dietary improvement, remain mainstays of caries management'. It was noted that high-quality evidence for prevention of caries with these products exists and these strategies comprise the first choices for professional use. Nonfluoride agents, such as xylitol, varnishes with chlorhexidine, amorphous calcium/casein products and others, are presented in a table with designations as 'strong', 'in favor', 'weak', 'against' or those with a lack of evidence which could only be given a designation as 'expert opinion'. The agents which were recommended for use were stipulated to be used as adjunctive, not for primary caries management. The panel stated that recommendations in the report were not intended to define a standard of care and should be integrated with the practitioner professional judgment, the patient needs and patient preferences.¹

Dietary Improvements

Research from the Vipeholm studies in the 1940s provided information for dietary caries control in the human mouth.^{2,3} The studies were initiated in response to findings of a tremendous need for dental care in the Scandinavian

population. The enormous cost associated with dental care motivated the government in Sweden to request research concerning what measures should be taken to decrease the frequency of the most common dental diseases in Sweden. A clinical study on diet and dental caries at the Vipeholm hospital, a facility for individuals with mental handicaps, situated close to the university dental program in Lund. It was speculated that an institution with a large number of virtually permanent patients, where dietary patterns could be controlled, would provide an opportunity for long-term nutritional studies performed in a controlled environment. The goal was to provide definite answers to basic questions regarding if dental caries should be regarded as a disturbance of the general health of the patient, e.g. was it a deficiency disease or was it due to local oral factors related to the diet? This question was posed soon after an early study showing that fluoride in drinking water could have a caries-protective effect and the lack of conclusive data regarding the role of carbohydrate intake on caries development. The government funded study (supplemented with funds from the Swedish sugar industry, chocolate and sweet manufacturers and various research foundations) began in 1945 and ended in 1954. In the carbohydrate I study, there were several groups: Sugar in solution (nonretentive) group, retentive or sticky form of sugar at meals, a retentive sugar given between meals in a toffee form and the comparison group which contained no sugar products. Results showed that the caries incidence was very low in the basic diet and also when sugar was consumed at mealtimes only. Sugar given in sticky forms between meals increased caries activity significantly. The publication of the Vipeholm study resulted in the concept that frequent consumption of sugar promoted dental caries. Another consequence was that research for development of noncariogenic sugar substitutes began. The Vipeholm study has become a citation classic. The reason the study is cited so often is likely because a clinical problem was studied under well-controlled conditions, and the main results were supported by supplementary and special studies.² A review of the results in various groups in the studies concluded that, for the caries-susceptible person, between meal consumption of sugary foods is still a risk factor for caries.⁴ In 1955, the Swedish government decided it was unethical to use patients in the Vipeholm hospital as research subjects in future studies due to the suggestion practice was unethical. It is obvious a research study such as this, would not be approved today by the institutional review board.

Nonfluoride Agents for Caries Prevention

The following describes findings for anticaries efficacy for the various nonfluoride agents:

Sucrose-free Polyol Gum

Nine RCT and six nonrandomized studies were used to determine the efficacy of sucrose-free polyol gum products (sorbitol, xylitol or combinations of both) on coronal caries. Experimental groups were given gums of these types to chew and were compared to subjects who were not provided gums. Subjects were between 5 and 13 years of age and chewing was supervised. Chewing frequency ranged between 2 and 6 times/day and lasted for 10 to 20 minutes. None of the children enrolled had caries risk determination as part of the study, so it was not possible to determine caries risk status of the subjects. When studies were judged for quality, two studies were of good quality, four studies were of fair quality and the remaining studies were judged to be of poor quality. Data from nine studies were combined through MA. Six were excluded from MA because of incomplete reporting of data, comparisons to sealants, toothpastes or due to a noncomparable outcome measure. Results showed there is a statistically significant reduction in caries with the use of sucrose-free polyol gums compared with no gum chewing with xylitol gum, having the greatest caries reduction. It is possible that chewing itself stimulated salivation which could result in remineralization and be responsible for the caries reduction. No study had an arm of chewing without an active ingredient to measure this potential effect. The low quality of most studies limited the confidence in the observed results and the recommendation was judged as weak.¹ However, the number of studies showing a consistent preventive effect led the majority of the panel to conclude with moderate certainty that '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 coronal caries.' The majority of the panel determined 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. The panel disagreed on the benefits of polyol gum chewing for adults and made the recommendation based on 'expert opinion' to 'advise adults that use of sucrose-free polyol (xylitol only or polyol combinations) chewing gum for 10 to 20 minutes after meals may reduce the incidence of coronal caries.'

