Errata Sheet for EPC Report No. 88

Effectiveness of Antimicrobial Adjuncts to Scaling and Root Planing Therapy for Periodontitis (Volume 1: Evidence Report and Appendixes)

Please note the following corrections that have been made to this PDF version of the report:

- In Table 12, on page 66, for the Soskolne et al. 1997 article, the correct treatment group PD reduction should be *+0.46*, not -0.46.

- On page 84, under the Chlorhexidine heading, the third line should read: *"Even so, only three of these trials (all using chlorhexidine chips) produced statistically significant PD reductions for the experimental groups, ranging from 0.26 mm to 0.46 mm."* The next line should be deleted; it is incorrect.

- In Table 16, on page 88, for Chlorhexidine local, the correct number of positive studies is *3*, not 2. Also in that table, in the next column, the correct upper end of the range should be *0.46*, not 0.33.

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Evidence Report/Technology Assessment
Number 88

Effectiveness of Antimicrobial Adjuncts to Scaling and Root Planing Therapy for Periodontitis

Volume 1. Evidence Report and Appendixes

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www.ahrq.gov

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Prepared by:
RTI International-University of North Carolina Evidence-based Practice Center
Research Triangle Park
North Carolina

Investigators
Arthur J. Bonito, Ph.D.
Kathleen N. Lohr, Ph.D.
Linda Lux, M.P.A.
Sonya Sutton, B.S.P.H.
Anne Jackman, M.S.W.
Lynn Whitener, Dr.P.H.
Christian Evensen, M.S.

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Preface

The Agency for Healthcare Research and Quality (AHRQ), through its Evidence-Based Practice Centers (EPCs), sponsors the development of evidence reports and technology assessments to assist public- and private-sector organizations in their efforts to improve the quality of health care in the United States. This report, *Effectiveness of Antimicrobial Adjuncts to Scaling and Root-Planing Therapy for Periodontitis,* was requested and funded by the National Institute of Dental and Craniofacial Research. The reports and assessments provide organizations with comprehensive, science-based information on common, costly medical conditions and new health care technologies. The EPCs systematically review the relevant scientific literature on topics assigned to them by AHRQ and conduct additional analyses when appropriate prior to developing their reports and assessments.

To bring the broadest range of experts into the development of evidence reports and health technology assessments, AHRQ encourages the EPCs to form partnerships and enter into collaborations with other medical and research organizations. The EPCs work with these partner organizations to ensure that the evidence reports and technology assessments they produce will become building blocks for health care quality improvement projects throughout the Nation. The reports undergo peer review prior to their release.

AHRQ expects that the EPC evidence reports and technology assessments will inform individual health plans, providers, and purchasers as well as the health care system as a whole by providing important information to help improve health care quality.

We welcome written comments on this evidence report. They may be sent to: Director, Center for Outcomes and Evidence, Agency for Healthcare Research and Quality, 540 Gaither Road, Rockville, MD 20850.

Carolyn M. Clancy, M.D.
Director
Agency for Healthcare Research and Quality

Jean Slutsky, P.A., M.S.P.H.
Acting Director, Center for Outcomes and Evidence
Agency for Healthcare Research and Quality

Lawrence Tabak, D.D.S., Ph.D.
Director
National Institute of Dental and Craniofacial Research

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We are deeply appreciative of the clinical and research assistance for this systematic review provided by James D. Bader, DDS, MPH, and Daniel A. Shugars, DDS, PhD, of the University of North Carolina at Chapel Hill School of Dentistry and Cecil G. Sheps Center for Health Services Research (Dr. Bader). Both were instrumental in advising on the key questions, designing literature search strategies, selecting critical outcomes, identifying consultants, reviewing titles and abstracts, and initially reviewing clinical articles (Dr. Bader, tetracycline; Dr. Shugars, minocycline). Dr. Bader in addition was extremely helpful with data abstraction and abstractor training and provided a thoughtful review of the draft evidence report. We are singularly indebted to Anne Jackman, MSW, of UNC's Cecil G. Sheps Center for Health Services Research for her unwavering project management and research support. We thank our abstractors, Nancy Fan Lenfestey, MHA, of RTI and Laura Sterling, MD, and Gerald Gartlehner, MD, of the University of North Carolina at Chapel Hill. Finally, the investigators deeply appreciate the considerable support, commitment, and contributions from RTI staff Ghada Homsi, ME, Loraine Monroe, and Terri Kissiah.

In addition, we would like to extend our appreciation to the members of our Technical Expert Advisory Group (TEAG), who served as vital resources throughout our process. They are: Gary Armitage, DDS, Division of Periodontology, University of California at San Francisco School of Dentistry, San Francisco, Calif.; Jack Caton, DDS, Eastman Dental Center, Rochester, NY; Daniel Fine, DMD, Department of Oral Biology, University of Medicine and Dentistry of New Jersey, Newark, NJ; Sarah D. Grossi, DDS, MS, Department of Oral Biology, State University of New York at Buffalo, Buffalo, NY; Marjorie Jeffcoat, DDS, Department of Periodontology, University of Alabama-Birmingham, Birmingham, Ala.; and Anthony Neely, DDS, School of Dentistry, University of Detroit Mercy, Detroit, Mich.

We owe our thanks as well to our external peer reviewers, who provided constructive feedback and insightful suggestions for improvement of our report. Our peer reviewers included Drs. Armitage, Caton, Fine, and Neely from the TEAG, and Dr. Debora Matthews, DDS, Dipl. Periodontics, MSc, Division of Periodontics, Dalhousie University, Nova Scotia, Canada. Our Federal Reviewers included Dr. William Maas of the Centers for Disease Control and Prevention, David Atkins, MD, Chief Medical Officer at ARHQ and David Lewin, of the AHRQ editorial staff, and several other anonymous reviewers from NIDCR and AHRQ.

Structured Abstract

This systematic review concerns chronic periodontitis (bacterial infections of the soft tissue and bone supporting the teeth), which affects many adults in the United States, some severely enough to threaten loss of teeth. The key question is whether, in adults with chronic periodontitis, scaling and root planing (SRP) accompanied by an adjunctive antimicrobial agent when compared to SRP alone improves outcomes that persist over time. Adjunctive antimicrobials include systemic and/or locally applied tetracycline, minocycline, metronidazole, metronidazole plus amoxicillin, chlorhexidine, a grouping of other antibiotics, and a grouping of other antimicrobials. Primary outcomes are reductions in probing depth (PD), gains in clinical attachment level (CAL), and decreases in selected pathogens, especially spirochetes.

Search Strategy. The RTI-UNC Evidence-based Practice Center did a series of MEDLINE searches covering 1966 through December 2002 and an EMBASE search through February 2002 to identify published primary research on this key question; we conducted hand searches of relevant leading journals and used literature identified by clinical experts that the searches did not identify.

Selection Criteria. We included clinical trials published in English that (a) involved adults with chronic periodontitis but no serious comorbidities, (b) tested one or more chemical antimicrobial agents as an adjunct to SRP alone (or with a placebo), (c) had a concurrent control group that received the same SRP as the treatment group, (d) reported outcomes for specified, fixed time periods, and (e) if multiple antimicrobials were tested, reported outcomes for each agent separately.

Data Collection and Analysis. From a pool of nearly 11,000 articles, we retained 599 for independent dual reviews; we retained 70 of these articles, although we used some more than once because they involved more than one antimicrobial arm. A single abstractor abstracted data that were then entered into evidence tables; at least one author independently confirmed data in the evidence tables against original articles and verified data in text and text tables.

We did descriptive and qualitative syntheses of this evidence, focusing on the PD, CAL, and microbiological outcomes, mainly percentage change in spirochetes, reported for the longest time period of each trial. We conducted several meta-analyses of PD and CAL effect sizes when we had necessary data on at least three studies at 6-month follow-up (plus or minus 3 months).

Main Results. Findings differed markedly by antimicrobial and mode of delivery. While this literature has numerous limitations, locally administered adjunctive drugs appear to be more efficacious than systemic drugs; most positive results occurred for tetracycline, minocycline, metronidazole, and chlorhexidine. Adjunctive therapies generally reduced PD levels; differences between treatment and SRP-only groups in the baseline-to-follow-up changes typically favored treatment groups but usually only modestly (e.g., from about 0.1 mm to nearly 0.5 mm) even when the differences between groups were statistically significant. Effects for CAL gains were smaller and statistical significance less common.

Conclusions. Some antimicrobials show promise as adjunctive therapies to SRP for treating non-aggressive chronic periodontitis in patients without other comorbid conditions such as diabetes or immune deficiency, but the marginal improvements in PD and CAL are a fraction of the improvements from SRP alone. Thus, whether such improvements, even if statistically significant, are clinically meaningful remains a question. A substantial agenda of future research to address that and other issues (e.g., costs, patient-oriented outcomes) remains.

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Errata Sheet for EPC Summary No. 88

Effectiveness of Antimicrobial Adjuncts to Scaling and Root Planing Therapy for Periodontitis

Please note the following corrections that have been made to this PDF version of the summary:

On page 3, column 1, under the heading Chlorhexidine,

- Line 4: two is now *three* and both has been changed to *all*
- Line 7: 0.33 has been changed to *0.46*
- Line 8: the entire sentence beginning “Conversely, one large trial…” has been deleted.
- Line 12: the next sentence that begins “The statistically significant overall effect size…” now ends with the word “results." The rest of the sentence has been deleted.

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Agency for Healthcare Research and Quality

Evidence Report/Technology Assessment

Number 88

Effectiveness of Antimicrobial Adjuncts to Scaling and Root-Planing Therapy for Periodontitis

Summary

Objectives

Periodontal diseases are bacterial infections that occur at or below the gum line. In contrast to gingivitis, which affects only the gums, periodontitis (severe periodontal disease) may involve the soft tissue and bone supporting the teeth. An estimated 70 percent of the adult U.S. population is affected by these infections. This includes 20–30 percent who have periodontitis that threatens the loss of teeth. Approximately $5 billion is spent on treatment of periodontal diseases each year. This report deals with the treatment of chronic periodontitis in adults.

The key question is whether scaling and root planing (SRP) accompanied by an antimicrobial agent, as a supplemental or adjunct treatment, results in improved outcomes that persist over time in adults with chronic periodontitis when compared with SRP alone (or SRP and placebo). The primary outcomes of interest in this report are reductions in probing depth (PD) and gains in clinical attachment level (CAL). Of secondary interest are reductions in selected disease-causing bacteria, particularly reduction in the percentage of spirochetes present in dental plaque or in fluid from the gingival crevice.

Methodology

Search Strategy

The research team performed automated searches of MEDLINE™ and EMBASE™ to identify published primary research that contained evidence related to the key question. The authors tailored the searches to the key question. They did not seek out unpublished research, but hand-searched the last 12 months of the three most relevant journals, to be sure to include recent articles that might not have been indexed in time for the searches. Using key words, the authors limited the MEDLINE searches by dental condition (periodontitis), treatments (scaling, root planing, use of specific antimicrobial drugs), and study designs (controlled clinical trials) of interest. EMBASE was searched by condition and study design.

Selection Criteria

Only research articles published in English involving human subjects, and whose study design was a controlled clinical trial, were included in the review. The trials all had to test one or more chemical antimicrobial agents as an adjunct to SRP. To be included, the study needed to have a concurrent control group that received the same type of SRP as did the treatment group. Generally, if multiple antimicrobials were being tested, the study had to report outcomes for each agent separately. An exception was made for one commonly used drug combination (metronidazole and amoxicillin). Outcomes had to be reported for specified, fixed time periods.

The authors included only studies in which their samples were described as persons with chronic (or adult) periodontitis; thus, studies of forms of the disease described as aggressive, early onset, juvenile, and refractory were excluded. Also excluded were studies of people with diabetes, smokers, and those infected with HIV/AIDS, because of behavioral or comorbid factors that can complicate treatment. Despite the authors' effort to standardize the type of disease studied, the samples of subjects remained diverse, including persons never before treated for periodontitis, those on maintenance regimens,

and subjects with active disease. In addition, the patient samples typically were described as covering a range of disease severity, such as moderate to severe periodontitis.

Data Collection and Analysis

The researchers performed independent, dual reviews of titles or abstracts on a total of 599 articles that were found using automated searches of MEDLINE and EMBASE and through hand-searches of reviews and recent journals. These searches were used to identify potentially useful articles that were obtained and abstracted. Data from these abstracted articles was included in evidence tables separately by the type of antimicrobial agent used and whether the agent was delivered systemically or locally.

A single reviewer read the relevant portions of each article to establish its eligibility for inclusion in the report. Another reviewer independently assessed the excluded articles to assure that they were properly removed from full review and abstraction. Individual abstractors extracted data from the tables and text of included articles, and the report's authors independently confirmed the abstracted data as they prepared the evidence and text tables, and analyzed the results. Articles excluded after the start of data abstraction were reviewed by a second reviewer, as described above, for confirmation of the exclusion decision.

This process reduced the total number of included articles to 67. Suggestions made during peer review of the draft report led to the inclusion of an additional three studies, for a total of 70 articles. Several studies had multiple intervention arms, so that a single study could contribute to the evidence on more than one adjunct therapy. Analysis of these studies consisted of a descriptive synthesis—primarily of changes in PD, CAL, and microbiological composition. When necessary data was available from at least three studies, the authors also conducted a meta-analysis to provide a quantitative synthesis and overall estimates of the adjunct's effectiveness.

Findings

The authors conducted separate analyses of the following agents as adjuncts to SRP: tetracycline, minocycline, metronidazole, the combination of metronidazole and amoxicillin, and chlorhexidine. For tetracycline, minocycline, and metronidazole, they did separate analyses for systemically and locally delivered adjunct treatments. Local treatment delivery methods included irrigants, gels, ointments, microcapsules, and impregnated strips, chips, and fibers.

The authors also analyzed agents that appeared in the literature as part of only one or two identified eligible studies. These were grouped together, either as other antibiotics (doxycycline, azithromycin, spiramycin, and ofloxacin), or as other antimicrobials (fluorides, hydrogen peroxide, povidone iodine, triclosan, and tetrapotassium peroxydiphosphate).

Tetracycline. For systemic tetracycline (five studies), there was a greater reduction in PD with adjunct treatment than using SRP alone, but no individual difference reached statistical significance. The meta-analysis produced an estimated overall difference of 0.15 mm in PD reductions, favoring the use of SRP with systemic tetracycline over SRP alone, but this difference also did not reach statistical significance. One of the four studies that measured CAL gain produced a statistically significant reduction of 0.31 mm, favoring the use of the adjunct with SRP over SRP alone.

The weight of the available evidence supports the effectiveness of locally applied tetracycline as an adjunctive therapy. Of the 16 studies of locally applied tetracycline preparations, four demonstrated statistically significant PD reductions ranging from 0.41 mm to 0.93 mm, favoring the experimental group. The overall estimated PD reduction—0.47 mm—was statistically significant, favoring the adjunct treatment. Only two studies in this group showed a statistically significant gain in CAL, 0.15 mm and 0.48 mm, respectively; the overall effect size from the meta-analysis was a statistically significant 0.24 mm CAL gain.

Minocycline. Neither of the two studies of systemic minocycline used as an adjunct to SRP provided any statistically significant evidence for its use in reducing PD or increasing gains in CAL.

The eight studies of locally applied minocycline are more supportive of its use as an adjunct to SRP. Four studies reported statistically significant reductions in PD. These ranged from 0.30 mm to 1.10 mm, with this latter amount reported for persons whose initial probing depth was 7 mm or greater. The mean effect size from the meta-analysis was a statistically significant 0.49 mm reduction in PD, favoring use of local minocycline. A very similar result was reported for CAL gain, with three studies showing statistically significant gains in CAL of 0.39 mm to 0.80 mm. The mean effect size from the meta-analysis was a statistically significant 0.46 mm gain in CAL and favored the use of the adjunct.

Metronidazole. Only two of the seven studies of systemic metronidazole used as an adjunct to SRP reported statistically significant reductions in PD over SRP alone. They ranged from 0.47 mm to 1.64 mm and represented subpopulations with initial probing depths of 4 mm to 6 mm and more than 6 mm, respectively. Two studies also reported statistically significant gains in CAL with the adjunctive use of systemic metronidazole, ranging from 0.47 mm to 1.19 mm, again in persons with relatively deep initial PD.

