# Silver Diamine Fluoride 38%

# Scientific Literature Review

# March 2016

Silver Diamine Fluoride (SDF) 38% has been receiving a great deal of attention by U.S. dental professionals since it was cleared for use by the Food and Drug Administration in August 2104 under the provisions of the Federal Food, Drug and Cosmetics Act. The Cleared Indications For Use are for the "Treatment of dentinal hypersensitivity. For use in adults over the age of 21."

In the age of the Internet, access to information that can sometimes be credible and sometimes not, could cause confusion about the histroy, safety and efficacy of SDF. In addition, a number of local television news programs and social media postings around the U.S have recently begun communicating information about the use of SDF by both general and pedictric dentists who have begun using it for the treatment of carious lesions in populations of all ages.

While SDF only recently received FDA Clearance it has been used by dental professionals outside the U.S for both the treatment of dentinal hypersensitivity and as a caries therapy for more than 45 years. This review is intended to provide U.S medical professionals with an understanding of the history of SDF around the world, including the most current information available regarding its use in the U.S.

Under federal law, the use of a drug or medical device by a licensed medical professional for an indication not Approved or Cleared by the FDA is allowable and not uncommon. This is termed "off-label" use.

As the organization permitted to market the only FDA Cleared SDF product in the United States, (Advantage Arrest™ Silver Diamine Fluoride 38%,) it is our intention to provide a review of all scientific literature available to us in order to help insure that medical professionals, and through them, their patients are as well informed as possible about this therapy.

This document is not assumed to contain all published information regarding SDF, as that would be virtually impossible, since SDF has been in use in many countries around the world for decades. It is however meant to provide a fair and balanced view of the benefits and risks of the use of SDF. If, after reading this document, you have any questions please send an email to the address below and we will get back to you promptly.

Please address any questions to:

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**Table of Contents**

## Advantage Arrest Package Insert

# Advantage Arrest™

### Silver Diamine Fluoride 38%

Professional Tooth Desensitizer

**Rx Only**

**Desensitizing Ingredient:** Aqueous Silver Diamine Fluoride, 38.3% to 43.2% w/v

**Inactive Ingredients:** Purified water

**Clinical Pharmacology:** Product forms insoluble precipitates with calcium or phosphate in the dentinal tubules to block nerve impulses.

**Indication and Usage:** Treatment of dentinal hypersensitivity. For use in adults over the age of 21.

**Contraindications:** This product is contraindicated in patients with ulcerative gingivitis or stomatitis, or known sensitivity to silver or other heavy-metal ions. Patients with more than six affected sites, patients having had full mouth gingivectomies and patients showing abnormal skin sensitization in daily circumstances are recommended for exclusion.

**Warnings:** This product is intended for local application only. Not for ingestion. Protect the patient's eyes. Use caution to avoid contact with skin or clothing. In the event of exposure to eyes or skin, flush the area copiously with water and immediately seek medical consultation. This product yielded positive cytotoxicity in standard testing.

**Precautions for Use:**

1). Advantage Arrest does not normally stain enamel or burnished dentin. Advise patients that soft dentin or margins of composite restorations may be stained. Staining may be reversed by gentle polishing with tincture of iodine (weak iodine solution).

2) Advise patients that air-drying and product application can cause momentary transient pain to hypersensitive areas. Advantage Arrest has not been shown to cause pulpal necrosis even when soft dentin is treated.

3) Minimize product contact with gingiva and mucous membrane by using recommended amounts and careful application. Advantage Arrest may cause reversible short-term irritation. When applying Advantage Arrest to areas near the gingiva, apply petroleum jelly or cocoa butter and use cotton rolls to protect the gingival tissues. Alternatively, a rubber dam can be used to isolate the area.

4) If accidental contact occurs, thoroughly wash the area with water, saline solution or ~3% hydrogen peroxide. This includes contact with skin, clothes, floors and cabinets. Because Advantage Arrest is clear and thus may be difficult to see, use caution to avoid transferring the material from gloved hands to other surfaces.

**Precautions for Handling:**

1. Storage Precautions

   1) Store in original packaging in a cool, dark place.

   2) Replace cap immediately after use.

   3) Use as soon as dispensed.

2. Advantage Arrest will stain skin, clothes, counter tops, floors and instruments brown or black. Refer to the following for stain removal:

   1) Skin; wash immediately with water, soap, ammonia or iodine tincture and then rinse thoroughly with water. Do not use excessive methods in an attempt to remove difficult stains from skin as the stains will eventually fade.

   2) Clothing/Countertops/Floors/Instruments; use the same procedures as with stained skin. Difficult stains may be treated with sodium hypochlorite.

3. If Advantage Arrest is dispensed into a separate container, be sure to wash or thoroughly wipe the container clean immediately after use.

**Adverse Reactions:** Transient irritation of the gingiva has rarely been reported.

**Dosage and Administration:**

1. Isolate the affected area of the tooth with cotton rolls or protect the gingival tissue of the affected tooth with petroleum jelly. Alternatively, a rubber dam can be used to isolate the area.

2. Clean and dry the affected tooth surface.

3. For up to 5 treated sites per patient, dispense 1-2 drops of solution into a disposable dappen dish. Transfer material directly to the tooth surface with an applicator.

4. Air-dry.

If needed, one or two reapplications may be administered at intervals of one week.

**How Supplied:** Single 10 mL dropper-bottle containing 8 mL of product. Not sterile.

**Storage:** Do not freeze or expose to extreme heat. Keep in an air-tight container in a dark place.

**Caution:** Federal law restricts this device to sale by or on the order of a dentist or physician.

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# The Short-term Effects of Diammine Silver Fluoride on Tooth Sensitivity: a Randomized Controlled Trial

## ABSTRACT

Tooth sensitivity is a common clinical problem. This multi-center randomized clinical trial assessed the effectiveness and safety of topical diammine silver fluoride. From two sites (Lima and Cusco, Peru), 126 adults with at least one tooth sensitive to compressed air were randomly assigned to either the experimental treatment or sterile water, and pain was assessed by means of a 100-mm visual analogue scale at 24 hours and 7 days. The diammine silver fluoride reduced pain at 7 days at both sites. At the Lima site, the average change in pain scores between baseline and day 7 for the silver fluoride group was -35.8 (SD = 27.7) mm *vs*. 0.4 (SD = 16.2) mm for the control group ($P <$ 0.001). In Cusco, the average change in pain scores for the silver fluoride group was –23.4 (SD = 21.0) mm and -5.5 (18.1) mm for the control group ($P =$ 0.002). No tissue ulceration, white changes, or argyria was observed. A small number of participants in the silver fluoride group experienced a mild but transient increase in erythema in the gingiva near the tooth. No changes were observed in the Gingival Index. We concluded that diammine silver fluoride is a clinically effective and safe tooth desensitizer.

**KEY WORDS:** tooth sensitivity, silver diamine fluoride, diammine silver fluoride, silver diammine fluoride, fluorides, topical.

## INTRODUCTION

Tooth sensitivity to various stimuli, including cold air, has been explained by hydrodynamic changes within the dentinal tubules that activate intradental nerves (Markowitz and Pashley, 2008). Incidence is thought to be increasing. The etiology can be tooth wear, aggressive oral hygiene, and diet. Successful treatments physically block dentinal tubules (Arends *et al*., 1997).

Sodium fluoride varnish and fluoride solutions and gels have been shown to reduce sensitivity (Thrash *et al*., 1992; Ritter *et al*., 2006). However, there is continuing interest in finding effective treatments. Nevertheless, recent studies have designs that are weak or statistically underpowered (Erdemir *et al*., 2010; Jalali and Lindh, 2010).

The purpose of this study was to assess the clinical effectiveness and safety of topical diammine silver fluoride as a tooth desensitizer in adults.

## METHODS

### Design

This is a randomized clinical trial with two groups (Fig. 1). The study tested application of diammine silver fluoride in a single visit, because previous unpublished work had shown that a single application forms insoluble precipitates with calcium and phosphate that physically block dentinal tubules. The International Clinical Trials Registry number is NCT01063530.

### Study Sites

The study was conducted in two sites, Lima and Cusco, Peru.

### Participants

To be included, a participant must have at least one vital cuspid or premolar with a buccal cervical defect and clinical hypersensitivity in response to compressed air with a score $\geq 15$ on a visual analogue scale (VAS) for pain. The individual will have had generally healthy gum tissue surrounding this tooth and no ulceration and no leukoplakia in this gingival tissue.

Candidates were excluded if they were using any type of tooth desensitizer, had received a fluoride varnish treatment within the preceding month, or were taking prescription medications, aspirin, or non-steroidal anti-inflammatory drugs; women who were pregnant were also excluded. Individuals using smokeless tobacco or chewing coca leaves were excluded. Individuals with known sensitivity to silver or other heavy-metal ions were excluded.

203
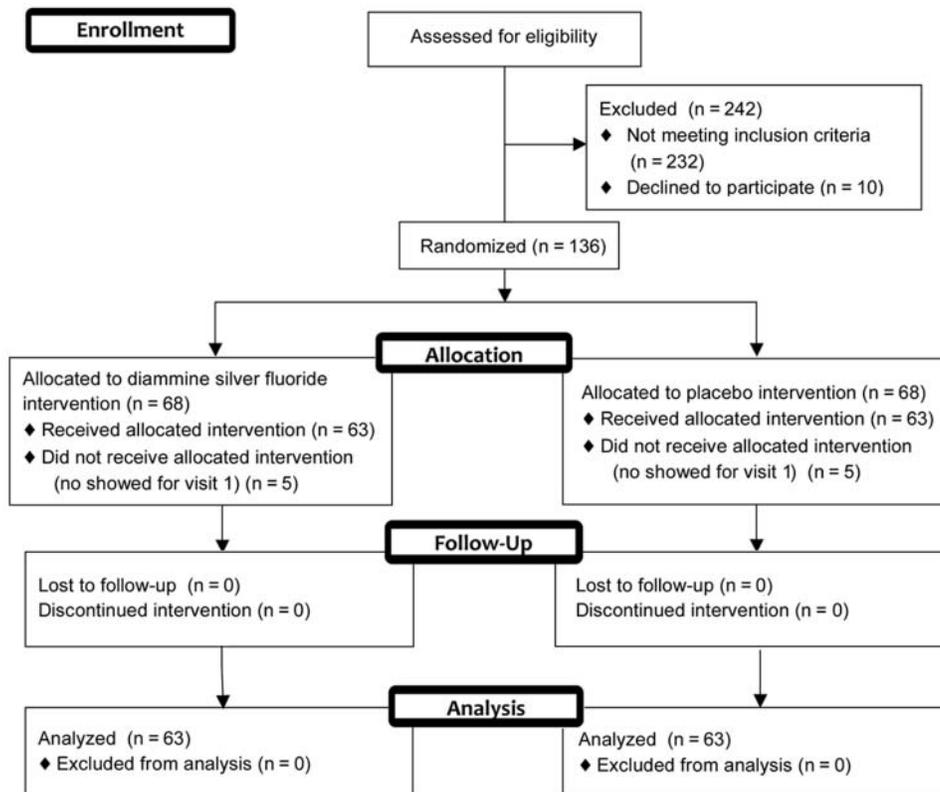
**Figure 1.** Flow chart for clinical trial sites combined.

two groups would be balanced across the study period and within each stratum. The stratification at 37 was chosen from the literature (Ritter *et al.*, 2006). A pre-test of the VAS with 10 individuals confirmed the mean response in this range. Block sizes were equal to 2 or 4, and were chosen randomly with 2/3 and 1/3 probability, respectively. The assignments were generated by the project statistician, using the "sample" function of R statistical software (Version 2.7.1, The R Foundation for Statistical Computing, 2008). The assignments were recorded on slips of paper numbered consecutively within each stratum and then placed inside sealed envelopes sequentially numbered by stratum. The statistician retained the master list until all the data were analyzed. The clinician would open the envelope and apply the agent. The agents (active or control) were packaged in identical dark glass bottles labeled as A or B. The packaging was done at Cayetano University.

Participants were recruited from the patient populations of Cayetano University School of Dentistry and the private dental practices of the investigators in Lima and Cusco between January and June, 2010, and were offered a small financial incentive for participation.

The Institutional Review Board of Universidad Peruana Cayetano Heredia approved the protocol, and the informed consent of all participants was obtained.

## Treatment Conditions

Diammine silver fluoride [$Ag(NH_3)_2F$, CAS RN 33040–28–7, Saforide, Toyo Seiyaku Kasei Co. Ltd. Osaka, Japan] was used. It is clear and colorless, with a weak odor of ammonia. According to the manufacturer, the solution includes not less than 24.4 w/v% and not more than 26.8 w/v% of silver (Ag), not less than 5.0 w/v% and not more than 5.9 w/v% of fluorine (F). Diammine silver fluoride is also referred to as silver diammine fluoride, silver diamine fluoride, or silver fluoride.

## Assignment to Conditions

Participants were randomly assigned to treatment with diammine silver fluoride or sterile water. The randomization was stratified on study site and baseline tooth sensitivity score (< 37 and ≥ 37) to a five-second blast of pressurized air at 2 cm distance from the tooth, and blocking was used to ensure that the

## Clinical Procedure

The clinical procedure was that a disposable microbrush was dipped into a drop of the diammine silver fluoride or the control and then applied to the surface for 1 sec. Then the surface was gently air-dried and the procedure repeated.

## Measures

### Primary Outcome-Clinical

*Reduction of pain (tooth sensitivity)*—The teeth were isolated with gauze, and participants were asked to report tooth pain on a 100-mm visual analogue scale (VAS; Ritter *et al.*, 2006) before treatment and after treatment with a five-second blast of pressurized air at 2 cm distance from the tooth. The VAS was anchored with "no pain" and "intolerable pain". The follow-up test was repeated at 24 hrs and 7 days later. A single person in each site conducted the assessment in Spanish. The scale was pre-tested to ensure that the descriptors were translated properly.

### Safety

*Damage to gingiva*—Tissues were photographed before treatment to establish the normal baseline condition. A single examiner examined gingival tissues surrounding each treated tooth immediately after treatment, and at 24 hrs and 7 days later. The primary safety measure is erythema. It was assessed visually

**Table 1.** Tooth Sensitivity by Study Site and Condition

| Study Site | Time | Condition | | |
|---|---|---|---|---|
| Lima | | Silver Fluoride (N = 37) | Control (N = 34) | |
| | | Mean VAS (SD) [Range] | Mean VAS (SD) [Range] | *P*-value* |
| | Baseline | 57.3 (26.7) [17, 99] | 49.3 (19.3) [15, 84] | 0.16 |
| | 24 hrs | 28.2 (22.1) [2, 75] | 52.1 (22.8) [16, 89] | |
| | Change from baseline | -29.1 (27.5) [-94, 10] | 2.6 (15.3) [-44, 32] | < 0.0001 |
| | 7 days | 21.5 (23.0) [1, 78] | 49.9 (21.2) [9, 85] | |
| | Change from baseline | -35.8 (27.7) [-97, 12] | 0.4 (16.2) [-38, 33] | < 0.0001 |
| Cusco | | Silver Fluoride (N = 26) | Control (N = 29) | |
| | | Mean VAS (SD) [Range] | Mean VAS (SD) [Range] | *P*-value |
| | Baseline | 51.7 (20.5) [22, 92] | 51.6 (22.4) [16, 99] | 0.98 |
| | 24 hrs | 45.2 (24.1) [11, 87] | 50.6 (22.0) [15, 95] | |
| | Change from baseline | -6.5 (13.1) [-34, 22] | -1.0 (11.7) [-37, 20] | 0.11 |
| | 7 days | 28.3 (21.8) [2, 94] | 46.1 (24.4) [3, 92] | |
| | Change from baseline | -23.4 (21.0) [-56, 24] | -5.5 (18.1) [-77, 18] | 0.0015 |

*Two-sample *t* test (unequal variances).

with the use of a standard dental light. Erythema (red changes) was rated on a 1 to 3 scale, where 1 is no redness, 2 is redness with bleeding on probing, and 3 is a severe change. The Gingival Index (Löe, 1967) was used to measure gingival inflammation in the mouth overall. White changes, ulceration, and staining were secondary measures. Changes were rated as present or absent. Examiners were trained to criteria using photographs and clinical cases. Intra- and inter-examiner reliability was established in 15 cases, and intraclass correlation was used to assess reliability. All intraclass correlations exceeded 0.8.