Xylitol Gum, Chlorhexidine (chx) Products in Pregnant Women

The panel evaluated four studies in pregnant females aimed at reducing caries in their children. One RCT of xylitol gum plus 40% chx varnish compared the experimental group with sodium fluoride varnish. Authors reported a statistically

significant reduction in caries in the children when xylitol gum was added. Out of the four studies, two were of fair quality and two of poor quality. Other trials included chx gel and calcium supplementation by the mother. Based on these four trials, which were conducted on different agents, the panel concluded ‘there is insufficient evidence that the use of xylitol gum, chlorhexidine varnish or gel or calcium supplementation in mothers lowers incidence of caries in children.’

Xylitol Candy, Lozenges and Syrup

Four studies were found evaluating xylitol candy, lozenges or syrup for caries reduction. Three trials were homogeneous in design and were combined in MA and found a statistically significant effect in favor of xylitol candy/lozenge. Benefits were dose related and 6 to 8 gm/day provided the greatest benefit. Polyols in large doses have been linked to adverse gastrointestinal effects in some individuals. Also the risk of choking should be considered and children supervised if candy is used. Out of the three studies, one study used deciduous dentition and the other two studies evaluated effects in the permanent dentition. Subjects were not evaluated according to caries risk. One study was judged to be of good quality, one of fair quality and one of poor quality. Although there were a limited number of studies, the panel concluded with low certainty, and upon expert opinion, that ‘In children reporting caries experience, consumption of xylitol containing lozenges or hard candy reduces the incidence of coronal caries. 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 gm/day divided into 2-3 doses).’

Only one study evaluated the use of xylitol syrup with children below the age of 2 years. The study reported a significant caries reduction and was of good quality; however, due to having a single study, the panel recommended ‘there is insufficient evidence that xylitol syrup prevents caries in children under 2 years of age.’

Xylitol Dentifrice

Two RCTs evaluated benefits of using 10% xylitol in a dentifrice with school-aged children at high caries risk. One was of fair quality and one of poor quality. This insufficient evidence led the panel to conclude there is insufficient evidence that xylitol in dentifrices prevents caries.

Chlorhexidine Products

Two forms of chlorhexidine (chx) are available in the United States, a 1:1 chx/thymol combination varnish and a 0.12%

chx gluconate rinse. Various concentrations of chx varnish and chx rinse are available worldwide. Neither of these agents is US Food and Drug Administration approved for caries control. Gels containing chx are available in Europe but not in the US. Twenty four studies were evaluated using the various chx products. Although chx has been shown to temporarily reduce *Streptococcus mutans* in the oral cavity, most of the clinical study investigations of coronal caries as the outcome did not have statistically significant reduction of caries with the use of chx in any formulation.

Chlorhexidine Varnish

Five RCTs (N = 1300+) evaluating efficacy for chx varnish alone, compared to a placebo comparison group, were reviewed. Preschool, school-age children and adolescents describe the study population. Two studies included children at a high caries risk. Chx varnish concentrations ranged from 10 to 40%. One study was judged as good quality and others were of fair quality. Data from all five studies were combined for the MA and a nonsignificant difference between 10 to 40% chlorhexidine varnish and placebo varnish was resulted. After excluding studies over 1 year that reported on white spot lesions, the results did not change. When only studies that included high-risk patients were considered the results did not change. This led the panel to conclude there was a lack of effect. Therefore, the panel had moderate certainty in concluding that ‘in children aged 4 to 18 years, professionally applied 10 to 40% chlorhexidine varnish does not reduce the incidence of caries.’ One RCT of root caries reduction with 40% chx varnish in adults yielded a statistically significant caries reduction in root caries, however, the study was judged to be of poor quality. This led the panel to conclude ‘in adults, there is insufficient evidence that use of 40% chlorhexidine varnish reduces the incidence of root caries.’