Four of the 11 studies of SRP plus locally delivered metronidazole yielded statistically significant reductions in PD ranging from 0.18 mm to 0.80 mm. The overall effect size

estimated from the meta-analysis was 0.32 mm favoring local metronidazole as an adjunct to SRP; this effect was found to be statistically significant. Two studies reported statistically significant CAL gains of 0.40 mm and 0.66 mm, again favoring the adjunctive use of local metronidazole. The mean effect size estimated from the meta-analysis was only 0.12 mm, favoring adjunctive local metronidazole, but it is statistically significant.

Metronidazole and Amoxicillin Combination. Only one of the four studies of this systemically administered drug combination plus SRP reported a statistically significant greater PD reduction than SRP alone (0.7 mm). One of the four studies of CAL gain reported a statistically significant improvement over SRP alone, but the exact amount of the difference was not reported.

Chlorhexidine. Of the 17 studies of locally administered chlorhexidine included in the review, most had small numbers of subjects but larger numbers of sites or pockets as the unit of analysis. Despite this, only three of these trials (all using chlorhexidine chips) produced statistically significant PD reductions. The reductions favoring the use of chlorhexidine as an adjunct to SRP ranged from 0.26 mm to 0.46 mm. The statistically significant overall effect size from the meta-analysis was 0.24 mm, reflecting the moderating effect of the contrary results.

Gains in CAL with the use of chlorhexidine as an adjunct were generally lower than were the reductions in PD. Three studies had statistically significant results ranging from 0.16 mm to 0.28 mm, favoring chlorhexidine use. The statistically significant mean effect size estimated from the meta-analysis was 0.16 mm.

Other Antibiotics. The seven trials in the group of other systemic antibiotics (doxycycline, spiramycin, the combination of spiramycin and metronidazole, azithromycin, amoxicillin and clavulanic acid, and amoxicillin plus chlorhexidine) were quite varied in size, duration, and other variables. The authors were not able to combine these trials into a meta-analysis. Three of the studies reported statistically significant results for PD reduction, ranging from 0.47 mm (for spiramycin) to 0.87 mm (for azithromycin, among patients with initial PD levels of 6 mm or greater). Two studies reported statistically significant results for CAL gains; only one gave specific data, a gain of 1.3 mm with doxycycline. Given the diversity of these therapeutic agents, means of therapy, and overall study designs, the authors believe that caution is warranted in interpreting these studies as convincing evidence of effectiveness, especially in the light of the generally negative results for other, more commonly studied systemic antibiotics.

Only two trials dealt with other local antibiotics (doxycycline gel and ofloxacin inserts), and only the one with doxycycline provided data showing a 0.44 mm PD reduction and a 0.37 mm CAL gain, both statistically significant. These results are promising, as they come from a relatively large trial, but the strength of the evidence should be interpreted conservatively when compared to that represented by the multiple studies of the more commonly used local adjunct therapies.

Other Antimicrobials. It is not possible to say much about the group of five studies (one with two experimental arms) grouped together as other antimicrobials (amine fluoride gel, stannous fluoride gel, triclosan gel and dentifrice, hydrogen peroxide, povidone–iodine, and tetrapotassium perioxydiphosophate), all of which are locally delivered. As regards PD reduction, one of the six trials reported a statistically significant 0.8 mm net reduction at 52 weeks, favoring hydrogen peroxide used as an adjunct to SRP; however, for CAL gains, no study had statistically significant improvements favoring the treatment group. In light of the level of improvements from adjunct use of some locally administered antibiotics, the PD findings for hydrogen peroxide may seem promising, but they are from only a single, small study.

Conclusions

Although the findings differ for each antimicrobial and mode of delivery, the authors make some important overall observations relating to the key question. First, relative to the PD reductions achieved from the baseline measurement to the study end-point measurement, the difference in measurements between the treatment and control groups typically favored the treatment group, but was relatively modest. With respect to CAL gains, the picture was similar, but the effects are smaller and statistical significance was less common.

Of the antimicrobials investigated, studies of locally applied tetracycline and minocycline—and locally delivered chlorhexidine—have fairly consistent results in moderately large studies that often reach statistical significance; improvements observed in these studies typically average in the neighborhood of 0.3 mm to 0.6 mm. The other agents and delivery modes produced less consistent outcomes and fewer outcomes that reached statistical significance; the majority of studies showed small, statistically nonsignificant PD improvements. CAL outcomes were not as positive as those for PD. The question remains, the authors note, whether such improvements are clinically meaningful.

Availability of Full Report

The full evidence report from which this summary was derived was prepared for the Agency for Healthcare Research and Quality by the RTI–University of North Carolina at Chapel Hill Evidence-based Practice Center, under contract No. 290-97-0011. A limited number of prepublication copies of this report are available free of charge from the AHRQ

Publications Clearinghouse by calling 800-358-9295. Requests should specify Evidence Report/Technology Assessment No. 88, *Effectiveness of Antimicrobial Adjuncts to Scaling and Root-Planing Therapy for Periodontitis*. The final report is expected to be available by spring 2004. At that time, printed copies may be obtained.

Internet users will be able to access the report online through AHRQ's Web site at: www.ahrq.gov/clinic/epcix.htm

Suggested Citation

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Chapter 1. Introduction

Periodontal Disease and Periodontitis

Periodontal diseases are bacterial infections that occur at or below the gum line; they include both gingivitis and periodontitis. The former affects only the gingival tissue, while the latter not only affects the gingivae but also the bone supporting the teeth. This systematic review concerns chronic periodontitis, which itself is typically described as mild, moderate, or advanced on the basis of gingival inflammation, pocket formation, loss of gingival attachment, bone resorption, and number of teeth involved.[1,2] According to the Surgeon General's report on oral health, most adults are affected by these infections; a decade ago, nearly 36 million persons ages 35 through 79 had some form of periodontitis.[1,3] Of persons ages 45 to 54 (one of the two most affected age groups), 14 percent have severe periodontitis.[1,4] Prevalence rates and severity of periodontitis are higher among males than females and among blacks and Mexican Americans than whites.[1]

Expenditures on dental services were estimated in 1998 to be almost $54 billion; they were expected to exceed $60 billion in 2000.[4] Of this dental bill, perhaps nearly $5 billion is now spent on periodontal services (in 1999, an estimated $4.4 billion was spent on periodontal procedures alone).[1] As documented in the Surgeon General's report, periodontal diseases can be associated with a variety of other serious health conditions (e.g., diabetes, cardiovascular disease, stroke); the diseases themselves and the need to seek dental or periodontal care can have impacts on numerous quality-of-life indicators (e.g., social interaction, limitations in usual daily activities, psychological status and sleep, and diet and nutrition) that reflect patient-oriented concerns.

For the past 100 years, many investigations have attempted to define the etiologic agents of these diseases.[5] The microbiology of periodontal infections is quite complicated, and numerous bacterial agents have been implicated in their etiology. Perhaps as much as 50 percent of the subgingival flora of chronic periodontitis has not yet been characterized (Gary Armitage, DDS, Personal Communication, May 7, 2003). Nonetheless, small groups of specific bacterial species are now considered to be important in the initiation or progression (or both) of periodontitis;[6] often mentioned are *Bacteroides forsythus, Porphyromonas gingivalis, Treponema denticola,* and *Actinobacillus actinomycetemcomitans*.[7-9]

Scaling and root planning (SRP) is generally the first treatment employed for periodontitis. It is considered a nonsurgical procedure for which local anesthesia is often given to numb the infected gingiva (gums) around the teeth to be subgingivally scaled and planed. Scaling may be performed with hand instruments alone or with the aid of an ultrasonic scaler. It is done to clean teeth thoroughly below the gum line, removing bacterial plaque, calculus (tartar), debris, necrotic tissue, and pus from pockets that form around infected teeth. Root planing involves cleaning and smoothing the root surface of an infected tooth after scaling so that the gingival tissue can heal close to the root, shrinking the tissue and reducing the depth of the pocket that had formed. SRP is intended to reduce the bacterial load, shrink swollen and inflamed gingiva, and recondition the subgingival ecology, making it biologically compatible with optimal healing and reattachment of epithelium to the root surface.

Two commonly used clinical measures of periodontal disease progression and restoration of oral health are probing depth (PD, sometimes referred to as probing pocket depth) and clinical

attachment level (CAL). These measures are made with specially marked periodontal probes held parallel to the tooth and inserted under the free gingival margin and gently "walked" to the base of the sulcus (i.e., pocket). The probes are typically marked with rings or bands that measure distance in millimeters. The PD is generally measured as the distance from the base of the sulcus to the top of the free gingival margin. The CAL is often measured as the difference between the PD and the distance from the free gingival margin and a natural fixed anatomical marker on the tooth called the cemento-enamel junction (CEJ). As the name implies, the CEJ is where the cementum and enamel on the tooth are joined. Specially fabricated stents are also used as an alternative to a fixed anatomical landmark to measure changes in CAL.

Concerted clinical effort at SRP is aimed at reducing the bacterial load and thus reduce the subsequent risk of periodontitis (Figure 1, Line segment A-B). The recognition that specific bacteria rather than nonspecific "plaque" are the etiologic vector for periodontitis has led to the development of antimicrobial treatment approaches for reducing or eliminating these bacteria and the infections (Figure 1, Line segment A-C). Antimicrobial agents could both reduce the bacterial load and shift the bacterial ecology from "disease promoting" to "health promoting." If mechanical therapy and antimicrobial therapy are both effective, then the combination of the two could potentially be even more effective (Figure 1, Line segment B-D), lowering both the risk of further disease and reducing the bacterial load to further promote periodontal health. This systematic review examines the evidence for this combined approach to therapy for periodontitis.

Specifically, we examine the evidence, for adults with chronic periodontitis, as to whether SRP accompanied by an adjunctive antimicrobial agent, compared to SRP alone, improves outcomes that persist over time. The primary outcomes of interest in this report are PD reductions, CAL gains, and secondarily, reductions in selected pathogens. The clinical rationale for this question relates to developments in controlling periodontal infections.

Controlling Periodontal Infections

The juxtaposition of three developments makes concerted efforts to control periodontal infections more realistic today than in the past. The first major advance was the development of molecular diagnostic tools that can rapidly and inexpensively examine large numbers of plaque samples and identify specific microbial species. A second advance was the recognition that specific microbial complexes occur together in plaque. The third was the development of new tools to reduce the supra- and subgingival bacteria, such as chlorhexidine mouthwash, triclosan dentifrice, electronic toothbrushes, and systemic and local drug delivery systems. From data derived from these three scientific avenues, three strategies have been proposed for reducing the risk of periodontal diseases. Each attempts to intercept the disease process at critical points in its development.

1. Reduce supragingival plaque. Supragingival plaque reduction by home care and professional cleaning is the most universally practiced periodontal treatment available; it is considered essential in the treatment of periodontal diseases.

2. Control pathogen transmission. Introduction of an antibacterial mouthwash and toothpaste may insulate sites from infected pathogen reservoirs elsewhere in the mouth. Hujoel et al. tested rinsing once per week and observed a 45 percent reduction in tooth loss after 1 year.[10] Quirynen et al.[11] and De Soete et al.,[12] examining one-stage, full-mouth disinfection,

observed a parallel significant reduction in periodontal pathogens and improvement in clinical health following chlorhexidine rinses.

3. Disinfect pathogen reservoirs. Many investigators have recognized disease reservoirs as seeding sources for intraoral spread of disease and as an important consideration in determining therapeutic outcome.[13] Of the infection sources in the oral cavity, untreated sites elsewhere in the mouth represent the most obvious potential source of re-infection. At least three mechanisms are used to address this threat: SRP; local drug delivery; and systemic antibiotics.

SRP. SRP has been used effectively in periodontal therapy for more than 1,000 years.[14,15] The concept that eliminating periodontal pockets that support pathogen growth decreases the risk of periodontal disease is generally accepted. Some clinical studies indicate that most patients with periodontal disease can be maintained by regular SRP alone.[16-19] By itself, SRP produces a very modest transient reduction in bacteria; they can return to pretreatment levels within 2 weeks.[20,21] When total bacterial load changes, a subset of bacteria associated with periodontitis is also depressed, including *P. gingivalis, B. forsythus,* and *T. denticola.*[22] The microbial impact, however, appears to be short lived with sites re-infecting after 3 months. This suggests that a more effective initial therapy might reduce the labor of continued maintenance and also further reduce the disease risk.

Local drug delivery. Several local antibacterial agents have been tested for intra-pocket delivery. These include doxycycline gel, metronidazole gel, chlorhexidine chips, minocycline microspheres, and tetracycline fibers. All these agents, either alone or in combination with SRP, appear to reduce pocket depth[23] and may also alter oral bacteria.

Systemic antibiotics. A host of systemic antibacterial agents has been tested: amoxicillin, metronidazole, metronidazole plus amoxicillin, azithromycin, clindamycin, and ciprofloxacin. The studies, some considered in recent systematic reviews examining these antibacterial agents, either alone or in conjunction with mechanical therapy, suggest that antibacterial therapy alone may, in some cases, be as effective as SRP therapy.[15,24]

Origins of this Evidence Report

This is the fourth in a series of systematic reviews of dental topics prepared for the Agency on Healthcare Research and Quality (AHRQ) with the support and collaboration of the National Institute of Dental and Craniofacial Research (NIDCR) (for Acknowledgments, see Appendix A). The first was a review of dental caries diagnosis and management that cut across the entire population and stages of life.[25] The second report, rather than focusing on a specific dental disease condition or a particular treatment approach for the general population, dealt with several aspects of the treatment of a special population subgroup – persons infected with human immunodeficiency virus (HIV) and those living with acquired immune deficiency syndrome (AIDS).[26] The third report reviewed the cardiovascular effects of the use of epinephrine – an ingredient of dental anesthesia and retraction cord inserted around teeth to reduce bleeding – in hypertensive dental patients.[27]

The specific clinical question to be addressed in this evidence report emerged from a working group meeting that NIDCR convened on the National Institutes of Health campus on April 2, 2001. This invited group of eight experts from the field of periodontics represented the range of experience, activity, and perspective within the discipline, including academia, public

health, clinical practice, and research. In selecting the area of periodontal disease, NIDCR sought to include in its array of evidence reports the next largest domain of the profession's clinical activities after dental caries, for which we had already prepared a report. In bringing together the working group, NIDCR was opening the topic selection process to the needs and sensitivities of the field.

A set of six questions emerged from the working group meeting. Two involved diagnostic issues; one related to distinguishing aggressive from chronic periodontitis, and the other to assessing the validity of methods to predict periodontal destruction. Four questions addressed disease management or treatment issues. These included assessments of the effectiveness of SRP compared to other treatments, the nature of professional maintenance needed after periodontal therapy, how risk factors modify the outcomes of periodontal therapy, and whether predictable therapies exist for regenerating supporting tissue lost to periodontal disease. For a variety of reasons, the group rated the question of the effectiveness of SRP therapy for chronic periodontitis as the top issue for the NIDCR to consider in the evidence report.

The project team subsequently refined and clarified the question through discussions with the NIDCR staff and later through communication with the Technical Expert Advisory Group (TEAG) assembled for this particular topic area. The original question on effectiveness of SRP was too broad to be covered in a single evidence report, as it would have involved too much literature and required more time and resources than were available. The consensus decision, therefore, was to focus on the primary comparison of interest: In adults with chronic periodontitis, does SRP therapy in conjunction with the use of chemical antimicrobial agents, when compared to SRP alone, improve clinical outcomes that persist over time?

Among many possible indicators of improved clinical outcomes, we chose to use reported measures of PD reduction, gain in CAL, and pathogen reduction, with no accompanying increase in adverse events. To answer the key question, the project team systematically identified, critically appraised, and synthesized the evidence emanating from published primary human clinical trials research that produced data to allow examination of this question.