### Data Analysis Plan

The data from the two sites were analyzed. To confirm reduction in pain, we calculated average difference scores between pre- and post-treatment VAS scores for each individual for each time-point (24 hrs and 7 days after treatment), and *t* tests were used to compare changes. The primary end point was at 7 days. Generalized estimating equations (GEE) linear regression was used in a secondary analysis to compare the reduction in pain across the 3 time-points, where the outcome is pain at the 3 time-points, the baseline pain is a covariate, and robust standard errors are used to account for multiple observations *per* participant and heteroscedasticity (Hardin and Hilbe, 2002). In addition, separate analyses of covariance were done at each time-point to compare the reduction in pain due to the active treatment between the two study sites, where the outcome is the pain at a particular time-point, baseline pain was entered as a covariate, and treatment and site, as well as a treatment-group-by-site interaction, were entered as factors.

We used Fisher's Exact Test to assess whether there were more participants with erythema score > 1 in the silver fluoride group *vs.* the control group at 24 hrs and 7 days post-treatment. The primary end-point was assessed at 24 hrs. A *t* test assessed any differences in Gingival Index. Any white changes, ulceration, and staining (argyria) were reported.

### Power Analysis

The data from the two sites were analyzed separately, and power is described below for the separate site analyses.

*Reduction in tooth sensitivity*—The primary end-point was assessed at 7 days post-treatment. In a similar desensitization study comparing fluoride varnishes (Ritter *et al.*, 2006), pain in response to air dropped from 36.9 (SD = 26.2) at baseline to 20.8 (SD = 4.3) at 2 wks post-treatment. We expected a similar or larger drop after 7 days with diammine silver fluoride, based on unpublished work from the University of Hong Kong, and little or no drop from the water. Thus, having 31 individuals in a group will allow for detection of effect size from 0.64 upwards, with an alpha of 0.05 and power of 0.8.

## RESULTS

### Participants

One hundred twenty-six adults (71 in Lima and 55 in Cusco) participated. About 378 candidates were screened between January and June 2010. The main reason (95%) for exclusion was lack of tooth sensitivity. The remainder were excluded because of the use of medications. No individuals were excluded because of tobacco use or coca. All of those eligible agreed to participate, but 10 were excluded because they failed to appear for the first visit. The proportion of women enrolled was 86% in Lima and 80% in Cusco. The average age of participants was 44 yrs and 43 yrs, respectively. There were no dropouts.

Participants and clinicians were blind to treatment assignment. Odor was not a threat to blinding, because the smell is not detectable clinically when such small quantities are used. Taste was not a threat in this study, because only minute amounts of material were applied and the tooth was air-dried after application.

**Table 2.** Numbers and Percentages of Participants with Erythema Score of 2 by Study Site and Condition

| Study Site | Time | Condition | | |
|---|---|---|---|---|
| Lima | | Silver Fluoride (N = 37) | Control (N = 34) | |
| | | n (%) | n (%) | *P*-value* |
| | Baseline | 3 (8.1) | 2 (5.9) | 1.0 |
| | 24 hrs | 3 (8.1) | 2 (5.9) | 1.0 |
| | 7 days | 3 (8.1) | 1 (2.9) | 0.61 |
| Cusco | | Silver Fluoride (N = 26) | Control (N = 29) | |
| | | n (%) | n (%) | *P*-value* |
| | Baseline | 6 (23.1) | 7 (24.1) | 1.0 |
| | 24 hrs | 10 (38.5) | 2 (6.9) | 0.0076 |
| | 7 days | 3 (11.5) | 3 (10.3) | 1.0 |
| Sites combined | | Silver Fluoride (N = 63) | Control (N = 63) | |
| | | n (%) | n (%) | *P*-value* |
| | Baseline | 9 (14.3) | 9 (14.3) | 1.0 |
| | 24 hrs | 13 (20.6) | 4 (6.3) | 0.035 |
| | 7 days | 6 (9.5) | 4 (6.3) | 0.74 |

*Fisher's exact test

## Clinical Effectiveness

The average pain scores before and after treatment, by site, are given in Table 1. At the Lima site, the silver fluoride group had slightly higher baseline scores (average = 57.3) than the control (average = 49.3; $P = 0.16$). At the Cusco site, the baseline scores were similar between the silver fluoride group (average = 51.7) and control (average = 51.6; $P = 0.98$). The primary study endpoint was the change from baseline to 7 days. In Lima, the average change in pain score between baseline and day 7 for the silver fluoride group was -35.8 (SD = 27.7) mm *vs*. 0.4 (SD = 16.2) for the controls ($P < 0.0001$). In Cusco, the average change in pain score between baseline and day 7 for the silver fluoride group was -23.4 (SD = 21.0) mm *vs*. -5.5 (SD = 18.1) mm ($P = 0.0015$) for water.

Comparison of tooth sensitivity at 24 hrs and 7 days between study groups by analysis covariance, adjusted for the baseline sensitivity level, gave similar results.

There was no significant three-way interaction among study site, time, and study group (GEE linear regression; $P = 0.20$), but all two-way interactions were significant: study site by time ($P = 0.043$), study site by study group ($P = 0.0006$), and study group by time ($P = 0.0076$). Hence, an analysis of time effect was done separately by study site. In Lima, there was no significant time-by-study-group interaction ($P = 0.21$). The overall study group difference in tooth sensitivity (over both time-points), adjusted for baseline sensitivity, was 29.9 ($P < 0.001$). The overall difference in sensitivity between 24 hrs and 7 days was 4.5 ($P = 0.014$). In Cusco, there was a significant study-group-by-time interaction ($P = 0.015$), so the overall study group difference is not reported. The differences in sensitivity between 24 hrs and 7 days were 16.9 ($P = 0.005$) for silver fluoride and 4.5 ($P = 0.097$) in the control group, respectively.

## Safety

The number and percent of participants with a erythema score of 2 for the gingival tissue of the tooth treated for each treatment condition by site and time are given in Table 2. Scores were low; no individual had score 3, severe erythema, either before or after the application of silver fluoride. There was no difference in the proportion of participants with erythema score > 1 between the silver fluoride group and the placebo (Fisher's Exact Test, $P = 1.0$) at any time-point in the Lima population. There was a small but significant increase in the proportion of participants at the Cusco site who experienced an erythema score > 1 at 24 hrs ($P = 0.0076$). There was no difference in the proportion of participants with an erythema score > 1 between the groups in Cusco after 7 days ($P = 1.0$). No white or dark changes were noted in gingiva in any participant at any time in any condition at either site. An independent examiner, who was blind to treatment condition and time, examined the photographs and confirmed this lack of change.

The Gingival Index scores for each treatment condition and site are listed in Table 3. The mean (SD) Gingival Index scores for the mouth for treatment and control groups at baseline were: (Lima) silver fluoride, 0.29 (0.24), control 0.33 (0.35) ($P = 0.59$); and (Cusco) silver fluoride, 0.47 (0.24), control 0.38 (0.27) ($P = 0.19$). At 7 days, the mean (SD) changes in GI scores were: (Lima) silver fluoride, -0.02 (0.09), control 0.03 (0.13) ($P = 0.076$); and (Cusco) silver fluoride, -0.16 (0.27), control -0.03 (0.09) ($P = 0.023$). Similar results were observed after 24 hrs.

Photographs of the teeth suggest that the silver fluoride did not stain most exposed root surfaces (see Fig. 2 for an example). This result was found only when surfaces had untreated decay.

**Table 3.** Overall Gingival Index Score by Study Site and Condition

| Study Site | Time | Condition | | |
|---|---|---|---|---|
| Lima | | Silver Fluoride (N = 37) | Control (N = 34) | |
| | | Mean (SD) [Range] | Mean (SD) [Range] | P-value* |
| | Baseline | 0.29 (0.24) [0.0, 1.2] | 0.33 (0.35) [0.0, 1.5] | 0.59 |
| | 24 hrs | 0.28 (0.24) [0.0, 1.2] | 0.35 (0.36) [0.0, 1.7] | |
| | Change from baseline | -0.01 (0.05) [-0.2, 0.1] | 0.02 (0.07) [-0.2, 0.2] | 0.076 |
| | 7 days | 0.27 (0.23) [0.0, 1.2] | 0.36 (0.39) [0.1, 1.8] | |
| | Change from baseline | -0.02 (0.09) [0.2, 0] | 0.03 (0.13) [-0.5, 0.3] | 0.076 |
| Cusco | | Silver Fluoride (N = 26) | Control (N = 29) | |
| | | Mean (SD) [Range] | Mean (SD) [Range] | P-value* |
| | Baseline | 0.47 (0.24) [0.1, 0.9] | 0.38 (0.27) [0.0, 1.2] | 0.19 |
| | 24 hrs | 0.36 (0.21) [0.1, 0.8] | 0.36 (0.24) [0.0, 1.2] | |
| | Change from baseline | -0.11 (0.16) [-0.6, 0.1] | -0.02 (0.12) [-0.3, 0.3] | 0.020 |
| | 7 days | 0.31 (0.19) [0.0, 0.8] | 0.35 (0.26) [0.1, 1.2] | |
| | Change from baseline | -0.16 (0.27) [-0.8, 0.7] | -0.03 (0.09) [-0.3, 0.2] | 0.023 |
| Sites Combined | | Silver Fluoride (N = 63) | Control (N = 63) | |
| | | Mean (SD) [Range] | Mean (SD) [Range] | P-value** |
| | Baseline | 0.36 (0.26) [0.0, 1.2] | 0.35 (0.32) [0.0, 1.5] | 0.72 |
| | 24 hrs | 0.31 (0.23) [0.0, 1.2] | 0.35 (0.31) [0.0, 1.7] | |
| | Change from baseline | -0.05 (0.12) [-0.6, 0.1] | 0.00 (0.10) [-0.3, 0.3] | 0.0023 |
| | 7 days | 0.28 (0.22) [0.0, 1.2] | 0.35 (0.33) [0.1, 1.8] | |
| | Change from baseline | -0.08 (0.20) [-0.8, 0.7] | 0.00 (0.12) [-0.5, 0.3] | 0.0028 |

*Two-sample test (unequal variances).
**Analysis of covariance, adjusted for study site, with heteroscedasticity-consistent standard errors.

## DISCUSSION

In a population with teeth sensitive to air, this trial demonstrated that a topical solution of diammine silver fluoride was more effective than a placebo in reducing tooth pain. Reductions grew larger between 24 hrs and 7 days post-treatment. The study was conducted in two sites by different investigators to increase generalizability and had sufficient statistical power to detect clinically meaningful differences in pain. The study involved many more individuals than the typical study (Ritter *et al.*, 2006).

The results, however, are consistent with those from similar studies of other desensitizers, such as self-administered 0.717% fluoride solution (Thrash *et al.*, 1992) or fluoride varnish (Ritter *et al.*, 2006). In the fluoride solution study, the authors concluded that two one-minute applications reduced sensitivity to cold. Participants in the varnish study experienced a pain reduction in response to ice, but not to air, at 2 wks. The current study reported significant pain reductions in response to air in 24 hrs that were maintained at 7 days. The magnitude of reduction was considerably greater than in the other studies. The current study did not use ice as a stimulus.

There were no unintended effects on the gingiva, and any inflammation resulting from the treatment was minor and transient. No staining of the gingival tissues was observed.



**Figure 2.** Root caries at baseline (**left panel**), 24 hrs after treatment (**middle panel**), and 7 days after treatment with diammine silver fluoride (**right panel**).

Staining of teeth was found only when surfaces had untreated decay. The staining of carious dentin can be minimized by the application of potassium iodide solution after treatment without reducing the effect (Knight *et al.*, 2006).

Diammine silver fluoride has been shown to arrest caries in animal models (Tanzer *et al.*, 2010) and to be more effective than sodium fluoride varnish in human trials (Chu *et al.*, 2002; Llodra *et al.*, 2005; Rosenblatt *et al.*, 2009; Tan *et al.*, 2010). It did not cause abscesses in teeth with open cavities that were treated. The mechanism of action for caries arrest may be antimicrobial (Knight *et al.*, 2009). Studies have also shown that diammine silver fluoride is free of adverse effects (Chu *et al.*, 2002; Llodra *et al.*, 2005; Tan *et al.*, 2010). This suggests that diammine fluoride may be particularly effective in individuals in whom sensitivity is associated with demineralization and caries.

Diammine silver fluoride has been demonstrated to be a clinically effective and safe tooth desensitizer after 24 hrs and 7 days. Clinical trials are warranted to examine effectiveness over a longer period of time and in comparison with other agents.

## ACKNOWLEDGMENTS

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# UCSF Protocol for Caries Arrest Using Silver Diamine Fluoride: Rationale, Indications and Consent

Jeremy A. Horst, DDS, PhD; Hellene Ellenikiotis, DDS; and Peter L. Milgrom, DDS

**ABSTRACT**  The Food and Drug Administration recently cleared silver diamine fluoride for reducing tooth sensitivity. Clinical trials document arrest and prevention of dental caries by silver diamine fluoride. This off-label use is now permissible and appropriate under U.S. law. A CDT code was approved for caries arresting medicaments for 2016 to facilitate documentation and billing. We present a systematic review, clinical indications, clinical protocol and consent procedure to guide application for caries arrest treatment.

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Until now, no option for the treatment of dental caries in the U.S. besides restorative dentistry has shown substantial efficacy.[1] Silver diamine fluoride is an inexpensive topical medicament used extensively in other countries to treat dental caries across the age spectrum. No other intervention approaches the ease of application and efficacy. Multiple randomized clinical trials — with hundreds of patients each — support its use for caries treatment, thus substantiating an intervention that addresses an unmet need in American dentistry. In August 2014, the Food and Drug Administration (FDA) cleared the first silver diamine fluoride product for market, and as of April 2015, that product is available.

Since its approval in Japan more than 80 years ago,[2] more than 2 million containers have been sold. The silver acts as an antimicrobial, the fluoride promotes remineralization and the ammonia stabilizes high concentrations in solution.[3]

Because silver diamine fluoride is new to American dentistry and dental education, there is a need for a standardized guideline, protocol and consent. The University of California, San Francisco, School of Dentistry paradigm shift committee assembled a subcommittee with the following goals:

- Use available evidence to develop a list of clinical indications.
- Define a protocol that maximized safety and efficacy and minimized inadvertent staining of clinical facilities.

- Build an informed consent document at the eighth-grade reading level.

We conducted a systematic review, inquired of authors of published clinical and in vitro studies about details and considerations in their protocols and consulted experts in cariology and materials chemistry where evidence was lacking. The work of this committee resulted in the adoption of silver diamine fluoride use in the UCSF student clinics.

## Methods

A literature review was designed by a medical librarian to search PubMed and the International Association of Dental Research abstract archive with the following search terms: "33040-28-7" OR "1Z00ZK3E66" OR "silver diamine fluoride" OR "silver fluoride" OR "silver diamine fluoride" OR "diammine silver fluoride" OR "ammonical silver fluoride" OR "ammoniacal silver fluoride". Differences in nomenclature have led to confusion around this material. Another review was completed with the terms "dental" OR "caries" AND "silver nitrate" AND "clinical."