1% Chlorhexidine/1% Thymol Varnish

This 1:1 combination varnish was studied in six studies of coronal caries, three being RCT and all involved children. Three studies compared the 1:1 formulation with no varnish while the other three compared the 1:1 combination mixed with sodium fluoride to a group receiving sodium fluoride alone. When the reduction of coronal caries was the outcome most did not show a statistically significant reduction in caries with the use of any formulation of chx. One study was judged to be of good quality while all others were of poor quality. Five studies were combined into a MA and results showed a nonsignificant difference between groups. One study comparing 1:1 chx/thymol varnish to sodium fluoride varnish showed a nonsignificant difference between

the groups. Based on the poor quality of most studies, the panel had low certainty in concluding that ‘in children up to 15 years, application of a 1:1 mixture of chlorhexidine/thymol varnish does not reduce the incidence of caries.’

Three RCTs evaluating 1:1 chx/thymol varnish for adult root caries were evaluated as two of good quality and one of fair quality. Two studies compared the 1:1 combination with placebo varnish or no varnish and found a statistically significant benefit of root caries reduction. The third study compared chx/thymol plus sodium fluoride in the varnish with a sodium fluoride varnish. The chx/thymol/sodium fluoride product produced a reduction in lesion progression. Based on the three RCTs, all showing caries reduction benefit the panel concluded with moderate certainty that ‘in adults and elderly people, application of a 1:1 mixture of chlorhexidine/thymol varnish reduces the incidence of root caries.’

0.12% Chlorhexidine Mouthrinse

Four RCTs of 0.12% chx rinse with the outcome of effects on coronal caries were combined into a MA (N = 1200+) which revealed a nonsignificant difference between groups. Based on these four RCTs judged to be fair or good quality and the results of the meta-analysis showing a nonsignificant difference, the panel concluded with high certainty that ‘in children and adults, the use of 0.05 to 0.12% chlorhexidine rinse does not reduce the incidence of coronal caries.’

Two RCTs reported on the incidence of root caries in an adult and elderly population judged to represent the general population. Both trials appeared adequately powered (with one trial including almost 1000 subjects). Findings were that the use of chx rinse does not result in a statistically significant decrease in root caries incidence among adults and elderly compared to placebo rinse. Based on these two trials, the panel concluded with moderate certainty that ‘in adults and elderly people, use of 0.12% chlorhexidine rinse does not reduce the incidence of root caries.’

Amorphous Calcium and Casein Derivatives

These products have been heavily marketed with advertising materials stressing the ability of the various calcium/phosphorus product to promote remineralization. Remineralization is a requirement for demineralized enamel to ‘heal itself’ and become healthy. The logic proposed is that, if remineralization occurs, this leads to less caries incidence. Most products are included in a dentifrice formulation. Nine studies (8 RCTs) evaluated various calcium and/or phosphate containing agents with and without casein derivatives were found. Two were judged to

be of good quality, five of fair quality and two of poor quality. Study designs were varied as some combined the calcium derivatives with fluoride and compared to a placebo while others compared the calcium derivative with a sodium fluoride dentifrice. An arginine bicarbonate/calcium phosphate was formulated into a dentifrice and into a mint doseform. Both studies showed statistically significant caries reduction at 12 months.

Casein phosphopeptide complexed with amorphous calcium phosphate (CPP-ACP) was studied in chewing gum, mouthrinse and dental cream. Although the panel found several studies on calcium and phosphate agents with and without casein derivatives, the differences in composition of the products, their varying delivery mechanisms, differing study designs and the varied results made it difficult to determine the efficacy of each agent or to group them into MA. The panel found ‘there is insufficient evidence from clinical trials that the use of agents containing calcium and/or phosphates with or without casein derivatives lowers incidence of either coronal or root caries.’