The question reflects two fairly common concerns in dentistry. First, practicing dentists may not be aware of the available research with respect to the effectiveness over time of therapies adjunctive to SRP for persons with chronic periodontitis. Second, the research may not be as comprehensive or definitive as it should be. Thus, all judged this particular focus to be of clinical, research, and practical significance.

Technical Expert Advisory Group

AHRQ guidelines require identification of a technical expert advisory group (TEAG) for evidence reports, in this case in the specialized area of managing periodontal diseases. Our TEAGs advance AHRQ's broader goals of (a) creating and maintaining science partnerships and public-private partnerships and (b) meeting the needs of an array of potential consumers and users of its products. Thus, a TEAG is both an additional resource and a sounding board throughout the project.

The TEAG for this systematic review comprised six individuals who are acknowledged technical or clinical experts in this area (Table 1). One member specifically represented the

American Academy of Periodontology (AAP) and another the American Dental Association (ADA), both potential user groups.

To ensure scientifically robust work, we asked the TEAG to provide reactions to work in progress and to advise on substantive issues or possibly overlooked areas of research. TEAG members participated in e-mail communications

- to discuss the key clinical questions, initial drafts of causal pathways, and proposed inclusion and exclusion criteria for research articles;
- to provide comments concerning the article abstraction forms, the content proposed for inclusion in the evidence tables, and the final versions of the key clinical question; and
- to discuss the proposed content of the evidence tables and the completeness of the search.

Because of their extensive knowledge of the literature and ongoing research in this specialized area of dentistry dealing with treatment of chronic periodontitis, as well as their active involvement in the associated professional societies, we also asked TEAG members to participate in the peer review process by commenting on the draft evidence report, and four did so.

Organization of this Report

The remainder of this evidence report is organized in the following manner. Chapter 2 provides details about our literature search and review methodology. Specifically included are the analytical framework for our key clinical question and our approach to conducting the systematic review, applying the inclusion/exclusion criteria, abstracting data from articles, maintaining quality control, and similar details. Chapter 3 presents the results of our analyses. Chapter 4 gives our concluding discussion, and Chapter 5 notes weaknesses and gaps we found in the research and offers recommendations for a research agenda related to the question addressed on the added effectiveness of therapies adjunctive to SRP in treating chronic periodontitis. Chapter 6 provides the references cited in the body of the evidence report.

Chapter 7 contains the evidence tables and supporting information. Finally, the complete bibliography of literature considered and used in developing the evidence report (including all articles reviewed in the literature search and all references cited in Chapters 1 to 5) appears in Chapter 8. The three appendices provide acknowledgments (Appendix A), our data abstraction form (Appendix B), and the quality review checklist (Appendix C).

Chapter 2. Methods

Overview

This chapter documents the procedures that the RTI-University of North Carolina at Chapel Hill Evidence-based Practice Center (RTI-UNC EPC) used to develop a comprehensive evidence report on the effectiveness over time of adjunctive therapies used in addition to scaling and root planing (SRP) in treating adults with chronic periodontitis. To set the framework for the review, we discuss first the key question that we address and the related underlying causal pathway for this topic. A detailed description of the literature search process follows; it includes descriptions of the Medical Subject Headings (MeSH terms) used in the principal search, other search sources, the inclusion and exclusion criteria, and the application of these criteria to the results of the searches. We note steps for reviewing studies that met the inclusion and exclusion criteria, abstracting data onto data abstraction forms, creating evidence tables, writing a draft report for external peer review, and revising the draft following peer review. We also discuss quality issues, in particular, the RTI-UNC EPC's quality control procedures for determining eligibility for inclusion, carrying out data abstraction, checking evidence and text tables against articles, and grading the quality of individual studies.

Key Question and Casual Pathway

The overarching key question is: How does the effectiveness of SRP therapy by itself for the treatment of chronic periodontitis compare to SRP accompanied by adjunctive therapy at varying lengths of time after treatment? Figure 2, the basic causal pathway for this key question, indicates the characteristics of the patient population, the nature of the SRP services, the range of adjunctive therapies considered, the possible outcomes of interest, and the various time frames in which outcomes might be measured.

We constrained the review to chronic periodontitis among adults and excluded studies pertaining solely to more aggressive forms of periodontal disease. Thus, we did not examine studies relating to treatment of periodontitis that is described as refractory, localized, juvenile, aggressive, related to human immunodeficiency virus or acquired immune deficiency syndrome (HIV/AIDS), or related to diabetes; neither did we consider studies that included a mix of periodontal diseases but that did not present separate analyses of the chronic form of the disease.

Ultimately, we focused on the following adjunctive therapies, which in some cases include both systemic and local delivery modalities:

- Tetracycline
- Minocycline
- Metronidazole
- Metronidazole in combination with amoxicillin
- Chlorhexidine
- Other antibiotics (e.g., spiramycin, doxycycline, azithromycin, Augmentin), and
- Other antimicrobials (e.g., povidone iodine, hydrogen peroxide, fluoride).

The key question defines the population of interest as adults receiving SRP for chronic periodontitis. The principal audience for this review comprises dental practitioners and

researchers, especially in periodontology; however, we believe the issues may be of interest to physicians, and so we did not, in the searches, exclude studies done in medical care settings.

Of all the potential outcome measures in this literature, we had to constrain those for this systematic review to a very small number. As discussed in Chapter 1, after discussion with clinical experts asssisting the team and the Technical Expert Advisory Group, we focused our analyses on two clinical measures: probing depth (PD, measured in millimeters of reduction) and clinical attachment level (CAL, measured in millimeters of gain). Even with this narrow focus, the nature of these measures can vary significantly across studies (i.e., across dental examiners) on the basis of several factors: the level of gingival inflammation at the time of measurement, diameter of the probe tip, probing force, and angulation of the probe,[28] often these factors reflect the nature of the original or graduate training of the examiners, but in any case they raise the level of incomparability across studies to some unknown degree. We also targeted one microbiological measure - presence or percentage reduction in spirochetes - for the qualitative analyses, but we did not try to use this for the meta-analyses, as it was even less often reported than either PD or CAL.

We reported the longest period of follow-up for entering information into evidence tables; when data were provided only by subgroups (e.g., subgroups defined by different levels of PD at baseline), we attempted to retain all that information in evidence tables or, if the volume of information was too large, to highlight data from the subgroups with the worst baseline periodontal disease severity. In some cases, articles otherwise of interest did not report on these measures in any direct way but may have given other empirical evidence, and when such information showed a statistically significant *net* difference between the treatment and control groups (i.e., a difference of the differences between baseline and the end point), we tried to reflect that in discussing results.

Literature Search and Analysis Strategy

Literature Searches

To comprehend fully the scope of chronic periodontitis research, we had to design and implement several different search approaches. We searched for articles on clinical trial research on periodontitis that gave particular attention to SRP. We also searched for specific antibiotics and other chemical antimicrobials to see if those terms produced new articles or only ones we had already found. To find relevant articles on all aspects of periodontitis, we searched MEDLINE for papers published from 1966 through the second week of February 2002. This search is fully documented with the terms (MeSH and key words) and the counts of articles identified at each step of the search process in Table 2. Table 3 provides additional specifications of our inclusion and exclusion criteria.

Our initial MEDLINE search identified 10,670 articles (Table 3). After limiting to trials and human studies, 2,987 articles remained (Step 6). We further searched for "dental scaling" and "root planing" trials, yielding 836 articles, then searched for the specific drugs listed in Table 2. We had a total of 517 articles for consideration (Step 14); the 203 drug citations (Step 26) are a subset of the 517. This search was updated in November 2002, yielding 41 additional articles (step 29 of Table 2). In addition, we ran a somewhat different MEDLINE search in December 2002 starting with the term periodontal disease (instead of periodontitis); this search (line 30 of Table 2) yielded several dozen ostensibly new articles, but because periodontal

disease includes gingivitis, virtually all proved to be irrelevant to our topic, and we added only two new items. The supplemental EMBASE search (Table 3) identified 68 articles, of which 36 were new. We identified three additional studies through references. Finally, external peer reviewers brought three additional studies (from the international literature) to our attention. In all, we examined a total of 599 articles (cited in the Bibliography [Chapter 8]).

Inclusion/Exclusion Criteria

Table 4 specifies the major criteria that we applied to research studies for deciding on their inclusion or exclusion. We applied some in our searches, but opted to cast the net broadly and mainly exclude articles through review of titles and abstracts or the articles themselves. From an earlier preliminary search, we found a considerable number of trials in MEDLINE that appeared to be applicable to our question. For that reason, we searched only for reports of primary research described as trials and those with common characteristics of trials such as blinding and randomization. Although we included review articles that reported on similar types of research (to check references for additional articles), we did not incorporate them directly in this report. We excluded letters, commentaries, editorials, clinical case reports, and practice or treatment guidelines from our searches. Finally, we included only human populations in our search and did not review animal studies.

In our manual review of the articles identified and obtained, one of the senior investigators made an initial decision about inclusion for abstraction and another senior investigator reviewed that decision. In addition, the criteria for inclusion/exclusion were printed on the abstraction form so that abstractors could, if necessary, call for another senior review of eligibility. We determined whether the adjunctive therapy was antimicrobial and chemical at this point; we dropped articles about use of lasers (used presumably to destroy microbes but not a chemical or antimicrobial agent), and those about anti-inflammatory agents (clearly a chemical agent but not antimicrobial). Very late in the process, we also excluded articles reporting on sub-antimicrobial doses of doxycycline, clearly an antibiotic but, at such doses, not intended as an antimicrobial agent.

Many of the studies we identified in our search were not investigations directly relevant to our key question. Many were studying whether a chemical antimicrobial was as effective as SRP in treating periodontitis. However, several studies had a combined (SRP and antimicrobial) treatment group in addition to an SRP-only or SRP-with-placebo treatment group, an antimicrobial-only treatment group, and a no-treatment control group. If the investigators reported comparisons and outcomes of the combined treatment and SRP-only groups for measures we focused on for this report, we included the study. Further exclusions involved studies in which (a) the SRP provided to the group receiving the adjunctive therapy was not the same as that given to the SRP-only group, (b) the periodontitis being treated was not of the chronic (or adult) type but rather a more aggressive variety (e.g., juvenile, early onset, refractory), and (c) the population with the periodontitis had a complicating comorbidity (e.g., HIV/AIDS or diabetes) or a risk factor (e.g., smoking).

We included articles in languages other than English in our *searches* because often the titles and abstracts are translated into English; this allowed us to assess whether we were missing potentially important areas of work. If the full articles were not in English, however, we did not include them in the review. This approach may have caused us to omit some materials in other languages, but our previous systematic reviews have shown that relevant studies done outside of English-speaking nations that would otherwise have met our inclusion criteria would likely have been published in an English-language journal. Thus, we do not think that restricting the full review on this key question to English-language documents introduced any serious bias.

Title, Abstract, and Article Review

To narrow the literature identified through the search to studies with evidence that bore directly on the key question, two senior analysts independently reviewed titles and abstracts obtained in the initial searches. The reviewers were not blinded in any way to authors, journals, or affiliations. After some discussion of the inclusion/exclusion criteria, they retained research studies believed to be focused on the key question.

Of the 517 titles and abstracts independently examined at the first stage, both senior analysts agreed to retain 107 for further review. When they disagreed at this stage, they obtained the full article for review unless it was a foreign article or a review; this step led us to retain an additional 70 citations. Thus, we retained a total of 177 articles to be fully reviewed and possibly abstracted. In addition, we obtained six seemingly relevant review articles. The 36 articles from the EMBASE search and the 43 additional titles and abstracts identified through MEDLINE in November and December 2002 received the same type of review. Of the total 599 articles reviewed, we retained 67 studies to carry through to full article review, abstraction, and inclusion in this report. Finally, as noted, we added three studies that were brought to our attention during the peer review in May 2003.

Data Abstraction

For all retained articles, we obtained hard copies of the full articles. Meanwhile the project team developed a draft data abstraction form and tested it on a small number of articles. We trained abstractors on the initial forms, but the complexities and poor presentation of some of this literature dictated that we revise the abstraction form somewhat to make the process easier. Abstractors were then given an updated training session on the final abstraction form (Appendix B). Ultimately, data items included study identification information, design, descriptions of the sampling and characteristics of the treatment and control groups, description of the adjunctive interventions, reported outcomes and statistics, and other information or comments needed to characterize the study adequately. During this period, the project director, EPC Co-Director, and other EPC staff developed a tentative list of evidence tables, created draft evidence tables with provisional column headings, and established conventions for the order of entry of articles into those tables.

Two senior investigators trained the five main data abstractors, all with master's degrees in public health or another relevant master's degree. Training consisted of a thorough review of the key question, the inclusion/exclusion criteria, and the abstraction form, as well as a walk-through review of up to three articles and independent reviews of two others. We compared the independently abstracted articles to abstracts by the scientific director, noted variations, and provided additional training as needed.

We performed only single abstractions. The EPC's document preparation specialist then entered data from all completed data abstraction forms into the draft evidence tables. For quality control, early in the abstraction process the project director reviewed a small sample of each abstractor's completed data abstraction forms against the full articles; in addition, the EPC's administrator proofread all evidence table entries against the original articles so that needed corrections could be made immediately. Because of the number and size of the evidence tables for this substantial set of articles, we created numerous "text tables" for Chapter 3 that would summarize critical outcome information in a simpler format for users of the report. These tables

also helped us streamline collection of the data needed for the meta-analyses. The EPC administrator also proofread these text tables against both evidence tables and articles, to ensure absolute consistency.

Meta-Analysis

The studies in this evidence report were exclusively clinical trials, albeit many were small and underpowered as individual studies. Investigators often reported the two clinical outcome measures of interest - probing depth (PD) and clinical attachment level (CAL) - in ways that would allow us to express effect sizes in the same way (as millimeters of change). These conditions permitted us to consider performing a series of meta-analyses for studies of at least some of the adjunctive therapies, so that we could quantitatively summarize the work and calculate an overall effect size measure.

We had a total of 70 studies that were candidates for inclusion in one of the meta-analyses. Of those, 29 studies, five with multiple arms, met the criteria that we established for inclusion in the meta-analysis:

- The study had to provide a measure of the treatment effect at 6 months post-baseline, although we allowed for a 3-month window on either side of the 6-month point. Thus, we included studies reporting results from 3 to 9 months (i.e., 12 to 39 weeks). For some articles, the true endpoint of the study fell within this range and they were included; for studies lasting longer than 9 months, the authors had to have reported results from some point within this range; and studies shorter than 3 months were automatically excluded.

- Included studies had to indicate treatment effect by either PD change (i.e., reduction) CAL change (i.e., gain), or both.

- Included studies had to indicate the between-group difference in means (the treatment effect), the standard error or the 95 percent confidence interval of the treatment effect, and the sample size for each study group. Studies could also be included if they provided enough information to allow us to calculate these numbers, such as the within-group differences and their standard deviations or standard errors. Some studies gave the difference between the mean differences of the two study groups (i.e., the effect size of the adjunctive treatment), but often we had to calculate the overall effect size from the mean differences between the baseline to follow-up means for the experimental treatment group and the control group. Similarly, we often had to estimate the standard error of the difference of the mean differences.

- To proceed with a meta-analysis of a given therapy, we required that at least three studies related to one of the clinical outcomes meet the above criteria. The studies of systemic minocycline, systemic metronidazole, and combined metronidazole and amoxicillin failed to meet this requirement.

Comparisons

Regardless of the number of treatment groups and variations in multiple control groups, we narrowed our definition of "treatment" to refer to those groups that received SRP plus one of the following adjunctive therapies that had at least three eligible studies:

- Tetracycline used in systemic therapy and in local applications including fibers, gels, pastes, rinses, solutions, and strips;
- Minocycline used in local applications as a gel, ointment, or microencapsulated;
- Metronidazole, local applications of metronidazole gel; and
- Chlorhexidine used as a local application (e.g., chips, gels, strips, irrigants, and rinses).

Control groups received SRP alone, and no adjunctive drug therapy, other than placebos.

Outcomes

We chose to examine two clinical outcomes that map to our qualitative analyses: PD reduction and CAL gain. For each therapy we analyzed the extent to which the treatment led to a difference in the mean PD reduction or a difference in the mean CAL gain when compared to SRP alone. Our outcome is, therefore, the *difference of a difference* (the difference between the baseline and end-point between the treatment and control groups) or a net between-group difference.