## Material

Silver diamine fluoride (38% w/v $Ag(NH_3)_2F$, 30% w/w) is a colorless topical agent comprised of 24.4-28.8% (w/v) silver and 5.0-5.9% fluoride at pH 10,[4] and marketed as Advantage Arrest by Elevate Oral Care LLC (West Palm Beach, Fla.). Other companies may market silver diamine fluoride in the future following determination of substantial equivalence and FDA clearance.

## Mechanisms

Silver diamine fluoride is used for caries arrest and treatment of dentin hypersensitivity. In the treatment of exposed sensitive dentin surfaces,

topical application results in the development of a squamous layer on the exposed dentin, partially plugging the dentinal tubules.[5] High concentration aqueous silver has been long known to form this protective layer.[6] Decreased sensitivity in treated patients[7,8] is consistent with the hydrodynamic theory of dentin hypersensitivity.[9]

Dental caries is a complex progression involving dietary sugars, bacterial metabolism, demineralization and organic degradation. The collagenous organic matrix is

> Silver diamine fluoride outperforms other anticaries medicaments in killing cariogenic bacteria in dentinal tubules.

exposed once a dentin surface is demineralized and destroyed by native and bacterial proteases to enable a lesion to enlarge.[10] Upon application of silver diamine fluoride to a decayed surface, the squamous layer of silver protein conjugates forms, increasing resistance to acid dissolution and enzymatic digestion.[11] Hydroxyapatite and fluorapatite form on the exposed organic matrix, along with the presence of silver chloride and metallic silver.[5] The treated lesion increases in mineral density and hardness while the lesion depth decreases.[5] Meanwhile, silver diamine fluoride specifically inhibits the proteins that break down the exposed dentin organic matrix: matrix metalloproteinases,[11] cathepsins[12] and bacterial collagenases.[5] Silver

ions act directly against bacteria in lesions by breaking membranes, denaturing proteins and inhibiting DNA replication.[13,14] Ionic silver deactivates nearly any macromolecule. Silver diamine fluoride outperforms other anticaries medicaments in killing cariogenic bacteria in dentinal tubules.[15]

Silver and fluoride ions penetrate ~25 microns into enamel[16] and 50-200 microns into dentin.[17] Fluoride promotes remineralization, and silver is available for antimicrobial action upon release by re-acidification.[18] Silver diamine fluoride arrested lesions are 150 microns thick.[19]

Artificial lesions treated with silver diamine fluoride are resistant to biofilm formation and further cavity formation, presumably due to remnant ionic silver.[20,21] More silver and fluoride is deposited in demineralized than nondemineralized dentin. Correspondingly, treated demineralized dentin is more resistant to caries bacteria than treated sound dentin.[22] When bacteria killed by silver ions are added to living bacteria, the silver is re-activated so that effectively the dead bacteria kill the living bacteria in a "zombie effect."[23] This reservoir effect helps explain why silver deposited on bacteria and dentin proteins within a cavity has sustained antimicrobial effects.

## Clinical Evidence

### Silver Nitrate Plus Fluoride Varnish

Before the FDA cleared silver diamine fluoride, some U.S. dentists sequentially applied silver nitrate then fluoride varnish to dentinal decay as the only available noninvasive option for caries treatment. Duffin rediscovered silver nitrate from the early literature,[24] which had been lost

to modern cariology. Surprisingly, there is no mention of silver nitrate in either of the American Dental Association Council on Scientific Affairs reports on *Nonfluoride Caries-Preventive Agents*[25] or *Managing Xerostomia and Salivary Gland Hypofunction*,[26] and it is not part of standard dental school curricula. Case series of carious lesions arrested by silver nitrate date to the 1800s. For example, in 1891, 87 of 142 treated lesions were arrested.[27] Percy Howe, DDS, then director of the Forsyth Institute in Boston, added ammonia to silver nitrate, making it more stable and effective as an antimicrobial for application to any infected tooth structure from early cavitated lesions to infected root canals.[28] Duffin added the application of fluoride varnish following silver nitrate, simulating silver diamine fluoride. While his clinic doubled in patients, cases needing general anesthesia disappeared. His review of randomly selected charts showed only seven of 578 treated lesions progressed within two and a half years to the point that extractions were needed.[24] Thus, with the exception of Duffin's and one other report, attention to silver nitrate largely disappeared by the 1950s. The lore is that use and teaching of this intervention were lost with the introduction of effective local anesthetic to enable painless restorations and fluoride for caries prevention. Because no high-quality clinical trials have been performed, we did not include the silver nitrate plus fluoride varnish regimen in our recommendation.

## Silver Diamine Fluoride

We found nine published randomized clinical trials evaluating silver diamine fluoride for caries arrest and/or prevention of at least one year in duration. These studies each involved hundreds of children aged 3 to 9 or adults aged 60 to 89 (**FIGURES 1** and **2**). Most participants had low (< 0.3 ppm) fluoride in the environmental water and reported using fluoride toothpaste (e.g., 73 percent).[29] Silver diamine fluoride was applied with cotton isolation. Lesions were detected with mirror and explorer only. All studies were registered and met the Consolidated Standards of Reporting Trials requirements. Clinical cases and studies not meeting these criteria can be found elsewhere.[30]

> When stannous fluoride was used to activate color change, a break in the black color within a lesion at six months was highly sensitive and specific for active caries.

Caries arrest increased dramatically after reapplication from one year posttreatment[31-33] to one and a half years,[31,34] and increasingly to two to three years (**FIGURE 1**).[29,31,35] Single application without repeat lost effect over time in the elderly.[32] Twice per year application resulted in more arrest than once per year.[31,35] Twelve percent silver diamine fluoride was markedly less effective.[32]

Darkening of the entire lesion indicated success at follow-up and is suggested to facilitate diagnosis of caries arrest status by nondentists. A longitudinal study reported that color activation of silver diamine fluoride with 10% stannous fluoride resulted in less first molar caries.[36] Tea extract was used in one group to activate color change for improved follow-up diagnosis; no differences in arrest were seen.[32] Indeed, when stannous fluoride was used to activate color change, a break in the black color within a lesion at six months was highly sensitive and specific for active caries.[37]

Silver diamine fluoride greatly outperformed fluoride varnish for caries arrest[29] and was equivalent or better than glass ionomer cement (GIC) (**FIGURE 1**).[31,33] The addition of semiannual intensive oral health education with the application of silver diamine fluoride in the elderly increased the arrest of root caries (**FIGURE 1**).[38]

## Caries Prevention

When silver diamine fluoride was applied only to carious lesions, impressive prevention was seen for other tooth surfaces.[29,35] Fluoride-releasing GIC can have this effect but it is limited to surfaces adjacent to the treated surface and of short duration. Direct application to healthy surfaces in children also helps prevent caries (**FIGURE 2**).[29,35,39] Two studies show great difference in the level of prevention in the elderly;[38,40] the difference is hard to reconcile. As seen for arrest, prevention is less after one year without repeat application.[41]

Annual application of silver diamine fluoride prevented many more carious lesions than four-times-per-year fluoride varnish in both children[29] and the elderly.[40] Prevention was roughly equivalent to twice-per-year varnish in one study (**FIGURE 2**).[39] The addition of semiannual intensive oral health education in a study of the elderly increased prevention.[38] Although many fell out, GIC or resin sealants outperformed silver diamine fluoride in preventing caries in the first molars of children,[39,41] though the cost was ~20 times more.

## Ongoing Trials

Unpublished reports of clinical studies unanimously confirm better caries arrest and/or prevention by silver diamine fluoride over control or other materials. A one-year report of a study of the elderly demonstrated that the addition of a saturated solution of potassium iodide (SSKI) to decrease discoloration did not significantly alter caries arrest or prevention.[42] This was confirmed in the two-year examinations (personal communication, Edward Lo). A one-year report of a study in children showed that the application once per week for three consecutive weeks, once per year, was more effective than that of single annual application.[43] Other studies have recently begun to evaluate the ability of silver diamine fluoride to arrest interproximal carious lesions, to compare the relative efficacy of silver diamine fluoride to the combination of silver nitrate plus fluoride varnish and to compare the effects on populations with or without access to fluoridated water. Final reports from these studies will follow in the coming years.

## Recommendations From the Literature on Clinical Efficacy

These studies show that 38% silver diamine fluoride is effective and efficient in arresting and preventing carious lesions. Application only to lesions appears to be similarly effective in preventing cavities in other teeth and surfaces as applying directly. Single application appears insufficient for sustained effects, while annual re-application results in remarkable success, and even greater effects with semi-annual application. From these data, we recommend twice-per-year application, only to carious lesions without excavation, for at least the first two years.
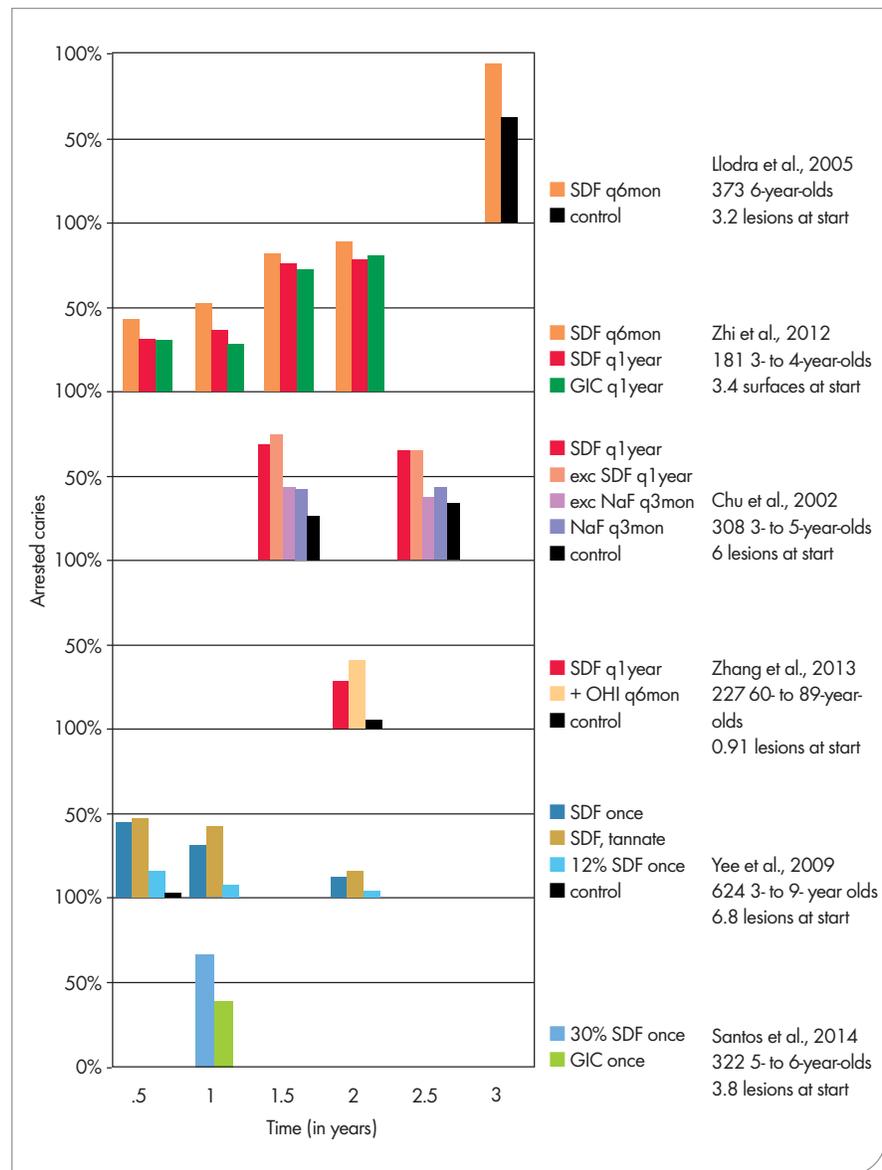


**FIGURE 1.** Graphic summary of randomized controlled trials demonstrating caries arrest after topical treatment with 38% silver diamine fluoride (SDF). Studies are arranged vertically by frequency of silver diamine fluoride application. Caries arrest is defined as the fraction of initially active carious lesions that became inactive and firm to a dental explorer. SDF (38% unless noted otherwise); q6mon, every six months; q1year, every year; q3mon, every three months; GIC, glass ionomer cement; NaF, 5% sodium fluoride varnish; + OHI q6mon, SDF every year and oral hygiene instructions every six months.

For any patient with active caries, we recommend considering replacement of fluoride varnish as the primary means to prevent new lesions, with application of silver diamine fluoride to the active lesions only. For patients without access to both sealants and monitoring, silver diamine fluoride is the agent of choice for prevention of caries in permanent molars — particularly as there is no margin to leak and thereby facilitate deep caries and it does not stain sound enamel.
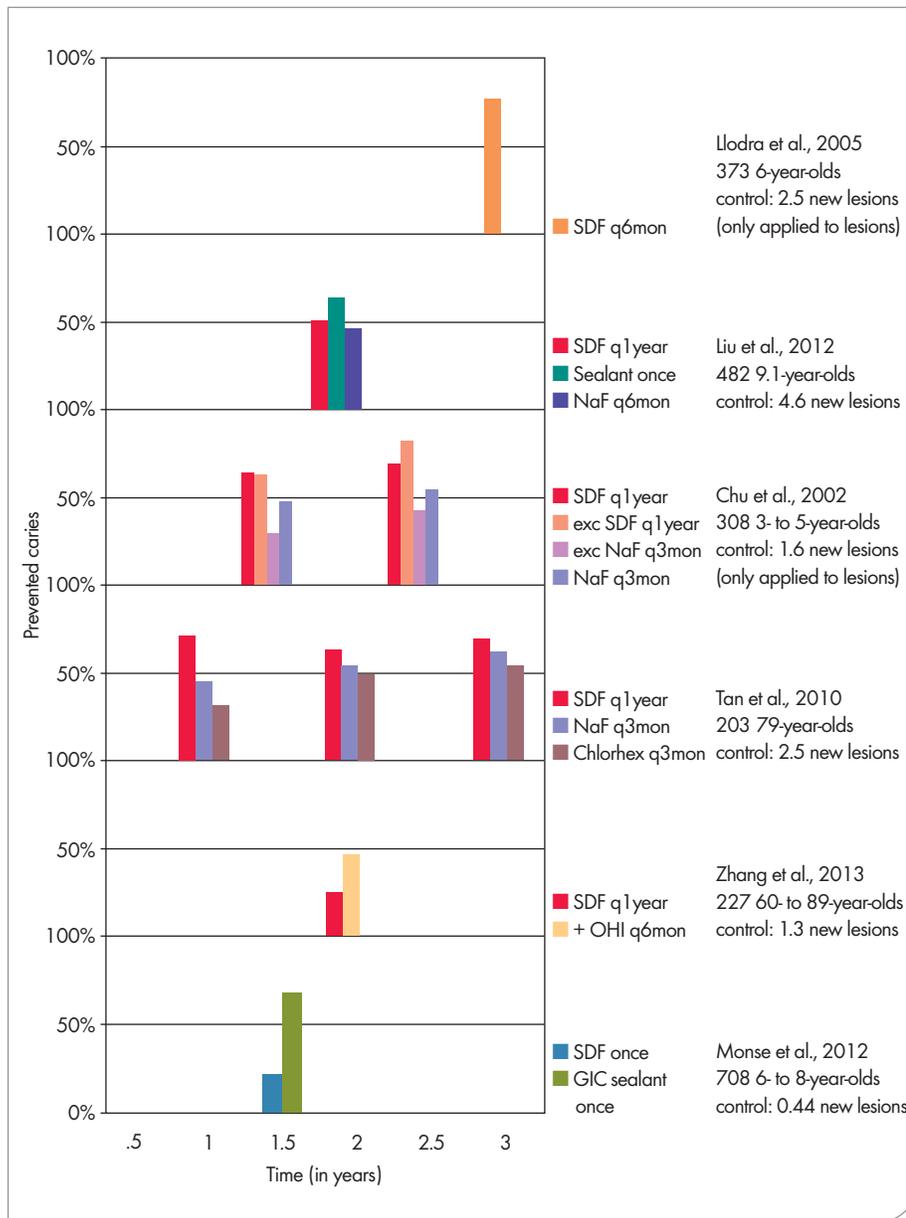
**FIGURE 2.** Graphic summary of randomized controlled trials demonstrating caries prevention after topical treatment of carious lesions with 38% silver diamine fluoride. Prevented caries is defined as the fraction of new carious lesions in treatment groups as compared to those in the placebo or no treatment control group. Chlorhex, 1% chlorhexidine varnish.