OTHER PRODUCTS (SIALOGOGUES, IODINE, TRICLOSAN)

Triclosan

There were no dentifrice studies evaluating triclosan alone, without fluoride, for anticaries effects. This led the panel to conclude ‘there is insufficient evidence that triclosan lowers incidence of caries.’

Iodine

Iodine can reduce the levels of *Streptococcus mutans* species in biofilm and saliva. Four RCTs lasting 12 months, conducted with preschool or school-aged children, evaluated 10% povidone-iodine on coronal caries. Two studies were of fair quality and two of good quality with studies having small numbers in groups. Combining data was not possible due to differences in study outcome measures. Two studies reported nonsignificant results while two reported some benefit. The panel concluded ‘There is insufficient evidence that the use of iodine lowers the incidence of caries.’

CLINICAL IMPLICATIONS

An oral exam to determine the risk for caries should be completed before a caries prevention plan is developed.⁶ Considerations include the patient’s oral health literacy, ability to understand health information and the degree of compliance for prevention recommendations. Discussions regarding a routine diet are essential. Parents and caregivers

should be encouraged to limit a child’s consumption of sugar-containing foods and drinks and, when possible, to confine consumption to meal times. The primary caries prevention strategies, identified in the ADA guidelines¹ should be used first while nonfluoride anticaries products recommended be considered for adjunctive use only. As future evidence is available, some recommendations may change. Along with the patient’s caries risk status, the professional judgment of the clinician and patients’ needs and preferences should guide clinical decision-making.

SUMMARY AND CONCLUSION

A systematic review was conducted based on evidence statements formulated by the Expert Committee. Research on each product category was graded for certainty and defined as high, moderate or low on the basis of a standardized grading system (Table 1). The panel developed clinical recommendations and graded the strength of each recommendation. These can be accessed from the ADA website provided above. Evidence for efficacy was weighted against potential adverse events reported in trials. When the panel was unable to reach a consensus for relevant clinical recommendations, a simple majority vote determined the final recommendation. The study design with the least risk for bias is the randomized controlled trial (RCT) and the panel included 71 published studies, 50 of which were RCTs. Only six of the studies used were conducted in the United States. Overall the published studies on the various nonfluoridated agents examined were deemed to lack good quality trials. For example, many did not follow the consolidated standards of reporting trial (CONSORT) guidelines according to proper randomization, allocation concealment of groups, account for losses to follow-up and intention to treat analyses.⁵ Many studies did not provide information on the caries risk status of subjects and there was lack of uniformity describing background fluoride exposures of subjects. Thus, the panel concluded nonfluoride preventive agents should be considered as

adjunctive agents. Evidence did not indicate agents were effective in subjects whose teeth may be refractory to proven methods of caries prevention.¹

The panel recognized that studies related to prevention of dental caries are needed to adequately answer clinical questions for nonfluoride agents. The panel made a list of criteria for future study designs and suggested RCTs follow the consolidated standard of reporting trial (CONSORT) guidelines.⁷ There are at least 10 ongoing investigations currently in progress and the ADA guidelines will be updated as new information becomes available.

Following a caries risk assessment by the oral healthcare professional, the primary strategies for anticaries effects should be considered, specifically a topical application of any form of fluoride, left on the teeth for 4 minutes.⁶ The client should be advised to return for dental assessment on a regular basis and the diet should be examined for frequent exposure to caries promoting carbohydrates. Along with the caries risk status, the professional judgment of the clinician and patients’ needs and preferences should guide clinical decision-making.

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Levels of certainty	Definition of level
High	Strong evidence for recommendation; conclusion is unlikely to be highly affected by results from future studies
Moderate	Preliminary determination from current best evidence; as additional studies are published, magnitude of effects could change which could change the recommendation
Low	There is insufficient evidence to support statement; more information could provide a more reliable estimation of effect

Paraphrase of Table 1¹