Preparing Study Data for Meta-Analysis

We used the RevMan 4.2 software package to conduct the meta-analysis.[29] RevMan is a software tool designed to manage the entire systematic review process; we used it here exclusively for the meta-analyses. We entered the following information for each study: (a) study ID (author citation) and year; and (b) study design information in the study characteristics table, including methods, participants, interventions, outcomes, and a rating of the allocation concealment or blinding. In the "comparison tables" section, we set up the comparisons (five for PD and four for CAL), listed the outcomes of interest with each comparison, and added the relevant studies to each comparison-outcome node.

Analysis

Analysis was based on the general inverse variance method of estimation available in RevMan. This method calculates a pooled, or overall, effect for each outcome, a test of significance for the treatment effect across all studies (a Z statistic), and a measure of heterogeneity. The heterogeneity statistic is a rough indicator of whether all included studies are indeed comparable (null hypothesis is that treatment effect does not differ among trials). The heterogeneity statistic is also used to calculate an I^2 statistic, which indicates, approximately, the proportion of total variation in the study estimates that can be attributed to heterogeneity rather than sampling error.[29] The method of estimation can handle situations in which effect is specified as fixed or random; we modeled both but have reported only fixed effects for our analysis, as the results were quite similar.

Eight studies did not provide required information on certain aspects of their results. Typically this meant that, to include them, we had to calculate or estimate standard errors ourselves.[30-37] Rather than risk dramatically overestimating the "real" standard error, possibly by as much as 100 percent or more, and unfairly reduce the likelihood of finding statistical significance, we used a set of statistical procedures incorporated in SAS macros[38] to estimate the standard errors of the difference of differences to include in the meta-analysis.

Quality Rating of Articles

To grade the quality of individual studies (articles), as is expected for AHRQ systematic reviews,[39] we developed a quality rating checklist for articles that dealt with internal validity, external validity, and analytic dimensions (Appendix C). The 13 items in the checklist relate mostly to study design elements. We customized items on the checklist to fit the question and literature, but many of the component items were taken directly from, or represent slight modifications of, existing rating scales used by the RTI-UNC EPC, reflecting suggestions from work done by this EPC. [39,40] CONSORT criteria also figured prominently in our thinking because the studies were trials of various kinds.[41]

We pretested draft forms on several articles and eliminated or reworded some items. We gave scores to articles by summing the number of items on the quality rating form checked as "yes" and dividing by 13, the number of items. The EPC Administrator and Project Director independently assigned quality grades to all studies using the final form (Appendix C). We entered both quality scores (essentially two percentages) into the evidence tables. Although not formally validated, our rating scheme adopts the basic strategy of quality grading and provides a relative basis by which we and others can assess the overall strength of the research available to address our key question. We do not employ the quality score as a way of reviewing articles for inclusion in the evidence report or the meta-analysis. This approach is in accord with what recent research has found: no reliable relationship between overall quality rating measures and estimates of treatment effects in trials.[42]

Development of the Evidence Report

Following completion of evidence and/or text tables, we sent them to main authors of the report, together with a general outline of the results chapter of the report. The authors had previously agreed to present mainly qualitative syntheses of the information in the tables, with primary attention to PD and CAL findings and data on spirochetes when available; they would call out information on specific articles only when those studies offered clinically significant findings or insights into the key question. Authors writing from either text or evidence tables were also asked to check data in the tables against articles whenever any table entry was unclear or inconsistent across tables. The authors returned their sections to the project director and EPC Co-Director, who developed an overall synthesis of the results and the discussion chapter. In addition, the project director and other members of the project team developed the research agenda chapter, drawing on the limitations and gaps in the existing literature and on promising leads from the studies reviewed.

We submitted the draft evidence report for external peer review in mid-April 2003 (see Appendix A). Upon receipt of reviews, the EPC staff compiled them into a peer reviewer matrix, discussed many issues with AHRQ and NIDCR staff, and then revised the report as

appropriate, documenting in detail the disposition of all significant clinical, analytic, or policy-relevant changes. We expanded the meta-analyses somewhat to include more studies where we were able to use the SAS macros to produce more estimates of standard errors than we had been able to do before peer review. As noted, we also added several recent articles mentioned by peer reviewers that met our inclusion criteria but had not appeared in any MEDLINE or EMBASE searches. The revised version of the report was submitted to AHRQ and NIDCR for further review before it was put into absolute final form.

Chapter 3. Results

Overview

This chapter presents the findings for the key question in this evidence report concerning the added effectiveness of therapy adjunctive to scaling and root planing (SRP) in the treatment of chronic periodontitis over time. The key outcomes are reductions in probing depth (PD), gains in clinical attachment level (CAL), and secondarily, microbial changes, chiefly reductions in the percentage of spirochetes present in crevicular fluid or plaque samples.

We present results in separate sections according to the specific agents used adjunctively and to the mode of delivery (either systemic or local) and when more than just one or two articles addressed a particular agent or combination of agents. The agents we report on in separate sections include tetracycline, minocycline, metronidazole, the combination of metronidazole and amoxicillin, and chlorhexidine. We grouped studies of azithromycin, spiramycin, amoxicillin clavenate, and doxycycline, which did not have enough studies to treat separately, into a sixth section called other antibiotics. Finally, we present a seventh section for other kinds of antimicrobial agents such as povidone iodine, hydrogen peroxide, and fluorides. Chapter 7 has the full evidence tables for each main category of treatment; brief summary tables appear at the end of this chapter.

Description of the Evidence

We reviewed 599 published clinical trials for possible inclusion in this evidence report. The final number of unduplicated studies included was 70. We tried to include as many trials as possible; thus, we retained some that did not report actual data on the comparisons of interest but that did make statements about statistical tests of those comparisons. Numerous studies examined the effectiveness of more than a single antimicrobial agent; thus, we have dealt with more comparisons between treatment and control groups than studies *per se*.

In all, we included 16 different adjunctive antimicrobial agents in this review. They include tetracycline, minocycline, metronidazole, amoxicillin, chlorhexidine, spiramycin, doxycycline, sodium bicarbonate and hydrogen peroxide, stannous fluoride, amine fluoride, triclosan, povidone iodine, azithromycin, tetrapotassium peroxydiphosphate, amoxicillin and clavulanic acid, and ofloxacin. These agents were tested as either systemic or local interventions (or both) and involved a variety of modes of delivery – capsule, gel, rinse, irrigant, paste, fiber, chip, and strip.

All test and control teeth received SRP. SRP was delivered all at once (e.g., two visits within 24 hours), one quadrant at a time at intervals of 2 weeks, on only selected teeth or all teeth, by hand or by hand and ultrasonic scaler, and with or without anesthesia. The extent of SRP varied from study to study, but so far as we can tell it was performed the same way within the test and control groups in a given study.

Limitations of the Evidence

As we indicated earlier, all primary studies in this report were controlled trials of some kind, mostly described as randomized, and often described as double or fully blinded. Thus, they represent in some ways a very high level of investigational activity about the added effectiveness over time of adjunctive antimicrobial therapies relative to SRP alone. In addition, we have to the best of our ability eliminated studies that involved patients with conditions (e.g., diabetes, HIV) or risk factors or behaviors (e.g., smoking) that are known to affect the prognosis of chronic periodontitis or with forms of periodontitis diseases not described as chronic or adult (e.g., juvenile, early onset, refractory). In this way, we attempted to ensure that the disease being treated and the associated risk factors in the studies are similar. Nonetheless, the studies we included were quite different along many important dimensions, and that fact has made drawing solid conclusions particularly difficult.

For only five agents – tetracycline, minocycline, metronidazole, the combination of metronidazole and amoxicillin, and chlorhexidine – did more than two studies qualify for inclusion in the main analyses. Moreover, even these particular drugs were often used in different doses, incorporated into different treatment regimens, and delivered via different modalities. We observed particularly great variation in delivery mode for local drug applications: microspheres, chips, fibers, and strips, gels, rinses, irrigants, ointments, and pastes.

Study periods differed greatly from just a few weeks to several years. Often, investigators either did not report intermediate points or gave only partial results for those points. As the ultimate time points did not correspond across studies, neither did intermediate results.

Outcomes measured varied enormously across the studies. Some focused exclusively on microbiological measurements; others focused exclusively on clinical measures. In both situations we encountered many more measures than we could reasonably analyze, and even the studies we ultimately included did not report on all key outcomes. Among the clinical measures reported were gingival indices, plaque indices, periodontal disease indices, bleeding indices, measures of periodontal PD and CAL, and a variety of microbial counts.

As discussed in Chapters 1 and 2, we narrowed the focus of our report to the two clinical measures – PD and CAL – that we believed are of practical importance to clinicians and that studies tended to measure in reasonably similar ways. To reflect microbiological measures, we included the one that was apparently the most frequently reported: percentage of spirochetes. Even though these outcomes were nominally the same, the way they were measured varied across studies. For example, some measurements of attachment level used the cemento-enamel junction as the fixed reference point, whereas others employed some other marker. In addition, different kinds of probes were used. As the variable of interest is change over time (PD reduction; CAL gain), however, these particular variations would not necessarily pose critical analytic problems.

Subjects in the studies differed in important ways too. Some had received prior periodontal treatment, as they were recruited through periodontal patient registries. Because there was no indication that the same sites were being treated again for active disease and because the term refractory was not mentioned, we retained the articles on the assumption that these were new sites or routine maintenance of formerly active sites. By contrast, for other subjects the investigational treatment was explicitly stated as their first for periodontal disease. Rarely was

any demographic information reported on study samples beyond the mean age, or the age range, and sex of subjects. Often such information was for the entire sample and not for each treatment group.

Another variation in the measurements was when they were taken, e.g., before or after SRP. In some cases we could not determine the timing.

The greatest variation occurred in how investigators reported their results. Many studies in this review had not originally been intended to address the question that we wanted to answer, but they had findings seemingly relevant to the question. Many were investigations of whether some form of antimicrobial agent performed as well as SRP alone, and we would have excluded these articles. In some cases, these studies had a SRP-only treatment group and a treatment group that included SRP plus the antimicrobial; when we saw those study groups, we would include the article and then use only the data from those two groups in our analysis.

Investigators often reported testing the change in PD or CAL from baseline to the endpoint for treatment and control or comparison groups and whether those within-group differences were statistically significant. By contrast, they often did not report whether any *differences between the changes from baseline to the end of the study for these groups* was significant. Although sometimes investigators gave the data needed to do that statistical test, such as a mean and a measure of variance (either standard deviation or standard error), often they did not. This was especially a challenge for split-mouth designs, for which observations in groups are not independent and an estimate of the covariance is needed to estimate correctly the confidence intervals around the difference in changes for the two groups.

Determining whether teeth, sites around teeth, or persons were the unit of analysis was often difficult, as investigators may have included only one tooth per mouth, one tooth per quadrant in split-mouth designs, or multiple teeth. Often the criterion for inclusion in the study was the presence of multiple qualifying teeth (by virtue of PD or bleeding, for instance) and all were included, but sometimes the number of teeth included for study was fewer than "all" or indeed only one. With respect to initial or baseline PD, inclusion requirements in these trials differed (e.g., from greater than 4 mm to greater than or equal to 7 mm), thereby presenting different clinical entities for study. It was also difficult, if not impossible, to distinguish when investigators calculated means across all the teeth or across means of multiple teeth in a single mouth, thereby making the group mean a mean of means across people rather than a mean across teeth.

Some investigators reported results only by depth of initial pocket rather for the entire group of subjects. This posed a problem for this review because the grouping of initial pockets often differed from study to study. Usually not enough information was provided to enable us either to aggregate or to split the data to make them more comparable to other studies.

In the presence of a variety of terms used to describe what we reasonably could consider to represent the equivalent of SRP – subgingival scaling and mechanical debridement – rarely could we find enough detail on the extensiveness or thoroughness of the procedure to assess comparability across studies. Some investigators noted the number of sessions and their spacing, average total time spent per subject, time spent per tooth, or time spent per quadrant performing the SRP. Only occasionally did researchers note whether they had used hand instruments, ultrasonic scalers, or both. Some articles mentioned use of an anesthetic in the SRP, but this was

not routine. Studies differed in whether the entire mouth received SRP, or only study teeth, or a particular jaw or quadrant. Terms such as "thorough," "meticulous," "rigorous," and "careful" were only rarely used to describe the SRP. Yet another source of variation may have been the use of dental hygienists in some studies but not others, although we did not document this variable in evidence tables. Overall, if we detected, within a given study, that the SRP differed between the treatment group and our designated control group, we excluded it.

Some studies reported attrition from the original study groups; some gave the number of subjects finishing the trial. In general, then, few research teams presented an intent-to-treat analysis. As one would expect, the longer the study period, the greater the loss to follow-up, and we were not always certain of the comparability of final treatment and control/comparison groups. In presenting numbers of subjects in this chapter, we use counts of completers insofar as possible.

Finally, sorting publications to eliminate duplicate studies (so as not to give multiple studies using the same data extra weight in the evidence pool) was difficult for several reasons. Authors often did not clearly acknowledge earlier or less complete versions in their later or more complete studies. We found several cases of articles published with early data that were published later in the completed study. Also, in some cases of multi-site studies, sites published their own results separately or conducted later follow-ups with their patients. For evidence tables, where one "row" constitutes a study, we combine data and give the multiple citations unless those citations give precisely the same information, in which case we cited the more recent or the more comprehensive publication. In the text, we cite the publication in which the data in question actually appeared.

Organization of this Chapter

The remainder of this chapter takes up the major anti-infectives – tetracycline, minocycline, metronidazole, metronidazole with amoxicillin, and chlorhexidine – and then the two groups of other antibiotics and other microbials. We present first our narrative synthesis of the evidence, accompanied by summary tables (at the end of the chapter) giving PD and CAL data. The qualitative results describe the studies, present PD and CAL data, and give spirochete data when available; we also present additional results for studies that may not have measured PD or CAL in typical ways but do provide insights into the likely effect of drugs adjunctive to SRP. The descriptive analysis focuses on results for the full length of every included study, which ranged from a few weeks to several years.

We conducted meta-analyses when more than two similar studies involved the same antimicrobial and mode of delivery. They focused on the two clinical measures (PD reductions and CAL gains) and were limited to studies with results reported at or around 6 months (plus or minus 3 months) after the initiation of the treatment. Meta-analytic results follow the qualitative discussions within the drug-specific sections. They are presented in Forrest plots (figures at the end of this chapter), which report the mean effect and its 95 percent confidence interval (CI) for each study in the meta-analysis and an overall mean effect and its 95 percent CI calculated across all of the studies. We explain included and excluded studies and, when possible, put those results in a broader context of the confidence intervals and the impact of SRP alone.

Tetracycline

Systemic Tetracycline

Qualitative and Descriptive Results

Five clinical trials appearing between 1978 and 2001 of systemic tetracycline, a broad-spectrum antibiotic of long standing that is effective against a wide array of bacteria, met the inclusion criteria (Table 5 and Evidence Table 1a). Four trials were randomized;[43-46] the most recently reported trial was not.[47] Taken together, the studies comprised 190 subjects who completed the studies, 81 on tetracycline regimens with SRP and 109 receiving SRP alone or with placebo. Subjects in the trials differed in periodontal disease experience. Three studies included subjects with advanced or severe periodontitis, one included "relatively young individuals" with severe disease,[43] and the fifth included only subjects who had demonstrated active disease with attachment loss equal to or greater than 2.5 mm at one or more sites in a pretrial monitoring period.[46]

The studies differed in the selection of sites used to characterize a subject's response to therapy. One study included only two sites per subject, both interproximal sites with PDs of 7 mm or more.[45] A second study based analyses on patients with at least three pairs of contralateral teeth with PDs of 5 mm or greater.[43] A third study included six measurement sites for all teeth present except third molars;[46] a fourth included two teeth per subject with 6 mm or greater PDs;[44] and the fifth study did not report the basis for the selection of sites.[47]

SRP procedures differed across these studies. In one trial, the investigators used modified Widman flap surgery for all sites determined to be active in the pre-intervention period and for all sites with PDs of 4 mm or greater;[46] SRP was repeated at 3, 6, and 9 months. Another study provided repeated SRP during the observation period at 15 and 22 weeks.[43] In the other studies, SRP was provided once, at baseline, and no other details were noted.