Longer studies are needed to determine whether caries arrest and prevention can be maintained with decreased application after two to three years, and whether more frequent use would enhance efficacy. Traditional or nontraditional restorative approaches, such as the atraumatic restorative technique (ART)[44] and Hall crowns,[45] should be performed as dictated by the response of the patient, disease progression and the nature of individual lesions.

## Safety

### Maximum Dose and Safety Margin

The margin of safety for dosing is of paramount concern. In gaining clearance from the FDA, female and male rat and mouse studies were conducted to determine the lethal dose (LD50) of silver diamine fluoride by oral and subcutaneous administration. Average LD50 by oral administration was 520 mg/kg and by subcutaneous administration was 380 mg/kg. The subcutaneous route is taken here as a worst-case scenario. One drop (25 µL) is ample material to treat five teeth and contains 9.5 mg silver diamine fluoride. Assuming the smallest child with caries would be in the range of 10 kg, the dose would be 0.95 mg/kg child. Thus, the relative safety margin of using an entire drop on a 10 kg child is 380 mg/kg LD50/0.95 mg/kg dose = four-hundredfold safety margin. The actual dose is likely to be much smaller, for example 2.37 mg total for three teeth was the largest dose measured in six patients.[46] The most frequent application monitored in a clinical trial was weekly for three weeks, annually.[43] Thus, we set our recommended limit as one drop (25 µL) per 10 kg per treatment visit, with weekly intervals at most. This dose is commensurate with the Environmental Protection Agency's (EPA) allowable short-term exposure of 1.142 mg silver per liter of drinking water for one to 10 days (Agency for Toxic Substances and Disease Registry, ATSDR, 1990).

Cumulative exposure from lower-level acute or chronic silver intake has no real physiologic disease importance, but the bluing of skin in argyria should obviously be avoided. The EPA set the lifetime exposure conservatively at 1 gm to safely avoid argyria. The highest applied dose for three teeth measured in the pharmacokinetic study, 2.37 mg, would enable > 400 applications.[46] Silver

nitrate (typically a 25% solution) has been used for more than 100 years in the U.S. without incident, including acceptance by the ADA, and in other countries for arresting dental caries.[3]

### Adverse Effects

Not a single adverse event has been reported to the Japanese authorities since they approved silver diamine fluoride (Saforide, Toyo Seiyaku Kasei Co. Ltd., Osaka, Japan) more than 80 years ago.[47] The manufacturer estimates that more than 2 million multi-use containers have been sold, including > 41,000 units in each of the last three reporting years.

In the nine randomized clinical trials in which silver diamine fluoride was applied to multiple teeth to arrest or prevent dental caries, the only side effect noted was for three of 1,493 children or elderly patients monitored for one to three years who experienced "a small, mildly painful white lesion in the mucosa, which disappeared at 48 [hours] without treatment."[29,31-33,35,38,40,41,48] The occurrence of reversible localized changes to the oral mucosa was predicted in the first reports of longitudinal studies.[49] No adverse pulpal response was observed.

Gingival responses have been minimal. In a pharmacokinetic study of silver diamine fluoride application to three teeth in each of six 48- to 82-year-olds, no erythema, bleeding, white changes, ulceration or pigmentation was found after 24 hours. Serum fluoride hardly went up from baseline, while serum silver increased about tenfold and stayed high past the four hours of measurement.[46] In a two-site hypersensitivity trial of 126 patients in Peru, at baseline 9 percent of patients presented redness scores of 2 (1 being normal, 2 being mild to moderate redness and 3 being severe); and after one day, 13 percent in silver diamine fluoride treated patients versus 4 percent

in controls. All redness was gone at seven days. Meanwhile, gingival index improved slightly in silver diamine fluoride treated patients.[7] Nonetheless, gingival contact should be minimized. In our experience, it has been adequate to coat the nearby gingiva with petroleum jelly, use the smallest available microsponge and dab the side of the dappen dish to remove excess liquid before application.

Concerns for fluoride safety are most relevant to chronic exposure,[50] whereas this is an acute exposure. Chronically high systemic fluoride results in dental

> At least for children, many parents have seen the color changes as a positive indication that the treatment was effective.

fluorosis. The ubiquitous use of fluoride-based gas in general anesthetics has shown that the first acute response is transient renal holding, and is rare.[51] Concerns have been raised about poorly controlled silver diamine fluoride concentrations[52] and fluorosis appearing in treated rats.[53] However, silver and fluoride levels are closely monitored for the U.S. product, and the Health Department of Western Australia conducted a study that found no evidence of fluorosis resulting from long-term proper use of silver diamine fluoride.[54] Therefore, we have concluded that the development of fluorosis after application of the U.S.-approved product is not a clinically significant risk.

Silver allergy is a contraindication. Relative contraindications include any significant desquamative gingivitis or

mucositis that disrupts the protective barrier formed by stratified squamous epithelium. Increased absorption and pain would be expected with contact. Heightened caution and use of a protective gingival coating may suffice.

A saturated solution of potassium iodide (SSKI) is contraindicated in pregnant women and during the first six months of breastfeeding because of the concern of overloading the developing thyroid with iodide; thyroid specialists suggested a pregnancy test prior to use in women of childbearing age uncertain of their status.

### Nonmedical Side Effects

Silver diamine fluoride darkens carious lesions. At least for children, many parents have seen the color changes as a positive indication that the treatment was effective.[29] Application of an SSKI immediately following silver diamine fluoride treatment is thought to decrease staining (patent US6461161). This is an off-label use; potassium iodide is approved as an over-the-counter drug to facilitate mucus release to breathe more easily with chronic lung problems and to protect the thyroid from radioactive iodine in radiation emergencies. In our clinical experience, SSKI helps but does not dramatically effect stain; arrested lesions normally darken. Most stain remains at the dentin-enamel or cementum-enamel junction. However, SSKI maintains resistance to biofilm formation or activity in laboratory studies.[20] Also, SSKI maintained caries arrest efficacy in the early results of an ongoing clinical trial.[42] Meanwhile, silver diamine fluoride-treated lesions can also be covered with GIC or composite (see below for discussion on bonding).

Patients note a transient metallic or bitter taste. In our experience, with judicious use, the taste and texture

response is more favorable than the response to fluoride varnish.

Even a small amount of silver diamine fluoride can cause a "temporary tattoo" to the skin (on the patient or provider), like a silver nitrate stain or henna tattoo, and does no harm. Stain on the skin resolves with the natural exfoliation of skin in two to 14 days. Universal precautions prevent most exposures. Long-term mucosal stain, local argyria akin to an amalgam tattoo, has been observed when applying silver nitrate to intraoral wounds; we anticipate similar stains with submucosal exposure to silver diamine fluoride.

Silver diamine fluoride stains clinic surfaces and clothes. The stain does not come out once it sets. Spills should be cleaned up immediately with copious water, ethanol or bleach. High pH solvents such as ammonia may be more successful. Secondary containers and plastic liners for surfaces are adequate preventives.

### Effects on Bonding

Using a contemporary bonding system, silver diamine fluoride had no effect on composite bonding to noncarious dentin using either self-etch or full-etch systems.[55] In one study, simply rinsing after silver diamine fluoride application avoided a 50 percent decrease in bond strength for GIC.[56] In another study, increased dentin bond strength to GIC was observed.[57] Silver diamine fluoride decreased dentin bonding strength of resin-based crown cement by approximately one-third.[58] Thus, rinsing will suffice for direct restorations, while excavation of the silver diamine fluoride-treated superficial dentin is appropriate for cementing crowns.

### Indications

Countless patients would benefit from conservative treatment of nonsymptomatic active carious lesions. We discuss the following indications.

First, extreme caries risk is defined as patients with salivary dysfunction, usually secondary to cancer treatment, Sjogren's syndrome, polypharmacy, aging or methamphetamine abuse. For these patients, frequent prevention visits and traditional restorations fail to stop disease progression. Similar disease recurrence occurs in severe early childhood caries.

Second, some patients cannot tolerate standard treatment for medical or psychological reasons. These include the precooperative child, the frail elderly, those with severe cognitive or physical

> Countless patients would benefit from conservative treatment of nonsymptomatic active carious lesions.

disabilities and those with dental phobias. Various forms of immunocompromise mean that these same patients have a much higher risk of systemic infection arising from untreated dental caries. Many only receive restorative care with general anesthesia or sedation and others are not good candidates for general anesthesia due to frailty or another medical complexity. The Centers for Disease Control and Prevention (CDC) estimates 1.4 million people in the U.S. live in nursing homes and 1.2 million live in hospice.[59] These individuals tend to have medical, behavioral, physical and financial limitations that beg a reasonable option.

Third, some patients have more lesions than can be treated in one visit, such that new lesions arise or existing lesions become symptomatic while

awaiting completion of treatment. This is particularly relevant to the dental school setting where treatment is slow. American dentistry has been desperately lacking an efficient instrument to be used at the diagnostic visit to provide a step toward controlling the disease.

Fourth, some lesions are just difficult to treat. Recurrent caries at a crown margin, root caries in a furcation or the occlusal of a partially erupted wisdom tooth pose a challenge to access, isolation and cleansability necessary for restorative success.

Following the above considerations, we developed four indications for treatment of dental caries with silver diamine fluoride:
1. Extreme caries risk (xerostomia or severe early childhood caries).
2. Treatment challenged by behavioral or medical management.
3. Patients with carious lesions that may not all be treated in one visit.
4. Difficult to treat dental carious lesions.

Finally, these indications are for our school clinics. They do not address access to care. The U.S. Department of Health and Human Services estimates 108 million Americans are without dental insurance, and there are 4,230 shortage areas with 49 million people without access to a dental health professional.[60] Unlike fillings, failure of silver diamine fluoride treatment does not appear to create an environment that promotes caries, and thus needs to be monitored. Thus, a final important indication is:
5. Patients without access to dental care.

### Clinical Application

We considered practical strategies to maximize safety and effectiveness in the design of a clinical protocol for the UCSF dental clinics (FIGURE 3).

The key factor is repeat application

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**Silver Diamine Fluoride (SDF)**
**UCSF Protocol for Arresting Dental Carious Lesions or Treating Tooth Sensitivity**

**Material**: Advantage Silver Arrest (38% SDF, purified water) from Elevate Oral Care.
Shelf life: three years unopened. Do not refrigerate. Avoid freezing or extreme heat.

**Indications:**
1. Extreme caries risk (xerostomia or severe early childhood caries).
2. Treatment challenged by behavioral or medical management.
3. Patients with carious lesions that may not all be treated in one visit.
4. Difficult to treat dental carious lesions.
5. Patients without access to dental care.

**Maximum dose:** 25 µL (1 drop) / 10kg per treatment visit.
**SDF Contraindication:** Silver allergy.
**SDF Relative Contraindications:** Ulcerative gingivitis, stomatitis.
**SSKI Contraindications:** Pregnancy, breastfeeding.

**Considerations:**
- Decayed dentin will darken as the caries lesions arrest. Most will be dark brown or black.
- SDF can stain the skin, which will clear in two to three weeks without treatment.
- SDF can permanently stain operatory surfaces and clothes.
- A control restoration (e.g., GI via ART or other material) may be considered after SDF treatment.
- Saturated solution of potassium iodide (SSKI, Lugol's Solution, various sources) can be used after SDF to decrease color changes.
- Re-application is usually recommended, biannually until the cavity is restored or arrested or the tooth exfoliates.

**Procedure:**
1. Plastic-lined cover for counter, plastic-lined bib for patient.
2. Standard personal protective equipment (PPE) for provider and patient.
3. One drop of SDF into the deep end of a plastic dappen dish
   (also obtain one drop of SSKI in a separate dappen dish if selected).
4. Remove bulk saliva with saliva ejector.
5. Isolate tongue and cheek from affected teeth with 2-inch by 2-inch gauze or cotton rolls.
6. If near the gingiva, consider applying petroleum jelly with a cotton applicator for safety.
7. Dry affected tooth surfaces with triple syringe or if not feasible dry with cotton.
8. Bend microsponge, immerse into SDF, remove excess on side of dappen dish.
9. Apply directly onto the affected tooth surface(s) with microsponge.
10. Allow SDF to absorb for up to one minute if reasonable, then remove excess with gauze or cotton roll.
    (If using SSKI, apply with a different microsponge. Repeat one to three times until no further white precipitates are observed.
    Wait five to 10 seconds between applications. Remove excess with cotton.)
11. Rinse with water.
12. Place gloves, cotton and microbrushes into plastic waste bags.

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**FIGURE 3.** Clinical protocol for the UCSF dental clinics.

over multiple years. We believe that dryness of the lesion during application is also important. Isolation with gauze and/or cotton rolls is sufficient, while air drying prior to application is thought to improve effectiveness. Allowing one to three minutes for the silver diamine fluoride to soak into and react with a lesion is thought to effect success.

Allowing only a few seconds to soak in due to the cooperation limits of very young patients commonly results in arrest. Application time in clinical studies does not correlate to outcome. However, our committee decided to be cautious in our recommendations for initial use. Longer absorption time also decreases concerns about removing silver

diamine fluoride with a posttreatment rinse. Removing any excess material with the same cotton used to isolate is routine to minimize systemic absorption.

Many clinicians place silver diamine fluoride at the diagnostic visit, then at one and/or three-month follow ups, then at semiannual recall visits (six, 12, 18, 24 months). Whether application needs

to continue after two or three years to maintain caries arrest is not known. Another approach is simply to substitute silver diamine fluoride for any application of fluoride varnish to a patient with untreated carious lesions. Increased frequency with higher disease burden follows the caries management by risk assessment (CAMBRA) principles.[61] It is relevant to take photographs to track lesions over time.

Efforts to improve the penetration of silver diamine fluoride into affected dentin by chemical cavity preparation have not been studied but are being explored clinically. Pretreatment with ethylenediaminetetraacetic acid (EDTA) to remove superficial hydroxyapatite in affected dentin may open the dentinal tubules to further silver diamine fluoride penetration. Pretreatment with hypochlorite (bleach) may help breakdown bacteria and exposed dentin proteins, but this may be redundant to the action of the silver. Hypochlorite to decrease discoloration after silver diamine fluoride treatment is not recommended, as the color comes from silver that cannot be broken down like organic chromophores and might break down dentin proteins stabilized against the effects of bacteria and acid by interactions with silver.

Experience with the combination of silver nitrate plus fluoride varnish (see above) has many practitioners asking about a topical varnish after silver diamine fluoride placement to prevent silver diamine fluoride taste and keep the silver diamine fluoride in the lesion. We see no evidence that varnish would help achieve either goal. Varnish does not seal. Rather, allowing more time for residence and diffusion of silver diamine fluoride to react with and dry into the lesion is more likely to improve effectiveness. Also, in our experience, silver diamine fluoride results in less aversive taste and texture responses than to fluoride varnish.