The experimental regimen varied across the five trials. The standard dose was 250 mg, with a frequency of either three or four times per day for different treatment periods lasting 14 days,[45] 21 days,[47] and 30 days.[46] One regimen repeated an initial 14-day dosing pattern at the beginning of the sixth week;[43] a fifth approach continued past 14 days to the end of the study (day 350) with a single 250 mg dose per day.[44] Finally, the trials varied in longest follow-up period: 24 weeks to 52 weeks. Three trials reported results from interim periods.

For four studies reporting overall PD measurements, experimental subjects had 0.8 mm,[44] 0.3 mm,[47] 0.29 mm,[46] and 0.2 mm[43] greater mean reductions in the experimental group; of these, three were not significant and one[44] was not tested. A fifth study reported PD reduction by original PD values, and the largest PD reduction was 0.19 (not significant) for those with initial PDs of 7 mm or greater.[45] No interim measures differed significantly between experimental and control groups.

Five studies examined CAL gains, but only three reported data on CAL gains. One trial found a 0.31 mm net gain at 52 weeks ($P < 0.001$) for the experimental group.[47] In the other two trials reporting CAL values, one noted a 0.3 mm net improvement[44] and the other reported gains from 0.04 mm to 0.49 mm (depending on initial PD value), but all were not significant.[45] No interim measure for these studies was reported as being significantly different between groups.

Of the two studies that did not report data, one did state that difference in CAL gain between the groups was not significant.[46]

Three trials analyzed the proportion of spirochetes in the oral microflora. One trial found that significant differences favoring the experimental group at 2 and 8 weeks had disappeared by week 24.[45] Another team reported a larger proportional change in the experimental group (48 percent to 0 percent) than in the control group (37 percent to 8 percent), but they did not test the difference statistically.[44] A third study found similar overall change in both groups (34.8 percent or 36.3 percent to 6.3 percent or 6.5 percent), with the experimental groups showing a larger decline to 0 percent (not tested) at an interim examination.[43] Finally, one trial examined oral microflora but did not separate results for the tetracycline groups from results for another experimental group assessing amoxicillin clavenate.[46] The percentage of sites colonized with several putative pathogens decreased significantly for both group combined.

Quantitative Analysis of Systemic Tetracycline Effects

Probing Depth. Of the five studies reporting on PD reduction reviewed above, we included three in the meta-analysis of PD effect size (Figure 3).[43-45] Both excluded studies had study periods greater than 9 months.[46,47]

The estimate of overall effect size for PD is 0.15 mm (95 percent CI, -0.29 mm to 0.58 mm). Effect sizes of the two studies favoring use of adjunctive local tetracycline range from 0.20 to 0.90. The third study demonstrated a greater reduction in PD for SRP alone (-0.05 mm).[45] Based on their 95 percent CIs, none of these PD effect sizes differed significantly from zero. Because of its appreciably smaller standard error of the difference and larger sample size, the Al-Joburi et al. study contributed more weight to the meta-analysis results.[45] Given the mixed direction of the differences and small study samples, the nonsignificant overall effect size in this meta-analysis is not surprising.

Clinical Attachment Level. Only two of the four studies examining gain in CAL reviewed above had data and ran for the appropriate length of time.[44,45] As explained earlier, we thus did no meta-analysis for CAL gain resulting from adjunctive use of systemic tetracycline.

Local Tetracycline

Qualitative and Descriptive Results

Sixteen clinical trials, published between 1985 and 2002, met the inclusion criteria (Table 6 and Evidence Table 1b). All but three used randomized designs. In 10 studies, the examiner(s) were not aware of treatment assignment, and in 13, placebos were not used. Most of the trials assessed the effects of the intervention on sites with at least 5 mm PDs; four studies either included patients with shallower PDs (as small as 3 mm)[33,48,49] or did not report site selection criteria.[50] Three studies assessed only sites with class II furcation involvements.[35,51,52] One study required demonstration of active disease immediately before inclusion.[53]

Five trials reported site-based analyses,[31,52,54-56] one used teeth, and the rest used the subject as the unit of analysis, with one tooth or site per quadrant per subject being most commonly assessed.

The extensiveness and methods used for the SRP varied, ranging from ultrasonic scaling during one visit to multiple visits over 4 to 7 hours for hand scaling. Tetracycline intervention vehicles included fibers, irrigation, collagen film, ointment, gel, and strips. In one study arm, tetracycline was combined with citric acid;[33] in all others, tetracycline was used alone. In one irrigation study, tetracycline was administered every 2 weeks for 22 weeks.[31] Effects were assessed over durations as short as 4 weeks and as long as 52 weeks. All but one of the studies that reported statistically significant differences had used tetracycline fibers.

Of these 16 studies, 12 reported PD data sufficient to determine the net reduction (i.e., the difference between the experimental and control groups' baseline to follow-up differences). Of these 12 studies, four found statistically significantly greater PD reductions associated with the experimental group. The differences were 0.93 mm at 12 weeks (combined with citric acid gel, $P < 0.05$),[33] 0.73 mm at 6 months ($P < 0.01$),[57] 0.67 mm at 26 weeks ($P = 0.008$),[53] and 0.41 mm at 7 weeks ($P = 0.047$).[56] In eight studies in which differences were either not tested or not significant, reductions in the experimental group were greater than those in the control group; some of these were of a magnitude similar to the statistically significant differences: 1.04 mm;[50] 0.7 mm;[52] 0.6 mm;[34] 0.4 mm and 0.5 mm with irrigation and fibers, respectively;[55] 0.43 mm and 0.87 mm with one and multiple strips, respectively;[58] 0.4 mm;[31] 0.4 mm;[35] and 0.27 mm without citric acid.[33] One study found a nonsignificant 0.43 mm difference favoring the control group.[59] The four remaining studies reported nonsignificant differences but did not give the magnitude or direction of those differences.[48,49,51,54] Interim results also showed statistically significant greater reduction in PD associated with the experimental arm in two studies.[35,53] In one of these,[35] the significant difference was not maintained at the final assessment.

Sixteen studies reported results of some kind for CAL gain, some for two different patient groups or treatments. Of these, two reported significantly greater CAL gains associated with local tetracycline treatment compared to SRP alone: 0.48 mm at 26 weeks ($P < 0.05$)[57] and 0.15 mm at 26 weeks ($P < 0.05$).[53] Nine studies reported nonsignificant or untested differences favoring the experimental group: 1.8 mm,[50] 1.0 mm,[34] 0.73 mm (with citric acid),[33] 0.44 mm and 0.48 mm for a single and multiple strips, respectively,[58] 0.34 mm and 0.33 for groups with initial PD values of greater than 3 mm and greater than 6 mm, respectively,[48] 0.3 mm,[31] 0.2 mm,[56] and 0.14 mm (gel).[33] Three studies reported nonsignificant differences favoring the control group: 0.23 mm,[59] 0.2 mm for tetracycline irrigation,[55] and 0.1 mm.[35] Finally, three studies reported nonsignificant differences but did not report the magnitude or direction of those differences.[49,51,60] No reported interim results were significantly different between the experimental and control groups.

Finally, five studies examined microbiological outcomes,[31,33,49,52,54] but none reported significant differences in these outcomes at final assessments. An interim (3-month) assessment in one study found a significantly greater reduction in the proportion of *P. gingivalis* in the experimental group.[49]

In general, the studies that reported side effects noted some irritation associated with the application of the experimental therapy and, less frequently, candidiasis. These conditions resolved when therapy ended.

Quantitative Analysis of Local Tetracycline Effects

Probing Depth. Of the 16 studies reporting on PD reduction reviewed above, we included six in the meta-analysis of PD effect size (Figure 4).[31,33,34,53,57,59] One study included two different adjunctive local tetracycline treatments – one without and the other with citric acid added to the tetracycline[33] – so the meta-analysis had seven entries. Of the 10 studies excluded, five had study periods of less than 3 months,[50,52,54-56] and four provided no data from which to calculate effect size measures or variances.[48,49,51,58] We excluded the final study because a test for heterogeneity showed that it was at too great variance with the other studies, suggesting that it represented a different intervention.[35]

The estimate of overall effect size for PD is 0.47 mm (95 percent CI, 0.22 mm to 0.72 mm). Effect sizes of included studies favoring use of adjunctive local tetracycline range from 0.27 to 0.93. All but one of the study effect sizes represented results that demonstrate greater PD reduction using adjunctive local tetracycline with SRP than using SRP alone. One study demonstrated a greater reduction in PD for SRP alone (-0.43).[59] Based on the 95 percent CIs, the PD effect sizes of only two studies differed significantly from zero.[33,57] Two studies with appreciably smaller[57] or larger[31] standard errors of difference between means contributed relatively more and less weight, respectively, to the meta-analysis results.

The statistically significant PD result supports the added effectiveness of locally applied tetracycline as an adjunct to SRP in the treatment of chronic periodontitis in adults. It does not address, however, whether a mean change of 0.47 mm is clinically meaningful. In contrast to this less than half a millimeter difference between using and not using some form of local tetracycline as an adjunct to SRP, the effects of SRP alone on reduction in PD in these studies ranged from 0.71 mm to 2.30 mm for the same periods of time.

Clinical Attachment Level. Of the 16 studies examining gain in CAL reviewed above, we were able to include nine in this meta-analysis (Figure 5).[31,33-35,48,53,57-59] Two studies included two different adjunctive local tetracycline treatments: citric acid in one gel group and none in the other,[33]and single and multiple tetracycline strips.[58] Thus, the final meta-analysis had 11 entries. Among the seven excluded studies, five had study periods of less than 3 months,[50,52,54-56] and two had no way for us to calculate CAL effect size measures or variances.[49,51]

The estimate of overall effect size for CAL is 0.24 mm (95 percent CI, 0.07 mm to 0.42 mm). Effect sizes of included studies favoring use of adjunctive local tetracycline ranged from 0.01 mm to 1.00 mm. All but two of the study effect sizes represented greater CAL gain using adjunctive local tetracycline with SRP than using SRP alone. Of these two, one demonstrated a greater reduction in CAL for SRP alone (-0.23 mm),[59] and one favored neither study group.[35]

Based on the estimated 95 percent CIs, only two studies had CAL effect sizes that differed significantly from zero.[33,34] One study had an appreciably smaller[35] standard error of difference between means and another had a standard error that was appreciably larger[31] than the others, so they contributed considerably more or less weight, respectively, to the meta-analysis results.

The statistically significant CAL result supports the added effectiveness of locally applied tetracycline as an adjunct to SRP in the treatment of chronic periodontitis in adults, but whether a mean gain of 0.24 mm is clinically meaningful remains unclear. In contrast to this 0.24 mm

difference, the effects of SRP alone on gain in CAL in these studies ranged from -0.13 mm to 1.61 mm for the same periods of time.

Minocycline

Systemic Minocycline

Qualitative and Descriptive Results. Two studies of systemic minocycline met inclusion criteria (Table 7 and Evidence Table 2a).[61,62] The 1982 trial by Ciancio et al. was a randomized, placebo-controlled, double-blinded trial,[61] whereas the 1996 Atilla et al. study did not report study blinding but noted that it was neither placebo controlled nor randomized. These were small trials of patients with moderate to severe periodontitis, comprising in all 47 subjects who completed the trials, 23 on minocycline regimens with SRP and 24 with SRP only. The studies differed in numerous ways: dosage and duration of minocycline (200 mg a day for 7 days[61] versus 100 mg a day for 4 days[62]); focus on probing depth (4 mm to 5 mm versus 6 mm or higher[62]); nature and periodicity of SRP; and outcomes assessed (the only overlap being PD).

With respect to PD levels, Ciancio et al. assessed outcomes at baseline and at 7, 14, 35, 49, and 70 days but only reported "no significant changes in any study group during the experimental period."[61] The Atilla et al. study reported PD differences according to the initial PD.[62] Among subjects with initial PD of 4 mm to 5 mm, those receiving systemic minocycline experienced 0.06 mm *less* reduction than those receiving SRP only (not significant). By contrast, among patients with initial PD of 6 mm or greater, those receiving adjunctive minocycline experienced 0.49 mm greater reduction than controls (not significant); nonetheless, the authors commented that systemic minocycline might be a useful adjunct to nonsurgical SRP "in the presence of deep pockets, especially for reinfected cases."

Neither study reported CAL data. One reported that patients receiving both SRP and minocycline had notable, long-lasting changes in subgingival microbiologic findings (e.g., cell counts of spirochetes).[61] Owing to the small size of these trials, their nonsigifncant findings on PD (and no data on CAL), and other differences, we did not do any meta-analysis.

Local Minocycline

Qualitative and Descriptive Results. We included eight studies of local applications of minocycline, all appearing between 1993 and 2002 (Table 8 and Evidence Table 2b).[32,53,63-68] All were randomized; five were placebo-controlled;[32,63-66] and all but one[67] were reported to be double-blind studies. Taken together, the eight trials involved 760 subjects who completed the trials; of these 396 received adjunctive minocycline (237 in the Williams et al. trial alone[66]) and 379 received only SRP (230 in the Williams et al. trial). The Williams et al. trial is described as an intention-to-treat design and is a multi-center trial.

Subjects were variously described as having moderate to severe chronic (or advanced) periodontitis. Specifics about site criteria for inclusion, such as minimum number of teeth or sites, minimum PD levels, or bleeding, differed across the studies.

Four trials reported SRP details: subjects were hand-scaled in both van Steenberghe et al. studies (for a maximum of 15 minutes per quadrant in the 1999 study),[63,65] and in the other studies, subjects had both hand and ultrasonic SRP for 90 minutes.[67,68] The trials differed in

many respects (when details were reported); for example, assessment times and duration of measurement included seven times (baseline through 15 months[65]), five times (baseline through 9 months[66]), for two studies three times (baseline through 6 months[53,67] and baseline through 12 weeks[32]), and for one study four times (baseline through 6 months).[68] Moreover, the experimental regimen also differed across the trials. Two studies used gels (2 percent at baseline and at 2 and 4 weeks[32,53]); two other studies used ointments (2 percent at baseline and at various weekly or monthly points thereafter;[63,65] one study used 1 mg of minocycline as a single application at baseline;[64] one used 1 mg of 2-percent minocycline microspheres in a 3-mg polymer gel (at baseline and months 3 and 6[66]); and two used single applications of 1-mg microencapsulated minocycline.[67,68]

With respect to PD effects, four trials reported a greater effect of adjunctive local minocycline – i.e., more reduction among experimental than control groups that was statistically significant for at least some patients. Experimental subjects experienced 1.0 mm more reduction at 12 weeks (for those with 7 mm or greater initial PD, $P = 0.0001$),[63] 0.77 mm and 1.10 mm more reduction at 65 weeks (respectively, for subjects with 5 mm or greater and 7 mm or greater initial PD, $P < 0.0001$ in both cases),[65] 0.7 mm at 26 weeks ($P \leq 0.05$),[67] 0.32 mm at 39 weeks ($P < 0.001$) and 0.3 mm at 12 weeks (for those with initial PDs of 5 mm or greater, $P = 0.0018$).[63] The remaining trials showed net PD reductions favoring the local minocycline groups for which significance was not reported or the test was not significant: 0.39 mm,[53] 0.34 mm,[32] and 28 mm.[68] The last study did not report data but did indicate the difference between the groups was not significant.[64] In the largest trial lasting 9 months, the investigators reported that the percentage of sites with PD reductions of 1 mm or greater, or 2 mm or greater, was higher in the treatment group by, respectively, 10 percent and 11.6 percent; both values reflected a statistically significant difference ($P < 0.001$) from those for patients receiving SRP and placebo.[66]

Of the six trials that reported actual CAL data, three reported significantly greater net gains in CAL for the minocycline treatment groups: 0.8 mm at 26 weeks ($P = 0.04$),[67] 0.49 mm at 65 weeks (patients with baseline pockets of 5 mm or greater, $P < 0.0001$), and 0.43 mm at 65 weeks (baseline pockets of 7 mm or greater, $P < 0.0001$),[65] and 0.39 mm at 12 weeks ($P < 0.05$).[32] Others reported no or nonsignificant differences in gains favoring the minocycline groups: 0.48 mm,[68] 0.4 for patients with initial PDs of 7 mm or greater,[63] 0.36 mm,[53] and 0.0 mm for patients with initial PD of 5 mm or greater.[63] Of the two remaining trials that did not report data on CAL gain, one indicated that the between group difference was not significant[64] and the other did not say.[66]

None of these trials reported on percentage changes in spirochetes. One trial reported that concentrations of *P. gingivalis* and *P. intermedia* were lower following a minocycline ointment treatment than following SRP with placebo ointment at 2, 4, 6, and 12 weeks post-treatment, as was the concentration of *A. actinomycetemcomitans* at weeks 6 and 12.[63] The van Steenberghe team then later reported significant differences in several microbiological outcomes (e.g., *P. gingivalis, P. intermedia, C. rectus, T. denticola, E. corrodens, F. nucleatum,* and *A. actinomycetemcomitans)* at various follow-up points from month 1 to month 15 between patients receiving adjunctive minocycline ointment and nonsurgical SRP treatment alone.[65] There were significantly greater reductions in the *P. gingivalis, T. denticola,* and *C. rectus* counts from baseline,[65] but for the other microbial outcomes the changes were not significant. The Jones team used DNA probes for microbiological assessments of *A. actinomycetemcomitans, P. gingivalis*, *P. intermedia, E. corrodens,* and *C. rectus.*[64] The *P. gingivalis* prevalence was

completely nondetectable at 1 month and had a 60 percent reduction at 6 months for the treatment group. The SRP-alone group reductions were never significant from baseline.

Attrition was not well reported in these studies. Authors reported a wide array of adverse effects (among both treatment and control groups), some relatively serious and some not. They included dental infection, abscesses, gingivitis, gingival edema, stomatitis, root sensitivity, tooth sensitivity, dental pain, local irritation, headache, diarrhea, and other "minor" clinical reactions (e.g., redness).

Quantitative Analysis of Local Minocycline Effects. Six of the eight studies examining the effect on PD of locally applied minocycline reviewed above were included in the meta-analysis (Figure 6).[32,53,65-68] Reasons for excluding the other two studies were that one had no data for us to calculate an effect size measure[64] and the other had too great variance with the rest of the studies according to a test of heterogeneity, suggesting that it represented a different intervention.[63]

The estimate of overall effect size for PD is 0.49 mm (95 percent CI, 0.40 mm to 0.58 mm). Effect sizes of included studies favoring use of adjunctive local minocycline range from 0.28 to 0.70. Despite the fact that all of the study effect sizes represent greater PD reduction using adjunctive local minocycline with SRP than using SRP alone, based on the 95 percent CIs, the PD effect sizes of only two of those studies differed significantly from zero.[65,66] Those same two studies had appreciably smaller standard errors of difference between means and larger study samples, and consequently they contributed almost all of the weight to the meta-analysis results.

The statistically significant PD result supports the added effectiveness of locally applied minocycline as an adjunct to SRP in the treatment of chronic periodontitis in adults. It does not address, however, whether a mean change of 0.49 mm is clinically meaningful. One context for judging the import of this half-millimeter difference is that the effects of SRP alone on reduction in PD in these studies range from 0.71 mm to 2.30 mm for the same periods of time.

Of the eight studies examining the effect on CAL of locally applied minocycline reviewed above, we included five in the meta-analysis (Figure 7).[32,53,65,67,68] Of the three excluded studies, two had no way for us to calculate CAL effect sizes,[64,66] and one had a test for heterogeneity of variances suggesting that that study represented a different intervention than that of the other studies.[63]

The estimate of overall effect size for CAL is 0.46 mm (95 percent CI, 0.32 mm to 0.60 mm). Effect sizes of included studies favoring use of adjunctive local minocycline range from 0.04 mm to 0.80 mm. All these effect size estimates represent greater CAL gains using adjunctive local minocycline with SRP than using SRP alone, but based on the 95 percent CIs, the CAL effect sizes of only one of those studies differed significantly from zero.[65] That study had an appreciably smaller standard error of difference between means and a larger study sample and consequently contributed almost all of the weight to the meta-analysis results.

The statistically significant CAL result supports the added effectiveness of locally applied minocycline as an adjunct to SRP in the treatment of chronic periodontitis in adults. As with the PD results, which were of about the same magnitude, the clinical ramifications of a change of this size remains unclear in the context of CAL reductions in these studies for SRP alone of -0.13 mm to 1.61 mm.

Metronidazole

This section concerns the adjunctive use of metronidazole, an antiprotozoa agent with bacteriocidal effects on anaerobic species such as spirochetes, when used either systemically or locally in conjunction with SRP in patients with periodontitis. We present qualitative and descriptive results for both systemic and local metronidazole and a meta-analysis of eligible studies for local metronidazole. Metronidazole used in combination with amoxicillin is presented in the following section.

Systemic Metronidazole

Qualitative and Descriptive Results. Eight studies, published between 1984 and 2002, used systemic metronidazole as the sole antibiotic in conjunction with SRP and otherwise met our inclusion criteria (Table 9 and Evidence Table 3a).[69-76] Six trials were randomized, placebo-controlled, and double-blind trials.[69-74] Two trials were randomized but not placebo-controlled,[75,76] one was blinded only for examiners,[76] and the other did not report blinding.[75]

In all, these trials had 305 completers, of whom 153 were treatment subjects. Subjects had adult periodontal disease characterized as moderate to severe (or advanced). All control subjects received SRP with or without a placebo; experimental subjects received SRP with metronidazole alone.

The trials differed markedly in both therapeutic regimens and outcomes. As to dose, frequency, and duration of the antibiotic: three studies used 200 mg three times a day, one trial for 5 days[71] and two for 7 days;[70,76] one team, in three trials, used 250 mg three times a day for 7 days;[69,73,74] another group used the same dosage but repeated SRP;[75] finally, one study used 400 mg three times a day for 7 days.[72] The studies lasted from 6 weeks to 156 weeks. The trial outcome measures also varied considerably: average mm PD reduction per subject or per site; average mm CAL gain per subject or per site; various microbial measures; the percentage of sites per patient gaining, losing, or not changing PD or CAL; the percentage without disease; the number of sites with a given level of disease; and the percentage of sites needing surgery.

With respect to PD differences, only one of the trials failed to report any PD data although it did report a significant difference between the groups favoring the metronidazole treatment.[70] Of the others, two studies from the same group reported statistically significant net PD reductions favoring the metronidazole group. For patients with initial PD levels of 4 mm to 6 mm, the earliest study reported 0.14 mm gain at 30 weeks (not significant) and the latest study, 0.47 mm at 104 weeks ($P < 0.01$); for subjects with initial PD values greater than 6 mm or 7 mm and higher, the figures were, respectively, 1.64 mm ($P < 0.03$) and 1.05 ($P < 0.01$).[69,74] Other studies reported net gains of 0.6 mm,[75] 0.41 mm,[71] 0.41 mm for patients with initial PDs of 7 mm or higher,[73] and 0.05 mm,[72] but either these values were not significant or significance was not reported. The 1991 Loesche et al. study reported a greater PD reduction of 0.06 mm in the control group at 52 weeks, though the results were not statistically significant.[73] One trial only presented percent change of original PD.[70]

Six of the eight trials reported CAL results.[69,70,73-76] The studies from the Loesche et al. teams reported the following net gains favoring the metronidazole groups:[69,73,74] for those with initial PDs of 4 mm to 6 mm, 0.47 ($P < 0.01$), 0.10 mm (not significant), and 0.13 (not

significant), and for those with initial PDs of either greater than 6 mm or 7 mm and higher, 1.19 ($P = 0.05$), 0.32 (not significant) and 0.66 (not significant). Two other trials reported net gains of 0.41 mm (test not reported)[75] and 0.16 mm (not significant).[76] The sixth study did not report data on the gain in CAL but did indicate that it was not significant.[70]

Five investigations reported on microbial results (specifically spirochetes).[69,72-74,76] For example, the proportions of spirochetes dropped from baseline to the final observation from 59.1 to 22.0 for the test group and from 60.0 to 34.8 for controls, with the difference between groups approaching significance ($P = 0.06$).[74] Similar findings were reported for the 1991 and 1984 studies from this research team.[69,73] Palmer et al. also reported reductions in percentages of spirochetes between baseline and 8-week and then 24-week follow-up for both experimental and control patients, but the 24-week findings (from 47.1 percent to 25.8 percent for the metronidazole group and from 47.2 percent to 25.6 percent in the SRP-only group) reflected no significant difference between the two study groups. Finally, Soder et al. reported that the total number of microorganisms counted at the follow-up visits did not differ significantly between the metronidazole and placebo groups.[72]

Other results covered numerous heterogeneous outcomes. For example, at 6 weeks the percentage of teeth per patient needing surgery was lower for the treatment than the control group.[73] At 24 weeks, the percentages of sites with PDs of 4 mm or greater and the percentages of sites improved per patient were greater for experimentals than controls.[76] Two studies examining a total of 18 experimental subjects in terms of the percentage of deep sites suggested that metronidazole in conjunction with SRP is less effective than scaling alone at 156 weeks[71] and 260 weeks.[72]

Finally, three trials reported some adverse effects.[69,72,74] They included severe diarrhea, gastric discomfort, and, less seriously, "metallic taste."

Local Metronidazole

Qualitative and Descriptive Results. In all, we identified 11 clinical trials appearing between 1986 and 2000 that used local metronidazole in conjunction with SRP and that met the inclusion criteria (Table 10 and Evidence Table 3b).[28,34,36,37,53,75-80] One trial was a randomized, placebo-controlled, double-blind design;[77] most of the studies were randomized, not placebo-controlled, and single-blind designs.[28,36,53,76,78-80] The studies lasted over a range of 6 weeks to 39 weeks (9 months). Overall, the completing number of subjects (treatment and control groups) was 368; units of analyses included subjects, sites, and surfaces.

All subjects had adult or chronic periodontal disease ranging from "mild to moderate" to "moderate to severe," but most authors did not comment on severity. Most research teams used a 25 percent gel of metronidazole as the intervention therapy, each with reapplications after 1 week or more often.[28,34,36,53,75,76,78-80] Other groups used a variety of dosages and modes, such as 0.05 percent solution used with jet irrigation subgingivally[77] and 20 percent ethylcellulose film.[37] Control subjects or sites received SRP with or without a placebo; the experimental subjects received SRP with metronidazole alone.

For the PD outcomes, all 11 studies gave some results. Three reported data showing a statistically significant difference in the net PD reduction that favored the treatment group: 0.8 mm at 13 weeks ($P < 0.03$),[80] 0.5 mm at 39 weeks ($P < 0.001$),[79] and 0.18 mm at 37 weeks ($P <$

0.05).[36] One additional study reported that the net difference between treatment and control groups was significant at 12 weeks ($P < 0.01$) but did not report the difference.[77] Four trials reported net PD reductions in favor of metronidazole that were not statistically significant: 0.9 mm,[37] 0.78 mm,[75] 0.22 mm,[53] for "defect sites" at 26 weeks,[34] and one study did not report the data.[76] Two studies reported nonsignificant net PD reductions favoring the control groups ─ 0.12 mm[28] and 0.1 mm for "nondefect sites"[34] ─ and one reported no net difference at all.[78]

Eight of these 11 studies provided information on CAL gains. Only two studies reported significant net gains for the treatment groups: 0.66 mm at 6 weeks ($P < 0.01$)[75] and 0.4 mm at 39 weeks ($P < 0.001$).[79] Several other studies reported nonsignificant CAL gains favoring local metronidazole groups: 0.17 mm,[78] 0.07 mm,[36] 0.03 mm, [37] 0.004 mm,[53] and 0.7 mm and 0.0 mm for defect and nondefect sites.[34] One study reported a nonsignificant greater net gain in the attachment level for the control group of 0.04 mm.[76]

As to changes in the presence of spirochetes, one trial showed that treatment lessened the percentage of spirochetes in both treatment and control groups. At 8 weeks of follow-up, the change was significantly less in the locally delivered metronidazole group, but at 24 weeks the differences were not significant.[76]

Generally, none of these studies reported adverse events. One group noted that about half of the patients receiving metronidazole as a gel reported a bitter taste.[36]

Quantitative Analysis of Local Metronidazole Results. Seven of the 11 studies examining the effect on PD of locally applied metronidazole reviewed above were included in the meta-analysis (Figure 8).[34,36,37,53,78-80] Two studies were not included because they lacked data allowing us to calculate PD effect size measures,[76,77]one was too short,[75] and the final one did not provide data on variation.[28]

The estimate of overall effect size for PD is 0.32 mm (95 percent CI, 0.20 mm to 0.44 mm). Effect sizes of included studies favoring use of adjunctive local metronidazole range from 0.18 mm to 0.90 mm. All but one of the study effect sizes represented results that demonstrate greater PD reduction using adjunctive local metronidazole with SRP than using SRP alone. The one exception found a zero difference between the treatment and control groups.[78] Based on the 95 percent CIs, the PD effect sizes of four studies differed significantly from zero.[37,53,79,80] The two studies with appreciably smaller standard errors of difference between means contributed relatively more weight to the meta-analysis results.[53,79]

The statistically significant PD result supports the added effectiveness of locally applied metronidazole as an adjunct to SRP in the treatment of chronic periodontitis in adults. It does not address, however, whether a mean change of 0.32 mm is clinically meaningful. In contrast to this approximately one-third of a millimeter difference between using and not using some form of local metronidazole as an adjunct to SRP, the effects of SRP alone on reduction in PD in these studies ranged from 0.71 mm to 2.50 mm for the same periods of time.

Of the eight studies examining CAL effects of local metronidazole, we used seven in the meta-analysis (Figure 9).[34,36,37,53,76,78,79] The excluded study was too short.[75]

The estimate of overall effect size for CAL is 0.12 mm (95 percent CI, 0.01 mm to 0.24 mm). Effect sizes of included studies favoring use of adjunctive local metronidazole range from

0.07 mm to 0.70 mm. Five of the study effect sizes suggest greater gain in CAL using adjunctive local metronidazole with SRP than using SRP alone. One of the exceptions found a zero difference between the treatment and control groups;[53] the other was an effect size favoring SRP alone.[76] Based on the 95 percent CIs, the CAL effect sizes of 0.4 mm and 0.7 mm in two studies differed significantly from zero.[34,79] The two studies with appreciably smaller standard errors of the difference between means again contributed relatively more weight to the meta-analysis results.[53,79]

As with PD effects of locally applied metronidazole, the statistically significant CAL result supports its added effectiveness as an adjunct to SRP, but the clinical importance of a mean change of 0.12 mm is open to question. By contrast, the effects of SRP alone on CAL gains in the same time periods ranged from 0.20 mm to 1.60 mm.

Metronidazole and Amoxicillin

We identified four studies that combined systemic metronidazole with amoxicillin as an adjunctive intervention to SRP (Table 11 and Evidence Table 4).[70,81-83] All were randomized trials; three were placebo-controlled;[70,81,83] two were double-blind, one was single blind,[82] and one did not report on blinding.[81] In all studies, patients received SRP (usually under local anesthesia). In total, 133 patients completed the trials (64 in treatment groups and 69 in control groups).