Decreased darkening of lesions in the esthetic zone improves acceptance. SSKI is an option if the patient is not pregnant, though significant darkening should still be expected. SSKI and silver diamine fluoride are not to be combined prior to application — SSKI can be placed after drying the silver diamine fluoride-treated tooth. Silver diamine fluoride does not prevent restoration of a lesion, thus it does not prevent esthetic options. While silver diamine fluoride has been shown to be more effective than ART or interim restorative treatment

> In our experience, silver diamine fluoride results in less aversive taste and texture responses than to fluoride varnish.

(IRT),[33] the two are compatible and can be combined across one or more visits.

The California Business and Professions Code permits dental hygienists and assistants to apply silver diamine fluoride for the control of caries because they are topical fluorides (Section 1910.(b)). Physicians, nurses and their assistants are permitted to apply fluorides in California and in many other states and federal programs. The recent decision of the Oregon Dental Board to allow dental hygienists and assistants to place silver diamine fluoride under existing rules for topical fluoride medicaments sets a precedent. Dental hygienists and assistants in Oregon were barred from providing silver nitrate in a previous decision. All providers need to be trained. Applications should be tracked if applied to the same patient by multiple clinics.

## Documentation and Billing

A new code, D1354, for "interim caries arresting medication application" was approved by the Code on Dental Procedures and Nomenclature (CDT) Code Maintenance Commission for 2016. The code definition is "Conservative treatment of an active, nonsymptomatic carious lesion by topical application of a caries arresting or inhibiting medicament and without mechanical removal of sound tooth structure." The CDT Code is the U.S. HIPAA standard code set and is required for billing. The Commission includes representatives from the major insurers, Medicaid, ADA, AGD and specialty organizations. Insurers are in the process of evaluating coverage for this treatment.

## Legal Considerations

Silver diamine fluoride is cleared by the FDA for marketing as a Class II medical device to treat tooth sensitivity. We are discussing off-label use as a drug to treat and prevent dental caries. This is a parallel situation to fluoride varnish, which has the same device clearance but is ubiquitously used off label by dentists and physicians as a drug to prevent caries. The same public health dentists who achieved the FDA device clearance are now applying for a dental caries indication. However, this is a more complicated process, normally only carried out by large pharmaceutical companies, and is likely to take longer.

## Consent

Because silver diamine fluoride is new in the U.S., it is important to communicate effectively. In the UCSF clinics, we are using a special consent form (**FIGURE 4**) as a way to inform patients, parents and caregivers, and

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### UCSF Dental Center Informed Consent for Silver Diamine Fluoride

**Facts for consideration:**

- Silver diamine fluoride (SDF) is an antibiotic liquid. We use SDF on cavities to help stop tooth decay. We also use it to treat tooth sensitivity. SDF application every six to 12 months is necessary.
- The procedure: 1. Dry the affected area. 2. Place a small amount of SDF on the affected area.  3. Allow SDF to dry for one minute. 4. Rinse.
- **Treatment with SDF does not eliminate the need for dental fillings or crowns to repair function or esthetics. Additional procedures will incur a separate fee.**
- I should not be treated with SDF if: 1. I am allergic to silver. 2. There are painful sores or raw areas on my gums (i.e., ulcerative gingivitis) or anywhere in my mouth (i.e., stomatitis).

**Benefits of receiving SDF:**

- SDF can help stop tooth decay.
- SDF can help relieve sensitivity.



**Risks related to SDF include, but are not limited to:**

- **The affected area will stain black permanently.** Healthy tooth structure will not stain. Stained tooth structure can be replaced with a filling or a crown.
- Tooth-colored fillings and crowns may discolor if SDF is applied to them. Color changes on the surface can normally be polished off. The edge between a tooth and filling may keep the color.
- If accidentally applied to the skin or gums, a brown or white stain may appear that causes no harm, cannot be washed off and will disappear in one to three weeks.
- You may notice a metallic taste. This will go away rapidly.
- If tooth decay is not arrested, the decay will progress. In that case the tooth will require further treatment, such as repeat SDF, a filling or crown, root canal treatment or extraction.
- These side effects may not include all of the possible situations reported by the manufacturer. If you notice other effects, please contact your dental provider.
- Every reasonable effort will be made to ensure the success of SDF treatment. There is a risk that the procedure will not stop the decay and no guarantee of success is granted or implied.

**Alternatives to SDF, not limited to the following:**

- No treatment, which may lead to continued deterioration of tooth structures and cosmetic appearance. Symptoms may increase in severity.
- Depending on the location and extent of the tooth decay, other treatment may include placement of fluoride varnish, a filling or crown, extraction or referral for advanced treatment modalities.

**I CERTIFY THAT I HAVE READ AND FULLY UNDERSTAND THIS DOCUMENT AND ALL MY QUESTIONS WERE ANSWERED:**

_____(signature of patient)　　_____(date)

_____(signature of witness)　　_____(date)

**FIGURE 4.** UCSF special consent form.

to standardize procedures because we have so many inexperienced student clinicians. All practices have established procedures for consent and an extra form may not be needed in the community. The normal elements of informed consent apply. We sought to ensure awareness of the expected change in color of the dentin as the decay arrests, likelihood of reapplication and contraindications in the presence of silver allergy and stomatitis. Note the importance of distinguishing between allergy to nickel and other trace metals rather than silver allergy, which is rare. We used readability measurements to guide intelligibility and included a progressively discoloring lesion to show stain of a lesion but not healthy enamel.

## Conclusion

Silver diamine fluoride is a safe, effective treatment for dental caries across the age spectrum. At UCSF, it is indicated for patients with extreme caries risk, those who cannot tolerate conventional care, patients who must be stabilized so they can be restored over time, patients who are medically compromised or too frail to be treated conventionally and those in disparity populations with little access to care.

Application twice per year outperforms all minimally invasive options including the atraumatic restorative technique — with which it is compatible but 20 times less expensive. It approaches the success of dental fillings after two or more years, and again, prevents future caries — while fillings do not. Silver diamine fluoride is more effective as a primary preventive than any other available material, with the exception of dental sealants, which are > 10 times more expensive and need to be monitored.

Saliva may play a role in caries arrest by silver diamine fluoride. Lower rates of arrest are seen in geriatric patients.[38] The elderly tend to have less abundant and less functional saliva, which generally explains their higher caries rate. In pediatric patients, higher rates of arrest are noted for buccal or lingual smooth surfaces and anterior teeth.[31] These surfaces bathe more directly in saliva than others. It is surprising that silver chloride is the main precipitant in treated dentin, as chloride is not a common component of dentin or silver diamine fluoride, so may come from the saliva.

Traditional approaches often provide only temporary benefit, given the highest rates of recurrent caries are in patients with the worst disease burden. The advent of a treatment for nonsymptomatic caries not requiring general anesthesia or sedation addresses long-standing concerns about the expense, danger and practical complexity of these services.

Experience suggests that dryness prior to application enhances effectiveness. Good patient management is still profoundly relevant to the very young and otherwise challenged patients, though this one-minute intervention is more tolerable than other options. Silver diamine fluoride can readily replace fluoride varnish for the prevention of caries in patients who have active caries. This as a powerful new tool in the fight against dental caries, particularly suited for those who suffer most from this disease.

Clinical evidence supports continued application one to two times per year until the tooth is restored or exfoliates, and otherwise perhaps indefinitely. Some treated lesions keep growing, particularly those in the inner third of the dentin. It is unclear what will happen if treatment is stopped after two to three years and research is needed. ■

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## CLINICAL USE OF SILVER DIAMINE FLUORIDE IN DENTAL TREATMENT

FEBRUARY 2016

**Compendium of Continuing Education article provides an overview on the use of Silver Diamine Fluoride in dental treatment.**

May L. Mei, BDS, MDS, PhD; Edward Chin-Man Lo, BDS, MDS, PhD; and Chun-Hung Chu, BDS, MDS, PhD.

ABSTRACT

The use of a topical fluoride solution, namely silver diamine fluoride (SDF), in dental treatment has been drawing increasing attention. SDF has been used in some countries in Asia, including Japan and China, as a caries-arresting and anti-hypersensitivity agent. It was recently cleared by the Food and Drug Administration in the United States as a fluoride to manage hypersensitive teeth. Topical application of SDF is a noninvasive procedure that is quick and simple to use. Promising results of laboratory studies and clinical trials have suggested that SDF is more effective than other fluoride agents to halt the caries process. A review concluded that SDF is a safe, effective, efficient, and equitable caries control agent that has a potentially broad application in dentistry and may meet the criteria of both the WHO Millennium Development Goals and the US Institute of Medicine's criteria for 21st century medical care. This article provides an overview of the clinical use of SDF in dental treatment.

Please use the link below to access the full article.

https://cced.cdeworld.com/courses/4990#sthash.d0aJoy9Y.dpuf

**FRESH APPROACH TO CARIES ARREST IN ADULTS**

SEPTEMBER/OCTOBER 2015

**Decisions in Dentistry article on the use of Silver Diamine Fluoride in adult patients.**

Dr. John Featherstone, Dean of the University of California San Francisco School of Dentistry and Dr Jeremy Horst, DDS, PhD.

KEY TAKEAWAYS
- Cleared by the U.S. Food and Drug Administration for treating dentinal hypersensitivity, in off-label use silver diamine fluoride can be used to prevent and arrest caries.
- The agent acts as an antimicrobial that remains active well after application. It also promotes remineralization and resistance to demineralization in enamel and dentin.
- In order to effectively implement treatment, clinicians should know the indications and contraindications, and gain informed consent for use.
- Dentists and (if allowed by state practice acts) dental auxiliaries who apply this agent must understand precautions for handling silver diamine fluoride.
- Repeat application completely stops many, but not all lesions. Research is needed to determine why some caries are not arrested.

Please use the link below to access the full article.

http://decisionsindentistry.com/article/fresh-approach-to-caries-arrest-in-adults/

## CRITICAL REVIEWS IN ORAL BIOLOGY & MEDICINE

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# Silver Diamine Fluoride:
# A Caries "Silver-Fluoride Bullet"

## ABSTRACT

The antimicrobial use of silver compounds pivots on the 100-year-old application of silver nitrate, silver foil, and silver sutures for the prevention and treatment of ocular, surgical, and dental infections. $Ag^+$ kills pathogenic organisms at concentrations of < 50 ppm, and current/ potential anti-infective applications include: acute burn coverings, catheter linings, water purification systems, hospital gowns, and caries prevention. To distill the current best evidence relative to caries, this systematic review asked: Will silver diamine fluoride (SDF) more effectively prevent caries than fluoride varnish? A five-database search, reference review, and hand search identified 99 human clinical trials in three languages published between 1966 and 2006. Dual review for controlled clinical trials with the patient as the unit of observation, and excluding cross-sectional, animal, in vitro studies, and opinions, identified 2 studies meeting the inclusion criteria. The trials indicated that SDF's lowest prevented fractions for caries arrest and caries prevention were 96.1% and 70.3%, respectively. In contrast, fluoride varnish's highest prevented fractions for caries arrest and caries prevention were 21.3% and 55.7%, respectively. Similarly, SDF's highest numbers needed to treat for caries arrest and caries prevention were 0.8 (95% CI = 0.5-1.0) and 0.9 (95% CI = 0.4-1.1), respectively. For fluoride varnish, the lowest numbers needed to treat for caries arrest and prevention were 3.7 (95% CI = 3.4-3.9) and 1.1 (95% CI = 0.7-1.4), respectively. Adverse events were monitored, with no significant differences between control and experimental groups. These promising results suggest that SDF is more effective than fluoride varnish, and may be a valuable caries-preventive intervention. As well, the availability of a safe, effective, efficient, and equitable caries-preventive agent appears to meet the criteria of both the WHO Millennium Goals and the US Institute of Medicine's criteria for 21st century medical care.

**KEY WORDS:** systematic review, caries, prevention, fluoride, silver.

116

## INTRODUCTION

With a wealth of fluoride-based caries-preventive agents (Table 1), why might one be interested in yet another fluoride delivery system? The answer lies in silver diamine fluoride's (SDF) hypothesized ability to halt the caries process and simultaneously prevent the formation of new caries. This hypothesized ability is thought to derive from the combined effects of: silver-salt-stimulated sclerotic or calcified dentin formation (e.g., Stebbins, 1891), silver nitrate's potent germicidal effect (e.g., Miller, 1905; Howe, 1917; Klein and Knutson, 1942), and fluoride's ability to reduce decay (e.g., Marinho et al., 2002, 2004a,b). [Dentists termed silver nitrate "Howe's solution" after Percy Howe, who reported on its use for caries prevention. Howe was The Forsyth Institute's first research director, and the Forsyth library is named after him.] The specific interest in SDF centers around its 5 presumed attributes (Bedi and Sardo-Infirri, 1999): control of pain and infection, ease and simplicity of use (paint on), affordability of material (pennies per application), minimal requirement for personnel time and training (one minute, once per year), and the fact that it is non-invasive. In this sense, SDF has the potentially unique ability to be a "silver-fluoride bullet," simultaneously halting the cariogenic process and preventing caries.

The need for agents like SDF is perhaps best understood in terms of the World Health Organization (WHO) Millennium Development Goals for Health (Wagstaff and Claeson, 2004), and in particular the oral health goals (Hobdell et al., 2003). The proposed path to achieving these goals is the provision of a basic oral health package, consisting of: emergency care, prevention, and cost-effective interventions, in that order (Frencken et al., 2008). To achieve these goals, the use of simple technologies will be required for 'scale up' to improve access to oral health care at a much lower cost. At the same time, all of these preventive interventions will need to be built upon a firm evidence base.

With the continuing population expansion, and the decreasing availability of dentists to provide emergency care and restorative treatment, the likeliest path to oral health will be an intense focus on prevention. Silver fluoride compounds may partially fill this need.

### Brief History

The first medicinal use for silver appears to have been around 1000 BC for the storing of potable water (see Russell and Hugo, 1994). Current uses of silver compounds in medicine revolve around the application of silver nitrate, silver foil, and silver sutures for the prevention of ocular and surgical infections (e.g., Credé, 1881; Halsted, 1895). Von Naegeli (1893) demonstrated that silver can kill spirogyra, and found that various forms of silver have different effects, with silver nitrate being a very effective antimicrobial agent.

**Table 1.** Fluoride Efficacy in Preventing Caries

| Fluoride Delivery System | Estimated Caries Reduction | Reference |
|---|---|---|
| Milk | ? | Yeung *et al.* (2005) |
| Salt | 15% | Marthaler and Petersen (2005) |
| Toothpaste | 24% | Marinho *et al.* (2004a) |
| Mouthwash | 26% | Marinho *et al.* (2004b) |
| Water (adults) | 27% | Griffin *et al.* (2007) |
| Gel (children) | 28% | Marinho *et al.* (2002) |
| Water (children) | 34% | Do and Spencer (2007) |
| Varnish | 46% | Marinho *et al.* (2002) |
| SDF permanent teeth | > 60% | Current review |
| SDF deciduous teeth | > 70% | Current review |

**Table 2.** Effects of Silver Nitrate and Silver Scraps on Decay Prevention (Stebbins, 1891)

| Year after Treatment | # Teeth | Success* | Partial Success | Unsuccessful |
|---|---|---|---|---|
| 1 | 64 | 37 (58%) | 17 (27%) | 13 (20%) |
| 2 | 27 | 10 (37%) | 5 (19%) | 12 (44%) |
| 3 | 142 | 87 (61%) | 33 (23%) | 22 (15%) |

\* Success = no further decay; Partial success = expansion of decay; Unsuccessful = no silver discoloration.

From a dental perspective, Stebbins (1891) reported that teeth restored with amalgam displayed black surfaces where the progress of decay had ceased. Then, reasoning from the current use of silver nitrate treatment for sensitive teeth, and the resulting tooth coloration, he mixed nitric acid with amalgam scraps and applied them to caries lesions in 35 children. Stebbins' results suggest that this treatment successfully inhibited decay in 61% of cases at 3 yrs (Table 2). Stebbins hypothesized that caries inhibition was the result of bacterial killing and the deposition of a "black crust," generating a sclerotic protective coating of secondary dentin. Subsequently, Howe (1917) directly applied silver nitrate to caries lesions with similar results. "Howe's solution" was used for this purpose for the next 50 yrs.