The combined antibiotic regimens differed in dosage, frequency, and duration. Three studies used the combination of 250 mg of metronidazole and 375 mg amoxicillin three times a day for 7 days,[83] 8 days,[82] and two times a day for 2 weeks;[81] one used 200 mg metronidazole and 250 mg amoxicillin three times a day for 7 days.[70]

Two trials gave data on mean PD outcomes. The net PD reduction favoring the treatment groups were 0.7 mm at 13 weeks ($P < 0.05$)[83] and 0.5 mm at 104 weeks (significance not reported).[81] In the remaining trials, data were not reported, although one noted that the net difference for initial probing depths of 6 mm or greater was significant favoring the treatment ($P \leq 0.001$).[70]

Similarly, two studies reported data on CAL gains: a net gain of 0.3 mm at 104 weeks where significance was not reported[81] and one of 0.4 mm at 24 weeks (not significant).[83] Of the two studies not giving CAL data, one said the net difference was significant ($P \leq 0.05$) for probing depths greater than 6 mm[70] and one said it was not significant.[82]

None of the studies examined spirochetes, but all four reported on other microbiological outcomes.[70,81-83] One team found that the treatment eliminated *A. actinomycetemcomitans, P. gingivalis* and *P. intermedia* at 8 weeks (significance not reported).[81] For subjects with *A. actinomycetemcomitans* microbes, another team found that a significantly higher incidence of CAL gain of 2 mm or more was achieved in the experimental group over control ($P < 0.05$), but the opposite was true for subjects with *P. gingivalis*, who had a loss of attachment ($P < 0.05$) at 52 weeks.[82] A third team reported significant differences for the treatment versus control for microbiological outcomes (*A. actinomycetemcomitans, P. gingivalis*, *P. intermedia* and others) only at 1 month and not for the final assessment at 6 months.[70] Finally, the remaining team found significant differences between the experimental and placebo groups in the decreased

number of subjects who were positive for other microbiological outcomes (*P* value not reported).[83]

Some of these trials also reported positive findings for other measures. In one study, for example, at 12 weeks the percentage of deep sites per patient and mean deep and shallow site attachment levels were all improved for the treatment group compared to controls.[83] In another, at 26 weeks the percentage of sites for those with initial PD 6 mm or greater dropped from 15.9 percent to 1.3 percent for the treatment group; figures for the full placebo-control group were 19.3 percent and 12.4 percent, for a net difference favoring the dual antibiotic group of 7.7 percentage points (reported as statistically significant);[70] similar findings were reported for sites with 3 mm or less PD initially. CAL findings indicated that patients in the combination antibiotic group had significant improvements—i.e., decreased percentage of sites with high attachment losses and increased percentage of sites with low attachment losses—compared with levels for the placebo group. Finally, some research teams reported greater elimination or suppression of some periodontal pathogens (e.g., *A. actinomycetemcomitans*).[81,82]

Various adverse effects were reported in these trials. They fell mainly into the category of gastrointestinal problems (e.g., diarrhea),[82,83] with two cases of skin rash and one case of nausea after alcohol use.[83]

Chlorhexidine

In all, we included 17 studies of chlorhexidine, a topical, iodine-free disinfectant (antiseptic) with broadly effective antimicrobial properties, applied locally to either the gingivae or the mouth in general through several modalities (Table 12 and Evidence Table 5). These included rinses, mouthwashes, irrigation, and application or introduction of chips or gels in various ways.

Below we discuss the nine studies, published between 1985 and 1994, that included chlorhexidine applied solely as a rinse or through irrigation.[30,31,54,77,84-88] Those are followed by seven studies involving direct applications via chips or gels (without additional chlorhexidine rinse or irrigation)[59,89-94]and then by one trial that involved complex one-stage "full-mouth disinfection" within 24 hours, comprising gel, rinse, spray, and/or irrigation in combination.[95]

Of these 17 studies, 15 are described as randomized and 10 as placebo-controlled; seven are double-blind; an additional five are single-blind studies (chiefly of examiners). All patients had periodontitis described variously as mild, moderate, severe, or advanced (or severity was not reported). In all, the total number of patients completing these studies was 767, but many analyses were done on sites, surfaces, or pockets.

Two trials were large and multi-site investigations (one of 419 subjects [211 treatment and 208 control][91] and one of 94 subjects [401 treatment pockets and 412 control pockets][90]); one was medium-sized (60 subjects);[88] and the remainder were small (no more than 24 completers, but most were in the 10-subject range).

The approaches to experimental treatments varied considerably in terms of timing, frequency, and relationship to SRP; some trials included Bass brushing as part of the test approach. However, dosage of irrigated chlorhexidine was variable (ranging from 0.02 percent to 2.0 percent); some trials using chips identified it as Perio-Chip® (2.5 mg chlorhexidine); and

gels tended to be either 0.2 percent or 1 percent chlorhexidine. Control subjects tended to receive SRP alone or with some form of saline or water irrigation.

Similarly, the trials measured a wide array of clinical and microbiological outcomes at quite heterogeneous follow-up periods. Of the trials that reported on PD changes, some reported data in terms of the percentage of sites with smaller depths after treatment, rather than actual depths in millimeters; few studies reported on CAL in millimeters; and virtually no studies reported on spirochetes. Only a small number of research teams looked for or commented on adverse events, but as chlorhexidine is considered easily tolerated, this may not be surprising.

Irrigation and Mouthwash

We determined that ten trials of chlorhexidine irrigation and/or mouthwash with SRP versus SRP alone, all published between 1985 and 1994, met our inclusion criteria (Table 12).[30,31,54,77,84-88] Of these, seven used split-mouth designs. These studies ran from 4 weeks to 52 weeks.

With respect to PD, four studies reported net reductions favoring the chlorhexidine solution groups, but none was significant: 1.0 mm,[31] 0.3 mm,[30] and 0.1 mm.[85,87] Three other studies provided no tabulated or quantitative data but reported that the differences in the change from baseline to follow-up between the treatment and control groups were not significant.[54,77,84] One team noted that the percentage of sites with PD reductions was significantly greater for a chlorhexidine-irrigation group than for a water-irrigation group at 2 and 4 weeks.[88] One of the trials reported a nonsignificant net reduction in PD of 0.1 mm favoring the SRP-only group.[86]

Six chlorhexidine irrigation trials provided data on CAL gains.[30,31,54,85-87] Net CAL gains favoring the treatment group (none statistically significant) were 0.9 mm,[31] 0.2 mm,[30] and 0.1 mm.[86,87] One study reported nonsignificant net CAL gains favoring the control group by 0.1 mm.[85] Finally, one team remarked only that CAL did not differ significantly between groups.[54]

With respect to microbial outcomes, three teams reported on percentages of spirochetes at baseline and at last follow-up.[30,31,87] Patients in the chlorhexidine treatment groups all experienced decreases in the percentages of spirochetes; the largest decrease was from 32 percent to 2 percent.[31] Nonetheless, at the end of the studies, the net reductions in proportions of spirochetes for the chlorhexidine groups relative to the control groups were not significant; irrigation with chlorhexidine did not appear to have more than limited microbiological effect compared to SRP alone.

In short, the results of these trials suggest that, with respect to PD and CAL, using local irrigation with chlorhexidine as an adjunct to SRP confers virtually no material benefit over SRP alone.

Direct Gingival Applications

Chlorhexidine Chips. Five trials appearing between 1997 and 2002 tested a chip application of chlorhexidine as an adjunct to SRP against either SRP alone or SRP with a placebo chip (Table 12).[90-94] These were 2.5 mg chips inserted into pockets of varying depths at baseline and at various points after that; the trials lasted from 26 to 39 weeks.

With respect to PD, two trials reported statistically significant net improvements for the treatment group: 0.33 mm at 26 weeks ($P = 0.05$)[92] and 0.26 mm at 39 weeks ($P < 0.0056$).[91] Another study cited a 0.2 mm improvement in favor of the control group but did not report significance,[94] and a fourth gave no data but reported a nonsignificant difference.[93] Finally, the fifth study reported a 0.46 mm net PD reduction favoring the SRP-only group ($P < 0.001$).[90]

Three of the chip trials cited net CAL gains favoring the chlorhexidine chip groups: 0.28 mm at 26 weeks ($P = 0.048$),[92] 0.20 mm at 39 weeks ($P < 0.012$),[91] and 0.16 mm at 26 weeks ($P < 0.05$).[90] Of the other two studies, one did not report all final data in millimeters but commented that the changes were not significant[93] and the other showed only a nonsignificant 0.4 mm net PD reduction favoring the control group.[94]

No chip trial reported on percentages of spirochetes. One research team reported toothache, upper respiratory tract infection, and headache as adverse events but noted that such side effects generally happened with similar frequency for the treatment and control groups except for toothache (e.g., pain, tenderness, and sensitivity similar), which was significantly higher in the chlorhexidine group ($P = 0.042$).[91]

Chlorhexidine Gels. Two trials used chlorhexidine gel as an adjunct to SRP and tested this modality against SRP alone or SRP with placebo gel (Table 12).[59,89] One study did not give tabulated data on PD reductions but the net difference was noted as not significant;[89] in the other, the 0.25 mm net reduction (not significant) favored the control group.[59] One trial noted only a nonsignificant 0.34 mm CAL gain favoring the control group.[59] The one trial that addressed percentages of spirochetes showed a decrease over time for the treatment group, but no significant net benefit emerged for the treatment group at the conclusion of the study.[89] Neither study reported on adverse effects.

Chlorhexidine Combination Treatment. The one study that employed an all within-24 hours full mouth disinfection also employed multiple forms of chlorhexidine.[95] These included chlorhexidine gel for brushing, subgingival chlorhexidine irrigation, and chlorhexidine rinse and spray, the latter twice a day for 60 days. In this study, net PD reductions favoring the control group of 0.1 mm (single-root teeth) and 0.5 mm (multi-root teeth) were not significant. The same was true for CAL gains of 0.3 mm (single-root teeth) and 0.3 mm (multi-root teeth) that favored the control group.

Quantitative Analysis of Local Chlorhexidine Effects. Of the 17 studies examining the effect on PD of locally applied chlorhexidine reviewed above, we retained eight in the meta-analysis (Figure 10).[30,31,59,90-92,94,95] Of the nine excluded studies, one had a study period of less than 3 months,[54] two were longer than 9 months with no intermediate data reported,[86,87] and six did not report data that could be used to calculate a PD effect size.[77,84,86,88,89,93]

The estimate of overall effect size for PD is 0.24 mm (95 percent CI, 0.13 mm to 0.35 mm). Effect sizes favoring use of adjunctive local chlorhexidine range from 0.14 to 1.00 mm. Five of these effect sizes reflected greater PD reduction using adjunctive local chlorhexidine with SRP than using SRP alone; the other three studies had PD effect sizes of from -0.10 mm to -0.25 mm that favored SRP alone.[59,94,95] Based on the 95 percent CIs, the PD effect sizes of only three studies differed significantly from zero; all favored SRP with local chlorhexidine.[31,90,91] The two studies with appreciably smaller standard errors of difference between means contributed considerably more weight to the meta-analysis results.[90,91]

The statistically significant PD result supports the added effectiveness of locally applied chlorhexidine as an adjunct to SRP in the treatment of chronic periodontitis in adults. As with other adjunctive therapies with a mean changes in this range (0.24 mm), however, whether they are consequential clinically remains debatable, given that the effects of SRP alone on reduction in PD in these chlorhexidine studies ranged from 0.70 mm to 3.00 mm for the same periods of time.

Of the 13 studies examining the CAL effects of locally applied chlorhexidine reviewed above, we included seven in the meta-analysis (Figure 11).[30,31,59,90-92,94] Among the six excluded studies, one had a study period of less than 3 months,[54] two had study periods longer than 9 months with no intermediate data reported,[85,87] and three did not report data that could be used to calculate a CAL effect size.[86,93,95]

The estimate of overall effect size for gain in CAL is 0.16 mm (95 percent CI, 0.04 mm to 0.28 mm). Effect sizes of included studies favoring use of adjunctive local chlorhexidine range from 0.16 mm to 0.90 mm. Two of the study effect sizes, ranging from 0.34 to 0.40, represented results that demonstrate greater CAL gains using SRP alone.[59,94] Based on the 95 percent CIs, the CAL effect sizes differed significantly from zero for only two studies.[31,91] The two studies with appreciably smaller standard errors of differences between means and larger sample sizes contributed relatively more weight to the meta-analysis results.[90,91]

The statistically significant CAL result supports the added effectiveness of locally applied chlorhexidine as an adjunct to SRP, but the clinical significance of a mean change of 0.16 mm is also debatable. The effects of SRP alone on CAL gains in these chlorhexidine studies ranged from 0.31 mm to 1.40 mm for the same periods of time.

Other Antibiotics

Systemic Antibiotics

Seven clinical trials of other antibiotics, all given as systemic agents, met the inclusion criteria (Table 13 and Evidence Table 6a).[45,46,70,96-99] Two studies used spiramycin alone as the adjunctive therapy.[45,97] The others used different agents for the adjunctive systemic therapies: a combination of spiramycin and metronidazole,[96] doxycycline (a synthetic derivative of tetracycline),[98] azithromycin (an antibiotic related to erythromycin),[99] amoxicillin with clavulanic acid,[46] and amoxicillin with a placebo and chlorhexidine rinse.[70] All were randomized, placebo-controlled trials; all but one was a double-blind trial.[98]

Taken together, the trials comprised 359 completing subjects, 204 on antibiotic regimens with SRP (just under half from the Bain et al. trial[97]), and 199 receiving SRP with placebo. Subjects in the trials differed in terms of their periodontal disease experience or severity from severe or advanced periodontitis to moderate. One study included subjects with at least two sextants with scores on the Community Periodontal Index of Treatment Needs (CPITN) of 4.[99] All studies used the subject as the unit of analyses.

All studies reported details of the SRP procedures. In two studies, SRP was started at baseline appointment and completed in two sessions of 3 hours each, performed within 1 week of each other by one operator.[45,96] In another, SRP was started at baseline and performed in 3 to 5 hours during the 2 weeks of drug therapy; this involved seven operators in different centers.[97] In another study, 152 teeth received one session of SRP performed under local anesthesia using ultrasonic and hand instruments.[98] Finally, in the most recent study, SRP was performed by one hygienist using hand instruments.[99]

Experimental regimens differed widely across these trials. Two studies had the standard dose of 500 mg of spiramycin, twice a day for 14 days;[45,97] another had a combination dose of 750,000 IU of spiramycin and 125 mg of metronidazole twice a day for 14 days.[96] Other regimens included: 200 mg of doxycycline the first day followed by 100 mg per day for 6 weeks;[98] 500 mg azithromycin capsules once a day for 3 days at week 2 after the final session of SRP;[99] 250 mg amoxicillin with clavulanic acid three times per day for 30 days[46] and the other had 250 mg amoxicillin with a placebo three times a day for 7 days along with a chlorhexidine rinse.[70] Studies ranged in length from 22 to 43 weeks.

Only five studies reported PD data.[45,46,97-99] While the remaining two studies did not report data, they did report that the difference between the groups was not significant.[70,96] In the doxycycline trial, the experimental group was significantly different from the placebo group only at weeks 3 and 6; at 12 and 24 weeks, the two groups did not differ significantly, with the 0.6 mm nonsignificant difference at 24 weeks favoring the placebo group.[98] One spiramycin study found significant differences in PD reduction favoring the drug group at 2 weeks into the study; at 24 weeks, the net reduction favoring the group receiving spiramycin was 0.47 mm (P = 0.0075).[97] Another spiramycin study showed greater reductions in PD favoring the experimental group in only the least severe class (probing PD $\leq$ 3 mm) of 0.42 mm at 24 weeks but the difference was not significant. For the other severity groups, the results favored the placebo groups—0.40 mm in those with PD 4 mm to 6 mm and 0.28 mm in those with PD $\geq$ 7 mm—and neither was significant.[45] In the azithromycin study, the mean values of subjects' average PDs differed between the azithromycin and the SRP-only groups at baseline; thus, the investigators

used analysis of covariance to render the experimental and control groups equivalent at baseline. The study results showed greater reductions in PD favoring the experimental group in each of three severity classes (probing depths of 1 mm to 3 mm, 4 mm and 5 mm, and 6 mm or greater) at various measurement points. At 22 weeks, the net reductions in PD for patients with the most advanced periodontitis was 0.87 mm ($P < 0.05$) and for these in the intermediate group, 0.52 mm ($P < 0.01$).[99]

Six trials measured CAL.[45,46,70,96-98] The doxycycline trial showed a 1.3 mm gain in CAL at 24 weeks ($P \leq 0.05$).[98] The three spiramycin studies had mixed results. In one (used with metronidazole), the experimental group exhibited a significantly ($P < 0.05$) greater gain in attachment level than did the control group but provided no data;[96] another reported a nonsignificant 0.29 mm gain in CAL for the experimental group.[97] In the third, at 24 weeks a gain of 0.92 mm favoring the treatment group was not significant (for those with least severity), and results favored control groups (although also not significant) for those with greater severity.[45] The amoxicillin and clavulanic acid trial reported only a nonsignificant difference at the end of the trial,[46] and in the other amoxicillin trial no data or significance test were given.[70]

Two trials performed microbiological examinations on the studies' subjects and found a significant decline in the spirochetes level. In one, the proportion of spirochetes among experimental subjects receiving spiramycin decreased from 28 percent at baseline to 3 percent at 24 weeks; the respective values for the placebo group were 30 percent and 11 percent ($P < 0.05$).[45] In the other, the proportion of spirochetes declined significantly among experimentals relative to controls at 14 days and thereafter; at 6 months, the proportions were 3 percent for experimental subjects and 15 percent for controls ($P < 0.05$).[96]

Most of these studies did not report adverse events or effects of the experimental intervention (or reported that they did not observe any). Adverse reactions mentioned, which occurred infrequently, included nausea, diarrhea, gastrointestinal upset, and abdominal pain.