Over the last 40 yrs, numerous preliminary *in vitro* and *in vivo* trials examined the potential efficacy of silver-fluoride regimens in caries prevention. *In vitro* studies suggested that silver-fluoride regimens inhibit *S. mutans* growth (Thibodeau *et al.*, 1978; Ostela and Tenovuo, 1990), metabolic activity of dental plaque (Oppermann and Johansen, 1980; Oppermann and Rölla, 1980), and caries lesion depth progression (Klein *et al.*, 1999). Similarly, *in vivo* studies in primary teeth indicated that silver-fluoride application inhibits the lateral spread of caries (Nishino *et al.*, 1969, using AgF), occlusal and approximal caries by AgF + SnF$_2$ + stomahesive (Craig *et al.*, 1981, using AgF + SnF$_2$ + stomahesive), and 95% of caries progression (McDonald and Sheiham, 1994, using AgF + SnF$_2$). Finally, *in vivo* studies in permanent teeth indicated that silver fluoride arrests approximal caries progression (Hyde, 1973, using AgNO$_3$) and the initiation of caries lesions
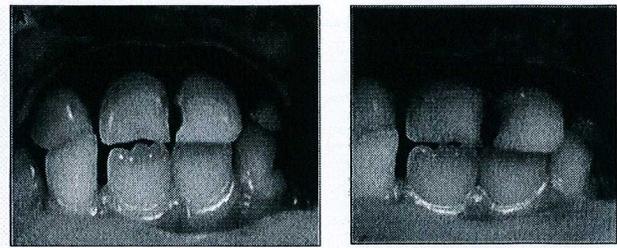


**Figure 1.** Clinical photographs prior to and following application of silver diamine fluoride. **(A)** Clinical photographs of interproximal caries lesions in maxillary incisors of a 5-year-old girl. **(B)** Clinical photograph of brown staining following a 60-second application of Cariestop® 12% silver diamine fluoride. Note that only the caries lesion, not the tooth, is stained.

(Green, 1989, using AgF + SnF$_2$). These early studies led to the use of silver diamine fluoride in Australia (Gotjamanos, 1997), Japan (Yamaga and Yokomizo, 1969), and Mexico (Aron, 1995).

While the preliminary studies of silver fluoride demonstrated an anti-caries effect, they also recognized that silver fluoride can blacken caries lesions (but not sound tooth surfaces) (Fig. 1). Therefore, newer *in vitro* experiments are examining silver fluoride followed by potassium iodide (Knight *et al.*, 2006), which produces a white silver iodide reaction product. However, the ability of this product to prevent caries *in vivo* has not yet been demonstrated.

## Mechanisms of Action

Soft Lewis acids, like the transition metal silver, have high polarizing power (a large ratio of ionic charge to the radius of the ion) and typically form strong bonds with soft Lewis bases. These include sulfur and nitrogen ligands such as cysteine and histidine residues in proteins. As indicated below, these interactions may account for the effects of silver on bacteria and teeth.

### Bacteria

Multiple modes of action have been proposed for silver (*e.g.*, Lansdown, 2002a, 2006; Wu *et al.*, 2007). This may, in part, be explained by the multiple biological organisms (*e.g.*, bacterial, protozoan, fungal, and viral), subcellular targets (*e.g.*, cell membranes, organelles, nuclei), and mechanisms (*e.g.*, metabolism, replication) that have been examined. Studies have indicated that silver interacts with sulfhydryl groups of proteins and with DNA, altering hydrogen bonding and inhibiting respiratory processes, DNA unwinding, cell-wall synthesis, and cell division (*e.g.*, Oppermann *et al.*, 1980; Lansdown, 2002a, 2006). At the macro level, these interactions effect bacterial killing and inhibit biofilm formation (*e.g.*, Wu *et al.*, 2007). The central mechanism for these diverse effects is proposed to be the interaction of silver with thiol groups by the following mechanism (Russell and Hugo, 1994):

$$A/N - SH + AgX \rightarrow A/N\text{-}S\text{-}AgX + HX$$
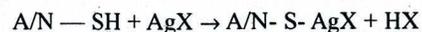
**Table 3.** Relationship of Silver to Effector Genes and Enzymes

| Target Effect* | Interaction | Description | Reference |
|---|---|---|---|
| —\| Arabinase | Inhibition | Arabinase is inhibited by Ag | Takahashi et al. (1985) |
| — Azu | Binding | Cu replaced by Ag in azurin | Tordi et al. (1990) |
| —\| β-galactosidase | Inhibition | Beta-galactosidase is inhibited by Ag | Wutor et al. (2007) |
| —\| Chitosanase | Inhibition | Chitosanase is inhibited by Ag | Park et al. (1999) |
| —+> CopA | Induction | CopA induced by Ag | Stoyanov et al. (2001) |
| —+> CopA, CopB | Induction | CopA and CopB induced by Ag | Odermatt et al. (1994) |
| — CopB | Transport | CopB extrudes Ag from cells | Rensing et al. (2000) |
| — Crd1p | Resistant | Cu pump effects Ag resistance | Riggle and Kumamoto (2000) |
| —\| GNPTA | Inhibition | GPT is inhibited by Ag | Goil (1978) |
| —\| GOT and GPT | Inhibition | GOT and GPT are inhibited by Ag | Goil (1978) |
| —\| Keto-reductase | Inhibition | Ketoreductase is inhibited by Ag | Costello et al. (2000) |
| —\| Mono-oxygenase | Inhibition | Monooxygenase is inhibited by Ag | Green et al. (1985) |
| —+> PacS | Induction | PacS is induced by Ag | Rensing et al. (1999) |
| —+> pH | Collapse | Trans-membrane pH collapse by Ag | Dibrov et al. (2002) |
| —+> YlcBCD–YbdE | Induction | YlcBCD–YbdE effects Ag resistance | Franke et al. (2001) |

* — indicates interaction; —\| indicates inhibition; —+> indicates induction.

where A/N represents amino (A) or nucleic (N) acids (respectively), SH represents a thiol group, Ag represents silver, and X represents an anion (in the current example, diamine fluoride). This interaction indicates how silver diamine fluoride, when applied to caries lesions, might interact with bacteria and mediate caries arrest through bacterial killing and inhibit caries progress through the inhibition of biofilm formation.

To identify the potential molecular interactions, we searched the Ariadne Genomics ResNet bacterial cartridge for silver-bacterial relationships and used Ariadne Genomics Pathway Studio to map these relationships (http://www.ariadnegenomics.com/). The results identified a specific set of silver targets that affect the inhibition or induction of genes and transporter systems (Table 3).

## Teeth

In examining the modes of action of sodium fluoride and silver nitrate on teeth, investigators found that the 2 compounds have complex mechanisms (Yamaga and Yokomizo, 1969; Yamaga et al., 1972) (Table 4). The most commonly recognized interaction is sodium fluoride with calcium phosphate to form fluorapatite and sodium hydroxide (and a basic environment) (reaction 1). The less commonly recognized interaction is the combination of tooth calcium to form calcium fluoride and a basic environment (reaction 2). The initial reaction of silver nitrate is the formation of calcium nitrate, silver phosphate, and silver oxide (reaction 3).

**Table 4.** NaF and Ag(NO$_3$) Reactions

| Reaction | Reactants | Products |
|---|---|---|
| 1 | $Ca_{10}(PO_4)_6(OH)_2 + NaF$ | $\rightarrow Ca_{10}(PO_4)_6F_2 + NaOH$ |
| 2 | $Ca_{10}(PO_4)_6(OH)_2 + NaF$ | $\rightarrow CaF_2 + Na_3O_4 + NaOH$ |
| 3 | $Ca_{10}(PO_4)_6(OH)_2 + Ag(NO_3)$ | $\rightarrow Ca(NO_3)_2 + Ag_3PO_4 + Ag_2O + H_2O$ |

Knowledge of these reactions led to the development of silver diamine fluoride. In this context, fluoride and silver interact synergistically to form fluorapatite (Table 5). The first step is the formation of calcium flouride and silver phosphate in a basic environment (reaction 4). The second reaction is the subsequent dissociation of calcium and fluoride (reaction 5). The last step is the formation of fluorapatite (reaction 6). The net result of these interactions is depicted in Fig. 2.

**Table 5.** Ag(NH$_3$)$_2$ F Reactions

| Reaction | Reactants | Products |
|---|---|---|
| 4 | $Ca_{10}(PO_4)_6(OH)_2 + Ag(NH_3)_2F$ | $\rightarrow CaF_2 + Ag_3PO_4 + NH_4OH$ |
| 5 | $CaF_2$ | $\rightarrow Ca^{++} + 2F^-$ |
| 6 | $Ca_{10}(PO_4)_6(OH)_2 + 2F^-$ | $\rightarrow Ca_{10}(PO_4)_6F_2 + 2OH^-$ |

*In vitro* studies have indicated that SDF penetrates enamel to a depth of 25 microns, and approximately 2-3 times more fluoride is retained than that delivered by NaF-PO$_4$, NaF, or SnF$_2$ (Suzuki et al., 1974). This suggests that the effect of SDF will be greater than that of NaF or SnF$_2$.

## Current Medical Uses of Silver

Applications for silver in health care are now highly evolved. Silver-containing topical ointments have been approved by the US Food and Drug Administration and marketed globally to prevent bacterial infections in burn victims (*e.g.*, silver sulfadiazide, Silvazine® and Flamazine®, Smith & Nephew, London, UK). A range of wound dressings with slow-release Ag compounds has been introduced, including, *e.g.*, Acticoat® (Smith & Nephew), Actisorb Silver® (Johnson & Johnson, Piscataway, NJ,USA), Silverlon® (Argentum Medical, Willowbrook, IL, USA), and others. Silver-containing catheters for urinary infection prevention are available (*e.g.*, DOVER® Covidien, Norfolk, NE, USA), and hospitals use colloidal silver to purify the water supply and reduce the spread of infectious diseases (*e.g.*, Modol et al., 2007). As well, silver fabrics are used for surgical gowns and draperies to prevent microbial transmission (*e.g.*, X-Static®, Noble BioMaterials, Scranton, PA, USA). Newer dental applications for
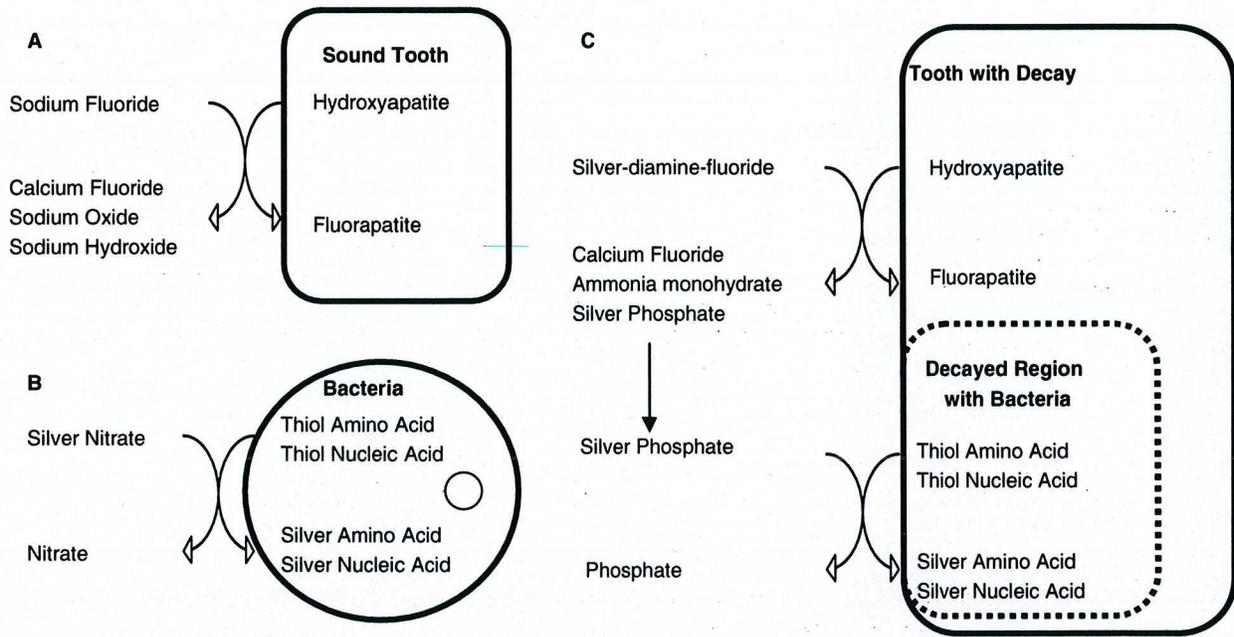
**Figure 2.** Diagrams representing effects of fluoride, silver nitrate, and silver diamine fluoride on teeth and bacteria. **(A)** In sound teeth, fluoride reacts with hydroxyapatite to form fluorapatite. Fluorapatite is less acid-soluble than hydroxyapatite, inhibiting the decay process. **(B)** In bacteria, silver reacts with thiol groups of amino and nucleic acids. Silver amino and nucleic acids are unable to carry out metolic and reproductive functions, leading to bacterial killing. **(C)** In teeth with decay, silver diamine fluoride reacts with hydroxyapatite to form fluorapatite, and the by-product silver phosphate. Silver phosphate subsequently reacts with bacterial amino and nucleic acid thiol groups to form silver amino and nucleic acids.

silver—beyond amalgam—are also extant for caries prevention or are being tested for composite filling materials (*e.g.*, Kawashita *et al.*, 2000) and the reduction of periodontal pathogens (*e.g.*, Spacciapoli *et al.*, 2001).

## Caries Treatment with SDF

For over 100 years, dentists surgically and successfully treated caries and periodontal disease with three metals: silver, gold, and stainless steel. But based on research over the last 30 years, we know that caries and periodontal disease are infections (*e.g.*, Gibbons and van Houte, 1975). For caries, the mechanism of pathogenic bacterial action is tooth decalcification. Perhaps, consequently, the current primary preventive agent for inhibiting caries is fluoride, which decreases acid solubility. Conversely, relatively little attention has been paid to controlling the infection. Given the apparent advantages (and potential disadvantages) of

SDF for infection control, preventing caries, and its clinical availability in Brazil, Argentina, and Japan (Table 6), this systematic review was undertaken. We addressed the following question: Will silver diamine fluoride, when compared with a control, arrest or prevent caries? Initial reports suggested that SDF may be effective in controlling caries *in vitro* (*e.g.*, Yamaga *et al.*, 1972; Gotjamanos and Orton, 1998; Klein *et al.*, 1999) and *in vivo* (McDonald and Sheiham, 1994). Further, clinical trials have suggested SDF's efficacy in preventing caries in both the primary and permanent dentition (*e.g.*, Nishino *et al.*, 1969; Almeida, 1994; Lo *et al.*, 2001; Chu *et al.*, 2002; Llodra *et al.*, 2005; Wong *et al.*, 2005). If SDF use proves to be safe, effective, patient-centered, timely, efficient, and equitable (Institute of Medicine, 2001), and widely implemented, SDF could become a key element for comprehensive and effective preventive programs that meet the WHO Millennium Goals. SDF could potentially increase access to care, improve oral health, and ultimately reduce the need for emergency care and treatment.

**Table 6.** Commercially Available and Approved Silver Diamine Fluoride Solutions

| Product Name | Manufacturer/Supplier | SDF Conc. | Registration # | Country |
|---|---|---|---|---|
| Cariostatic® | Inodon Labratorio | 10% | 80151700032 | Brazil |
| Cariestop® | Biodinâmica Quimica e Farmaceutica Ltda | 12% | 10298550010 | Brazil |
| Cariestop® | Biodinâmica Quimica e Farmaceutica Ltda | 38% | 10298550048 | Brazil |
| Bioride® | Dentsply Industria e Comercio Ltda | 30% | 10186370153 | Brazil |
| Saforide® | J.Morita; Toyo Seiyaku Kasei Ltd. | 38% | | Japan |
| FluoroplatV | Laboratorios Naf | 38% | M.S.yA.S. 5010 | Argentina |

**Table 7.** Search and Evaluation Results

| Evaluation | | Results |
|---|---|---|
| Database | MEDLINE | 66 |
| | LILACS | 29 |
| | EMBASE | 13 |
| | Cochrane | 7 |
| | BBO | 35 |
| | Potential Unique | 149 |
| Title & Abstract | Actual Unique | 110 |
| | Exclude | 98 |
| | Include | 12 |
| Hand Search | Identify | 3 |
| | Exclude | 3 |
| Evaluation | Exclude | 10 |
| | Include | 2 |

**Table 8.** Excluded Articles

| | Reference | Reason for Exclusion |
|---|---|---|
| 1 | Almeida *et al.* (1994) | No control group |
| 2 | Gotjamanos (1996) | SDF used beneath filling material |
| 3 | Gotjamanos and Orton (1998) | *In vitro* study |
| 4 | Klein *et al.* (1999) | *In vitro* study |
| 5 | Lo *et al.* (2001) | Early report of Chu *et al.* (2002) |
| 6 | McDonald and Sheiham, 1994 | SDF not used alone. |
| 7 | Nishino *et al.* (1974) | *In vitro* study |
| 8 | Nishino *et al.* (1969) | Cohort trial with tooth as unit of observation |
| 9 | Yamaga *et al.* (1972) | Commentary |
| 10 | Wong *et al.* (2005) | Bayesian analysis of Chu *et al.* (2002) |

## SYSTEMATIC REVIEW

### Search Strategy

A search strategy was developed for articles indexed in MEDLINE, LILACS, EMBASE, the Cochrane Library, and the Brazilian Dental Library databases that were written in English, Spanish, or Portuguese between the years 1966 and December 31, 2006. The following inclusion criteria were used to identify potentially relevant reports: addressed use of silver diamine fluoride and caries; study carried out in humans; clinical trial of a randomized controlled, cohort, or case-control type; patient is the unit of observation; and includes variance assessment. Exclusion criteria were: early reports of longer studies; *in vitro* or animal studies; narrative reviews or editorials; and articles published in languages other than English, Spanish, or Portuguese. The search concept for MEDLINE was:

("Silver Nitrate"[MeSH] OR "Silver Proteins"[MeSH] OR "silver diamine"[Substance Name]

OR "silver diamine fluoride"[Substance Name] OR "silver fluoride"[Substance Name]) AND

("Dental Caries"[MeSH] OR "Tooth Demineralization"[MeSH])

### Critical Appraisal

Two investigators independently read all the titles and abstracts from the multiple search results to identify articles for potential inclusion. The same two investigators obtained and reviewed complete articles that appeared to meet inclusion criteria. These investigators appraised the complete articles for inclusion, reviewed reference lists for additional articles, critically appraised the articles for quality (Jadad, 1998), and created evidence tables. A third investigator resolved disagreements.

### Quantitative Assessments

Prevented fraction (PF; also termed 'relative risk reduction') (Kleinbaum *et al.*, 1982) and number needed to treat (NNT) (Laupacis *et al.*, 1988; Guyatt *et al.*, 1998) were calculated from

the original data according to the following formulas for populations (van Rijkom *et al.*, 1998):

$$\text{Prevented Fraction: PF} = (Ic - Ie) / Ic$$

where $Ic$ = control group increment, $Ie$ = experimental group increment, and Increment = (starting active carious surfaces *per* person - ending active carious surfaces *per* person), or (ending new carious surfaces *per* person):

$$\text{Number Needed to Treat: NNT} = 1 / (Ic * PF)$$

The 95% Confidence Interval:

$$CI = 1.96 \sqrt{[(Ic * (1 - Ic)/\# \text{ control patients}) + Ie * ((1 - Ie)/\# \text{ experimental patients})]}$$

### Findings and Data Distillation

The MEDLINE, LILACS, EMBASE, Cochrane Library, and the Brazilian Dental Library (BBO) database searches identified, respectively, 66, 29, 13, 7, and 35 reports that appeared to relate to silver diamine fluoride and caries (Table 7). Examination of the references identified 110 unique reports. Inspection of the titles and abstracts by two investigators (AR and TS) excluded 98 reports (Appendix), leaving 12 reports that appeared to be relevant. These reports were obtained and their reference lists examined for additional relevant articles, which identified 3 additional potential reports. None of these 3 reports met inclusion criteria. Twelve articles were reviewed for inclusion, 10 were excluded (Table 8), and 2 met *all* inclusion criteria (Tables 9, 10). Both reports were critically appraised for internal validity, and subsequently used for data extraction.

Both included studies examined the clinical effect of silver diamine fluoride on caries arrest and prevention, and compared the results with a control of either fluoride varnish (Chu *et al.*, 2002) or water (Chu *et al.*, 2002; Llodra *et al.*, 2005) (Table 9). Llodra *et al.* (2005) used a blinded randomization and blinded examination protocol, while Chu *et al.* (2002) used a cohort design. Based on the absence of either reported randomization or blinding, Llodra *et al.* (2005), and Chu *et al.* (2002) scored 4 and 2 (out of 5), respectively, on the Jadad scale (Jadad, 1998).

**Table 9.** Included Articles

Reference Study Design

| | Problem | Experimental | Comparison | Outcome |
|---|---|---|---|---|
| Chu *et al.* (2002) | Carious primary maxillary anterior teeth | SDF (38%) 44.8 ppm F 1x/yr | (1) FV* (5%) 22.6 ppm F 4x/yr (2) Water 4x/yr | (1) Caries arrest (2) New caries at 2.5 yrs |
| Llodra *et al.* (2005) | Carious primary teeth Carious permanent first molars | SDF (38%) 2x/yr | Water 4x/yr | (1) Caries arrest (2) New caries at 3 yrs |

\* FV = fluoride varnish.

These studies examined the effect of SDF following application to primary teeth (Chu *et al.*, 2002) or both primary and permanent teeth (Llodra *et al.*, 2005). The frequency of SDF application was either biannual (Llodra *et al.*, 2005) or annual (Chu *et al.*, 2002), and trial duration ranged from 2.5 yrs (Chu *et al.*, 2002) to 3 yrs (Llodra *et al.*, 2005). The SDF concentration for both studies was 38%. The results from both studies indicated that SDF was effective in arresting and preventing caries (Table 7).

Chu *et al.* (2002) selected children with carious maxillary anterior teeth, and with or without carious excavation, and compared 1x *per* yr SDF application with 4x *per* yr fluoride varnish or 4x *per* yr water application. The results (Table 8) indicate that SDF was substantially more effective than fluoride varnish or water in both arresting and preventing caries. For example, the lowest SDF-prevented fractions were 96.1% and 70.3% for caries arrest and prevention, respectively. In contrast, for fluoride varnish, the highest prevented fractions were 21.3% and 55.7% for caries arrest and prevention, respectively. (The original report did not provide data for a determination of confidence intervals. The original article did, however, analyze and demonstrate significant differences between SDF and fluoride varnish.) The NNT also demonstrated the substantial benefit of SDF when compared with fluoride varnish. The highest SDF NNTs were 0.8 (95% CI = 0.5-1.0) and 0.9 (95% CI = 0.4-1.1) for caries arrest and prevention, respectively. In contrast, the lowest fluoride varnish NNTs were 3.7 (95% CI = 3.4-3.9) and 1.1 (95% CI = 0.7-1.4) for caries arrest and prevention, respectively.

Llodra *et al.* (2005) selected children with carious primary teeth and/or carious permanent molars, and compared 2x *per* yr SDF application with 2x *per* yr examination. The results (Table 8) indicate that for both primary teeth and permanent molars, SDF was beneficial. In primary teeth, the prevented fractions for SDF were 55.6% and 78.6% for caries arrest and prevention, respectively. In permanent teeth, the prevented fractions for SDF were 100% and 63.6% for caries arrest and prevention, respectively. (The original report did not provide data for a determination of confidence intervals. The original article did, however, analyze and demonstrate significant differences between SDF and examination.) The NNT also indicated a

substantial benefit of SDF. In primary teeth, the NNTs for caries arrest and prevention were 1.0 (95% CI = 0.4-1.3) and 0.9 (95% CI = 0.4-1.3), respectively. In permanent teeth, the NNTs for caries arrest and prevention were 10 (95% CI = 8.4-11.2) and 1.4 (95% CI = 0.3—1.9), respectively.

Regarding adverse events, both trials indicated that there was no significant difference between the control and experimental groups in pulpal incident (both < 1%). Staining was similar in both control and experimental groups, and troubled 7% of participants (Chu *et al.*, 2002). Finally, SDF did cause 24-hour tissue sensitivity in three of the 153 participants (Chu *et al.*, 2002).

## DISCUSSION

Analysis of the data from this narrative and systematic review suggests that the application of SDF, applied 1x or 2x *per* yr, can significantly arrest active caries, significantly reduce the incidence of new caries, and not substantially increase the risk of adverse events. The two controlled trials reported differences in pre- and post-measures of analysis. This review extrapolated from the original data to report the prevented fraction (also termed relative risk reduction) and number needed to treat (NNT), generating complementary assessments that can be applied to individuals, and could ultimately be applied to economic analysis.

### Quantitative Assessments

Prevented fraction in this context indicates the caries arrest or prevention in the experimental group relative to the control group (higher is better). Overall, SDF's prevented fractions for caries arrest and prevention in both primary and permanent teeth consistently exceed the 46% found for fluoride varnish (*e.g.*, Marinho *et al.*, 2002). From Chu *et al.* (2002), SDF's prevented fractions for caries arrest and prevention in primary teeth were > 96% and > 70%, respectively. From Llodra *et al.* (2005), SDF's prevented fractions for caries arrest and prevention in primary teeth were > 55% and > 75%, respectively. Llodra *et al.* (2005) found similar results for permanent teeth, with SDF's prevented fractions for caries arrest and prevention equal to 100% and 64%, respectively. Thus, while both studies used different designs and different application intervals, both demonstrated a substantial beneficial effect.

The NNT indicates the number of children who would need to be treated to prevent the development of 1 additional decayed surface (lower is better). For a given PF, it is dependent on the population incidence and study duration. NNT therefore provides a measure of the efficiency of the treatment in a given population. The NNT can also be used to extrapolate effects to individuals. Similar to prevented fraction, the NNTs for SDF were substantially lower than the 1.4 found for fluoride varnish (Marinho *et al.*, 2002). From Chu *et al.* (2002), the highest NNTs for SDF caries arrest and prevention in primary teeth were both < 1. From Llodra *et al.* (2005), the NNTs for SDF caries arrest and prevention in primary teeth were both ≤ 1. In

**Table 10.** Evidence Table

| Reference | Trial Type | N | Experimental + Comparison | Trial Length | Outcome* | | | | | | Outcome | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Chu *et al.* (2002) | Prospective controlled | | Carious maxillary anterior primary teeth | 30 months | Active caries Surf./Subj. Start | End | Inc | PF | NNT | 95% CI | New caries Surf./Subj. End | PF | NNT | 95% CI |
| | | 76 | Excavation + 38% SDF 1x/yr | | 4.13 | 1.64 | 2.49 | 96.1 | 0.8 | 0.5-1.0 | 0.26 | 83.5 | 0.8 | 0.2-1.0 |
| | | 77 | 38% SDF 1x/yr | | 4.26 | 1.44 | 2.82 | 122 | 0.6 | 0.3-0.8 | 0.47 | 70.3 | 0.9 | 0.4-1.1 |
| | | 76 | Excavation + 5% FV 4x/yr | | 3.92 | 2.47 | 1.45 | 14.2 | 5.6 | 5.3-5.8 | 0.89 | 43.7 | 1.5 | 1.1-1.7 |
| | | 73 | 5% FV 4x/yr | | 3.82 | 2.28 | 1.54 | 21.3 | 3.7 | 3.4-3.9 | 0.70 | 55.7 | 1.1 | 0.7-1.4 |
| | | 73 | Water 4x/year | | 3.75 | 2.48 | 1.27 | | | | 1.58 | | | |
| Llodra *et al.* (2005) | Prospective controlled randomized | | Decayed primary teeth and occlusal of permanent 1st molars | 36 months | Active caries Surf./Subj. | | Inc | PF | NNT | | New caries Surf./Subj. | PF | NNT | 95% CI |
| | | | Primary: | | Start | End | | | | | End | | | |
| | | 225 | 38% SDF 2x/year | | 3.0 | 0.2 | 2.8 | 55.6 | 1 | 0.4-1.3 | 0.3 | 78.6 | 0.9 | 0.4-1.3 |
| | | 227 | Examination 2x/year | | 2.9 | 1.1 | 1.8 | | | | 1.4 | | | |
| | | | Permanent: | | Start | End | | | | | End | | | |
| | | 225 | 38% SDF 2x/year | | 0.3 | 0.1 | 0.2 | 100 | 10 | 8.4-11.2 | 0.4 | 63.6 | 1.4 | 0.3-1.9 |
| | | 227 | Examination 2x/year | | 0.3 | 0.2 | 0.1 | | | | 1.1 | | | |

\* Inc = increment, PF = prevented fraction, NNT = number needed to treat.

other words, from the work of both Chu *et al.* (2002) and Llodra *et al.* (2005), every person with caries in primary teeth would benefit from SDF application. In contrast, for fluoride varnish, two people would need to be treated for one to benefit.

For permanent teeth, however, analysis of the data from Llodra *et al.* (2005) indicated that the NNT for caries arrest was 10, while caries prevention was 1.4. Thus, in permanent teeth, 10 people with caries would need to be treated with SDF for one to benefit in arrested caries. Similarly, two people with caries would need to be treated with SDF for one to benefit in caries prevention.

## Application to Individuals

While the foregoing was based on clinical trials, the NNT can be useful for extrapolating from clinical trials to make predictions for individuals and ultimately communities. For example, for individuals, NNT is calculated in two ways (Sackett *et al.*, 2000):

$$NNT_{individual} = NNT_{population} / f, \tag{1}$$

where f is the clinician's estimate of the individual's risk, compared with the experimental group; and

$$NNT_{individual} = 1/ (PEER * PF), \tag{2}$$

where PEER is the clinician's estimate of the individual's expected event rate without treatment.

In Eq. 1, for example, if the clinician estimated that an individual's risk of new caries in primary teeth was 0.5x that of Chu *et al.* (2002) [*e.g.*, ~ 0.75 new carious surfaces/person over 2.5 yrs *vs*. 1.58 new carious surfaces/person in Chu *et al.* (2002)], the $NNT_{individual}$ for this person would be: $1/0.5 = 2$. In other words, two people would need to be treated with SDF for one person to benefit. A similar analysis can be used to compare SDF with fluoride varnish (NNT = 1.4; f = DMFS = 1.6/yr; Marinho *et al.*, 2002). In this example, if f for new caries was 0.5x that of Marinho *et al.* (*e.g.*, f = 0.8), $NNT_{individual}$ for this individual would be: $1.4/0.8 = 1.75$. In other words, 1.75 patients would need to be treated with SDF for one person to benefit. (Note: NNT is normally rounded up, so the actual assessment would be that two people would be treated for one to benefit.)

In Eq. 2, if the clinician estimated that a person's expected event rate for new caries is 0.5 new carious surfaces in 2.5 yrs, the NNT would be: $1/ (0.5 * 70.3\%) = 2.8$ for primary teeth. In other words, 2.8 persons would need to be treated with SDF for one to benefit.

The foregoing suggests that SDF may offer substantial caries-preventive benefits over fluoride varnish. However, there are numerous caveats: safety, adverse events, study design, and effect in permanent teeth.

## Safety

Safety is a critical issue in the clinical application of SDF. The long-standing use of silver is both an asset and a concern. The historical efficacy data are plentiful and compelling (*e.g.*, Lansdown, 2002a, 2006), and toxicity and adverse events are rare (*e.g.*, Lansdown, 2002b, 2006; Lansdown and Williams, 2004). However, many long-standing agents were "grand-fathered" by government agencies (*e.g.*, in the US, by the Food and Drug Administration), allowing for their continued use with minimal safety testing as compared with new agents. Thus, while many potential adverse effects could occur, we could not identify published trials addressing this, other than the adverse events identified in this review. There are two major perspectives here: a person's and a practice's.

## Practice Perspective

There are several hypothesized adverse effects of SDF: pulpal irritation, caries staining, tissue irritation, and fluorosis. Three of these adverse events were examined in the reported studies: generation of non-vital teeth, staining of caries lesions, and tissue irritation. The hypothetical risks attributed to SDF and its possible toxicity to the pulp were not supported. On the contrary, there was a similar incidence of pulpal lesions in both the control and experimental groups, and in both the primary and permanent teeth. Reports of staining were also similar, and it did trouble 7% of participants. Reversible lesions in oral mucosa through inadvertent contact with SDF solution occurred in three reported individuals, with the appearance of a small, mildly painful white lesion in the mucosa, which disappeared within 48 hrs without treatment. The possibility of acute toxicity or the induction of fluorosis through the use of SDF has been debated (*e.g.*, Gotjamanos, 1997; Neesham, 1997). The nexus of this concern emanated from fluorosis in rats, where SDF was used at several-fold the concentration used in the studies reported here. However, without data, one cannot exclude (or support) this possibility.

From a practical standpoint, one can consider personal and general safety. Silver nitrate, when spilled on the skin, clothes, or countertops, causes dark staining—a well-recognized phenomenon for anyone working with radiographs. This staining on the skin is relatively short-term (wks), while the staining of clothing and counters is long-lasting. Thus, caution in the use of silver nitrate in a busy clinical setting is required. From a general safety perspective, the European Union classifies silver nitrate as both corrosive (C) and dangerous for the environment (N). The US National Fire Protection Association classifies silver nitrate as: 'An oxidizer (Ox); Can cause temporary incapacitation or possible residual injury (Blue 2); Will not burn (Red 0); At elevated temperatures and pressures may form explosive mixtures with water (Yellow 2)'.

## Individual's Perspective

From the individual's safety standpoint, there are 3 components of SDF: silver, amine, and fluoride. Silver alone has been used

for millennia as an antimicrobial agent, and has found a multitude of clinical and industrial disinfectant applications (*e.g.*, Silvestry-Rodriguez *et al.*, 2007) , including water purification and the control of dental unit waterline biofilms (*e.g.*, O'Donnell *et al.*, 2007). The more complex silver nitrate has been used for over 100 years for medical applications. Among the more common uses are eye drops for newborns to prevent infections, and cauterizing of oral aphthous ulcers. Finally, fluoride, identified some 50 years ago as an anti-caries agent, is used routinely in a multitude of applications for caries prevention, in a variety of delivery systems, including varnish, gel, salt, toothpaste, water, rinse, and milk (*e.g.*, Marinho *et al.*, 2004a,b).

For dose-related safety specifically associated with caries prevention, the delivered dose of SDF is approximately a drop for each quadrant, delivered with a brush, and rinsed off afterward. Thus, from both the historical and quantitative perspectives, while it is possible that SDF can generate adverse events, the likelihood seems low. That said, demonstrating safety still needs attention. A cautionary tale in this regard is the finding of fluorosis in ~ 10% of people associated with water fluoridation (McDonagh *et al.*, 2000).

## Study Design, Populations, and Optimization

In terms of study design, the implemented literature search identified only one cohort and one randomized controlled trial. Neither study provided a power calculation. This, therefore, is a limited dataset upon which to build a new preventive strategy. At the same time, the study sizes, study lengths, substantial differences between the experimental and control groups, and similar results between the studies suggest that the results are reasonable outcome estimates for caries control by SDF. Given the risk profiles of the persons in the two included studies, subsequent studies might consider a stratified random assignment to provide a better assessment of the potential benefits of SDF among people with different levels of risk.

Subsets in the study populations are also a consideration. Only one of the two identified and qualifying studies extended their research to permanent teeth (Llodra *et al.*, 2005). Further, one study (Chu *et al.*, 2002) examined only maxillary anterior, and not posterior, teeth. This limits the data upon which one might base clinical application of SDF. In contrast, caries is a bacterial infection leading to enamel and dentin demineralization. Thus, while the quantitative effect may vary between primary and permanent teeth, between anterior and posterior teeth, between populations, and between risk groups, the direction of effect should be similar. This assertion needs further investigation.

Finally, treatment optimization remains, in part, an open question. The two included studies applied SDF either once or twice *per* year, and obtained similar results. This suggests that 1 application *per* year may be sufficient. In contrast, an NNT for permanent teeth of 10 is relatively high, and permanent teeth may benefit from more frequent application.

## Conclusions

In sum, while numerous questions remain to be answered, the modest dataset identified here supports the hypothesis that SDF

can have a significant and substantial benefit in arresting and preventing caries. By implication, SDF could provide a new quantitative preventive benefit for individuals and populations. Application is simple, the solution is low-cost, and application does not require complex training of the health professionals. Thus, SDF appears to meet the criteria of both the WHO Millennium Goals, and the Institute of Medicine's criteria for 21st century medicine (Institute of Medicine, 2001). Clearly, however, broader study sets are required to investigate alternative protocols, delivery systems (*e.g.*, Kawasaki *et al.*, 2005), and age and risk groups for occlusal, proximal, and root caries. As well, the applications of SDF for treating tooth sensitivity (*e.g.*, Youssef, 1995), periodontal pockets (*e.g.*, Spacciapoli, 2001), and pulpal infections (*e.g.*, Englander *et al.,* 1958) need to be evaluated.

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**Frequently Asked Questions**

1. **Should SDF be used as a caries preventive therapy in a similar manner to how fluoride varnish is used "off-label" as a caries prevention therapy?**

   No. SDF is indicated for site-specific application only. Fluoride varnish can be applied to specific sites, but most fluoride varnish applications are full mouth. SDF is never a full mouth application.

   SDF treatment should be limited to up to five sites per appointment. Application to more than five sites should be spaced by 7 days. For patients with active caries, SDF can be considered as a replacement of fluoride varnish as the primary means to prevent new lesions, with application of SDF to the active lesions only.

2. **Is SDF safe for use in children?**

   Regarding the margin of safety for dosing, a study was conducted for FDA review for market clearance in rats and mice to determine the lethal dose by oral and subcutaneous administration. The worst case scenario is subcutaneous administration and that lethal dose was found to be 380 mg/kg. One drop (25uL) of 38% silver diamine fluoride (SDF) contains 9.5 mg silver diamine fluoride. Thus, one drop of 38% SDF applied to 10 kg (22 lb.) child would equal 0.95 mg/kg, equal to a four-hundredfold safety margin.

   In setting up protocols for undergraduate application of 38% SDF the University of California San Francisco set a recommended limit of one drop per 10 kg per treatment visit, with weekly intervals at most.

3. **Does SDF discolor skin or oral tissue?**

   Contact to skin and oral tissue is not harmful but is likely to cause temporary "tattooing". On skin and oral soft tissue the effect is not immediate, rather it will be noticed within hours. The speed of discoloration is accelerated with light contact. The staining will be limited to direct areas of contact and will fade over a period of 24-72 hours. Patients should be protected with bibs and safety glasses as in any clinical procedure. If you believe you have touched the applicator to the skin of a patient it is good to advise them of possible tattooing.

4. **Does the application technique differ between the label indication of relief of dentinal hypersensitivity and the off label indication of caries control?**

   In countries where SDF is used for the control of caries the application technique is identical to the instructions we provide in the Advantage Arrest Package Insert for the relief of dentinal hypersensitivity. No excavation, decay removal or anesthesia is required. The area to be treated should be "dry tooth brush" clean, free of plaque and debris. The area should be free of saliva, so

as not to dilute the material.Transfer the material from a disposable plastic dappen dish to the surface to be treated and allow time to dry, which generally occurs in 30-60 seconds. If accelerated drying is required due to patient compliance use a low/weak air stream to dry the material.

The chemical action of the SDF occurs almost immediately in the outer layers of the softened dentin and can be confirmed by changes in the hardness and density of the dentin surface, similar to caries that arrests naturally because of positive changes in oral hygiene, diet, or daily application of fluoride in custom trays. The darkening of the lesion occurs over 24 hours and may increase over a week. Reexamination of the lesion at the next regular recall is appropriate and reapplication of SDF may be warranted.  Repeat until the lesion has arrested

5.  **Is there a recommended frequency of application of SDF for caries control?**

Caries arrest studies were conducted with SDF applications of once and twice annually.  Arrested lesions were retreated every six-months.

Clinicians have reported that they will recall their first cohort of SDF patients within 3-6 weeks to evaluate the application and action of the treatment. Once they have a feel for the predictability of the material with their application technique they will set recall appointments based on the risk level and caries activity of the patient with higher risk patients at 3-month intervals. Moderate to high-risk patients, where it appears that home care and diet counseling has had positive impact, are recalled at 6-months.

6.  **Does the application of SDF to a lesion cause discoloration?**

Yes, darkening of decayed, demineralized sites occurs as the lesion arrests. This is similar to what is seen when caries arrests from changes in diet or increased use of other fluorides. A recent study showed that patients see the discoloration as a clear indication that the treatment is working. Similar to the treatment of eroded and hypersensitive dentin, the treated area can be restored using glass ionomer or with a sandwich restoration of both glass ionomer and composite. In lab studies, bond strength of composite by itself to treated surfaces is reduced but the clinical importance is unknown.

38% silver diamine fluoride should not be diluted in an attempt to reduce discoloration. Studies have shown that diluted solutions may not be effective for caries arrest.

Ionic silver adsorbs onto almost any protein surface and is especially tenaciously bound to denatured proteins. This accounts for the specificity to carious collagen over normal collagen, but both will stain. The differentiator between these stains is that with SDF use, intrinsic pigmentation of a carious lesion occurs and surface protein staining occurs primarily on healthy tissue. These oxides are bound to the tissue and don't wash or polish away. This is why the blackened lesion retains its dark color for so long, and is most likely

the reason the antimicrobial effect is long lasting.

The functional indicator of effectiveness is when the silver oxide is bound to the diseased collagen. If the surface doesn't turn black, the silver didn't bind and the antimicrobial effect will only be short lived.

7. **Can SDF be used on a prepared tooth just prior to restoration cementation?**

Desensitizing agents, have been shown to be protective of the pulp when placed on crown preparations to reduce dentin permeability. Advantage Arrest, a desensitizer, has been shown safe to the pulp when placed on exposed dentin. In addition, studies have shown desensitization and efficacy in treating softened dentin before placing direct restorations. Usually the tooth is first treated with silver diamine fluoride 38%. This provides the benefit of sealing tubules plus the antimicrobial benefits of both silver and fluoride

8. **Are there any contraindications for the use of SDF for the control of caries?**

SDF should not be placed on exposed pulps. Other topical fluorides (e.g. fluoride varnish) should not be used in the same appointment. Studies have shown that 38% silver diamine fluoride conveys more effective protection against decay in other teeth than fluoride varnish with reduced overall fluoride exposure.

9. **Is there evidence of caries prevention benefit to non-application sites following SDF use for a patient?**

Treating carious areas with silver diamine fluoride 38% acts as a whole mouth fluoride treatment. It can also be used in place of sealants in grooves. A protective effect has been shown to non-treated teeth and surfaces. These findings come from high quality randomized clinical trials.

10. **Are there any post appointment instructions for the patient or the caregivers/guardians?**

There are no postoperative limitations. Patients may eat or drink immediately. Patients may brush their teeth with fluoridated toothpaste on their regular schedule.

11. **Does SDF stain countertops, instruments etc.?**

Yes. When dispensing SDF it is a good idea to use an absorbent material that has a coated bottom, like a patient bib, under the dappen dish and applicator to avoid contact with metal trays and office countertops. If SDF comes in contact with instruments or countertops wash immediately with water, soap, ammonia or iodine tincture and then rinse thoroughly with water. Sodium

hypochlorite (household bleach) can also be used for difficult stains.

**12.  What are the safety implications for application of SDF for a patient that has more than six sites to be treated?**

The Margin of Safety for the volume of product needed to treat six sites is within 130 times the NOAEL (no-observed-adverse-effect-level).  Treating more sites in one visit will likely have little practical impact on patient safety. Like protocols for fluoride varnish application, the suspension for several days of fluoride supplements is advised.

**13.  How does an arrested lesion treated with SDF look like on radiographs?**

Arrested lesions look like a scar on radiographs. You will observe radio-opacity as the mineralization of the previously softened dentin increases.  Ultimately the best test of arrest is still the color change and tactile hardness of the dentin surface.

It is advised that you educate your referring dentist about your use of Advantage Arrest since the appearance of a treated lesion might be new and confusing for many practitioners.

**14. How can Advantage Arrest be coded using CDT?**

There is a new CDT code for 2016 specifically for the use of caries arresting medicaments; the off-label use of Advantage Arrest.

Code D1354

The nomenclature reads: "Interim caries arresting medicament application," with the descriptor; "Conservative treatment of an active, non-symptomatic carious lesion by topical application of a caries arresting or inhibiting medicament and without mechanical removal of sound tooth structure."

It is common for insurance providers to initially not reimburse for new codes as they are developing usual and customary rates for the procedure. However, it's important the new code is used so the providers can see the volume of use and determine future coverage. There are several providers that have announced coverage in various states.

For a current list of providers visit: https://en.wikipedia.org/wiki/Silver_diamine_fluoride

There are three other options to code the use of Advantage Arrest Silver Diamine Fluoride 38%.  These codes are:

D1208 - Topical application of fluoride

SDF is categorized as a fluoride and can be used to treat site-specific locations under this code if there is no active lesion present. It's application and effect is very different than most fluorides.

D 9910 - Application of a desensitizing medicament, per visit

SDF is indicated for dentinal hypersensitivity treatment and can be used to treat site-specific locations.

D1999 - Unspecified preventive procedure by report

From a third party payer perspective, this is the preferred code so providers can track the frequency of a procedure and develop usual and customary rates for future coverage.

It is also helpful to identify caries risk to justify the reimbursement with a recognized caries risk tool. Codes: D0601 (low), D0602 (moderate) and D0603 (high) codes are especially helpful in adult claims.

## 15. Can SDF be used as a cavity Liner?

SDF is cleared in the same FDA category as cavity liners. Although there are no head to head clinical trials comparing SDF as a cavity liner, it has been used successfully in this way.

SDF will not discolor intact enamel or dentin. SDF can discolor demineralized tooth structure brown/black. Some of this discoloration may shadow a restoration and can create less than optimal esthetic restorations.

## 16. Who is allowed to apply SDF in clinical practice in my State?

Each State dental practice act is different. Since SDF is a fluoride containing product indicated for the control of dentinal hypersensitivity it should fit into the same rules as fluoride varnishes. Please confirm that within your own State's dental practice acts.

## 17 . How far into enamel and dentin does SDF penetrate?

Approximately 25 microns into enamel and 300 microns into dentin. This will seal off the surface of any lesions and cause the remainder of the lesion to arrest. In a 2002 study by Dr. Chu, 100% of lesions stained black to the outer edge of the lesion were arrested.