Local Antibiotics

Two clinical trials of local antibiotics as the adjunctive therapy met the inclusion criteria (Table 14; Evidence Table 6b). One trial used local ofloxacin (a broad-spectrum antibiotic);[100] the other used doxycycline gel.[101] Both were randomized, placebo-controlled studies; one was a multi-center, double-blind trial.[101]

In all, 135 subjects completed the two trials. All subjects in both studies received SRP, and each subject had one site treated with the local antibiotic regimens with SRP and a different site treated with placebo.

These two trials differed in several dimensions. With respect to periodontal disease experience, one study included subjects with chronic periodontitis diagnosed by showing on affected teeth more than 30 percent bone loss by radiographs.[100] The other study included subjects suffering from moderate to severe periodontitis with at least 3 single-rooted teeth either with PD depth of 5 mm and bleeding on probing or with PD of 6 mm or more.[101]

Details of the experimental regimens and SRP procedures regimens also differed. In the doxycycline trial, investigators used a subgingival application of a newly developed, biodegradable 15-percent doxycycline gel (DOXI); subgingival SRP was performed with hand

instruments at all test and respective neighboring teeth under local anesthesia, and then mechanical debridement of one test tooth was limited to 10 minutes.[101] In the other study, investigators used a controlled-release, film-shaped insert of ofloxacin that was applied once a week from baseline through 35 days; supragingival SRP was done for the first 2 weeks and root planning and subgingival scaling for 4 weeks after that.[100]

Only the doxycycline trial reported on clinical measures.[101] At 26 weeks both net PD reduction (0.44 mm, $P = 0.0066$) and CAL gain (0.37 mm, $P = 0.038$) favored the experimental group over the control group.[101] Interim measures were said to show improvement compared to baseline but statistical significance was not reported. The ofloxacin trial analyzed the proportion of spirochetes over a 4-week period.[100] Two weeks after supragingival scaling period, the difference between the experimental and the placebo groups favored the former (9.5 percent versus 20.2 percent, $P < 0.05$); however, as the SRP treatment changed to mechanical subgingival debridement, proportions of spirochetes dropped for all groups, and differences between treatment and placebo groups were no longer statistically significant through the remainder of the study. Only the doxycycline study reported any adverse effects (swelling at one treatment tooth).

Other Antimicrobials

Five clinical trials of adjunctive use of antimicrobials other than antibiotics, published between 1987 and 2001, all used locally, met our inclusion criteria (Table 15 and Evidence Table 7).[85,89,102-104] They included (alone or in various combinations or forms): povidone-iodine solution, tetrapotassium peroxydiphosphate, hydrogen peroxide, triclosan, amine fluoride and stannous fluoride. Three were randomized, placebo-controlled, double-blind trials; one was randomized, placebo-controlled and single-blind; and one was described only as placebo-controlled. The duration of the studies ranged from 2 months to 13 years.

Although experimental regimens were applied subgingivally in all studies, none of these studies used exactly the same antimicrobial agent; the treatment regimens, including the SRP approaches, varied considerably too and included the following:

- irrigation with hydrogen peroxide 3 times a week, with SRP started at week 32 with six visits during a period of, on average, 6 weeks to complete;[85]
- application of 1.25 percent amine fluoride gel on one site (tooth) or application of 4 percent stannous fluoride gel on another site, with both treatments applied three times within 10 minutes and selected pockets subjected at baseline to mechanical debridement with hand or ultrasonic instruments;[89]
- application of supragingival gel and dentifrice, both containing triclosan, twice a day for two time periods, each lasting for 14 days with 1 week of wash-out period between them, as well as subgingival gel application at days 0 and 7 in each time period, with the assigned quadrant anaesthetized and teeth exposed to meticulous SRP until root surfaces were hard and smooth;[102]
- use of 0.1 percent of iodofor solution (a water solution of povidone-iodine) as a cooling liquid for an ultrasonic device to provide nonsurgical therapy, with nonsurgical supra- and subgingival SRP under local anesthesia using ultrasonic device for 1 hour for four to six sessions (intervals between sessions never exceeding 1 week);[104] and,
- subgingival irrigation of a 7-percent solution of tetrapotassium peroxydiphosphate twice a day for 8 weeks before SRP was done; SRP was performed through thorough

subgingival scaling by hand (which took place at week 32 of the study, so week 32 was considered the baseline of the reported clinical results).[103]

Taken together, the trials included 236 subjects and 326 sites (148 sites on antimicrobial regimens with SRP, and 178 sites on control regimens). Subjects in the studies experienced a full spectrum of periodontitis: moderate periodontitis;[102] moderate to severe;[85,103] only severe periodontitis;[89] and advanced destructive periodontitis.[104]

The studies differed markedly in the selection of sites used to characterize a subject's response to therapy, but generally all studies involved patients with PDs in the range of 5 mm to 10 mm. One study based analyses on two pairs of contralateral sites with at least 5 mm PD that bled on probing at baseline.[102] A second study selected for each experimental group one interdental pocket of 7 mm to 9 mm that affected a single-rooted tooth.[89] A third study included subjects with a minimum of eight nonmolar teeth, at least two of which in each dentate quadrant had PDs of 6 mm or more;[104] another study selected two or three interproximal sites in each jaw quadrant on the basis of the presence of PDs of 6 mm or more.[85] Finally, another study included subjects with PDs of 5 mm to 10 mm.[103]

All teams used net reduction in PD as a clinical outcome.[85,89,102-104] The hydrogen peroxide study reported net PD reduction of 0.8 mm at 52 weeks ($P < 0.05$);[85] two other trials reported nonsignificant reductions of 0.65 mm (tetrapotassium peroxydiphosphate solution[103]) and 0.6 mm (povidine-iodine[104]) after 8 weeks among persons at baseline with 4 mm to 7 mm probing depths. In the triclosan study, the 0.1 mm reduction favored the control groups;[102] the fluorides study did not report data but only that the results were not significant but favored the treatment group.[89]

Three trials reported results for CAL – two in terms of actual gains or losses in attachment[85,104] and one in terms of less of a loss of attachment.[103] The hydrogen-peroxide trial reported a CAL gain of 0.1 mm for the treatment group (not significant).[85] It also reported the percentage distribution of sites that demonstrated a gain of more than 1 mm of clinical attachment level at the end of the phase that included both SRP and hydrogen-peroxide treatment; for both hydrogen-peroxide and control groups, 40 percent of sites showed an attachment gain of that magnitude (for no difference between the groups). In the tetrapotassium peroxydiphosphate trial, the net difference in attachment level between test and control groups at the end of 8 weeks was 0.25 mm (a nonsignificant finding).[103] Finally, in the longest study (of povidine-iodine), the control group had a greater attachment *gain* after 13 years of 0.597 mm (significance not reported).[104]

Three trials examined microbiological outcomes including spirochetes.[89,102,103] None of these studies showed that the treatment groups differed significantly from the control or placebo groups at the end of their respective observation periods. In the triclosan trial,[102] the mean percentages dropped by day 14 to about 13 percent for both groups (from 46 percent among test patients and 37 percent among controls). In the tetrapotassium peroxydiphosphate study, the drop in percentage of spirochetes for both treatment and control groups was reported to be statistically significant between baseline and 8 weeks, but the net difference between groups was noted as not significant.[103] Finally, for fluoride gel treatment, the percentages of spirochetes was reported to have dropped significantly for both treatment groups (amine fluoride and stannous fluoride) and placebo between baseline and 36 weeks, but the differences between groups at the end were not significant.[89]

By and large, these trials did not report on adverse events or effects. The tetrapotassium peroxydiphosphate trial noted mucosal irritation.[103]

Table 5. Main Features and Findings on Probing Depth and Clinical Attachment Level: Trials of Systemic Tetracycline

Author, Year	Randomization Placebo Blinded	Duration	Number Completing Treatment Control	Dosage and Mode	Treatment Group PD Reduction (mm) Level of Significance	Treatment Group CAL Gain (mm) Level of Significance
Listgarten et al., 1978[43]	R NP NR	25 weeks	N: 12 subjects T: 6 subjects C: 6 subjects	250 mg tetracycline 4xday, days 0 to 14 and days 42 to 56	+0.20, NS	Data NR, NR
Lindhe et al., 1983[44]	R PL DB	50 weeks	N: 14 subjects T: 7 subjects C: 7 subjects	250 mg tetracycline 4xday, days 0 to 14 and 250 mg 1xday days 15 to 350	+0.8, NR	+0.3, NR
Al-Joburi et al., 1989[45]	R PL DB	24 weeks	N: 51 subjects T: 27 subjects C 24 subjects	250 mg tetracycline 4xday, days 0 to 14	Initial PD ≤ 3 mm: +0.12, NS Initial PD 4-6 mm: -0.05, NS Initial PD ≥ 7 mm: +0.19, NS	Initial PD ≤ 3 mm: +0.49, NS Initial PD 4-6 mm: +0.04, NS Initial PD ≥ 7 mm: +0.45, NS
Haffajee et al., 1995[46]	R PL DB	43 weeks (10 months)	N: 24 subjects T: 13 subjects C: 11 subjects	250 mg tetracycline 3xday, days 0 to 30, plus 0.12% chlorhexidine rinse for same 30 days	+0.29, NS	Data NR, NS
Ramberg et al., 2001[47]	Non-R NP NR	52 weeks	N: 89 subjects T: 28 subjects C: 61 subjects	250 mg tetracycline 4xday, days 0 to 21 and 0.2% chlorhexidine rinse 2xday	+0.3, NS	+0.31, $P < 0.001$

R, randomized; Non-R, nonrandomized; PL, placebo-controlled; NP, no placebo; DB, double-blind; SB, single blind; NR, not reported; N/A, not applicable because not one of the clinical measures used; NS, not significant.

Table 6. Main Features and Findings on Probing Depth and Clinical Attachment Level: Trials of Local Tetracycline

Author, Year	Randomization Placebo Blinded	Duration	Number Completing Treatment Control	Dosage and Mode	Treatment Group PD Reduction (mm) Level of Significance	Treatment Group CAL Gain (mm) Level of Significance
Goodson et al., 1985[48]	R NP SB	52 weeks	N: 10 subjects T: 9 teeth C: 9 teeth	25% tetracycline fibers for 10 days	Data NR, NR	Initial PD > 3 mm: +0.34, NS Initial PD > 6 mm: +0.33, NS
MacAlpine et al., 1985[31]	Non-R PL NR	24 weeks	N: 11 subjects T: 16 sites C: 16 sites	50 mg/ml tetracycline irrigation every 2 weeks for 22 weeks	+0.4, NR	+0.3, NS
Nylund and Egelberg, 1990[51]	Non-R PL NR	52 weeks	N: 20 subjects T: 20 subjects C: 20 subjects	50 mg/ml tetracycline irrigation once every 2 weeks for 3 months	Data NR, NS	Data NR, NS
Minabe et al., 1991[52]	R NP NR	8 weeks	N: 16 subjects T: 10 sites C: 8 sites	Tetracycline immobilized collagen film, 4 consecutive weekly administrations	+0.7, NS	Data NR, NS
Unsal et al., 1994[59]	R NP NR	12 weeks	N: 15 subjects T: 7 subjects C: 8 subjects	40% tetracycline in white petroleum, single application	-0.43, NS	-0.23, NS
Jeong et al., 1994[33]	R NP NR	12 weeks	N: 16 subjects T1: 16 subjects T2: 16 subjects C: 16 subjects	T1: 5% tetracycline in gel, 1 application T2: 5% tetracycline with citric acid in gel, 1 application	T1: +0.27, NS T2: +0.93, $P < 0.05$	T1: +0.14, NS T2: +0.73, NS
Newman et al., 1994[57]	R NP SB	26 weeks (6 months)	N: 105 subjects T: 105 subjects C: 105 subjects	12.1 cm of tetracycline fiber for 10 days	+0.73, $P < 0.01$	+0.48, $P < 0.05$
Shiloah and Patters 1994[54]	R PL SB	4 weeks	N: 7 subjects T: 12 sites C: 12 sites	5% aqueous tetracycline, 1 application	Data NR, NS	Data NR, NS

Table 6. Main Features and Findings on Probing Depth and Clinical Attachment Level: Trials of Local Tetracycline (continued)

Author, Year	Randomization Placebo Blinded	Duration	Number Completing Treatment Control	Dosage and Mode	Treatment Group PD Reduction (mm) Level of Significance	Treatment Group CAL Gain (mm) Level of Significance
Drisko et al., 1995[49]	R NP SB	52 weeks	N: 116 subjects T: 116 subjects C: 116 subjects	17 mg tetracycline fibers for 10 days	Data NR, NS	Data NR, NS
Darhous et al., 1995[50]	Non-R NP NR	8 weeks	N: 7 subjects T: 7 subjects C: 7 subjects	100 mg/ml tetracycline irrigation, 5 minutes, 1 application	+1.04, NR	+1.8, NR
Trombelli et al., 1996[55]	R NP SB	8 weeks (60 days)	N: 12 subjects T1: 20 sites T2: 24 sites C: 19 sites	T1: 100 mg/ml tetracycline irrigation, 4 minutes, 1 application T2: 25% tetracycline fibers for 10 days	T1: +0.4, *P* = 0.011 T2: +0.5, *P* = 0.011	T1: -0.2, NS T2: +0.4, NS
Lie et al., 1998[34]	R NP DB	26 weeks	N: 18 subjects T: 18 subjects C: 18 subjects	3% tetracycline ointment after each SRP session, 1 week apart	Defect sites:* +0.6, NS Nondefect sites:* -0.3, NS	Defect sites:* +1.0, NS Nondefect sites:* +0.2, NS
Tonetti et al., 1998[35]	R NP SB	26 weeks	N: 123 subjects T: 63 subjects C: 60 subjects	25% tetracycline fibers for 10±3 days	+0.4, NS	-0.1, NS
Yalcin et al., 1999[56]	R NP SB	7 weeks	N: 17 subjects T: 221 sites C: 191 sites	Slow-release tetracycline fibers for 10 days	+0.41, *P* = 0.047	+0.20, NS

Table 6. Main Features and Findings on Probing Depth and Clinical Attachment Level: Trials of Local Tetracycline (continued)

Author, Year	Randomization Placebo Blinded	Duration	Number Completing Treatment Control	Dosage and Mode	Treatment Group PD Reduction (mm) Level of Significance	Treatment Group CAL Gain (mm) Level of Significance
Kinane and Radvar, 1999[53]	R NP SB	26 weeks (6 months)	N: 39 subjects T: 19 subjects C: 20 subjects	25% tetracycline fibers for 10 days	+0.67, $P = 0.008$	+0.15, $P < 0.05$
Friesen et al., 2002[58]	R NP SB	26 weeks (6 months)	N: 24 subjects T1: 24 subjects T2: 24 subjects C: 24 subjects	13.5 mg tetracycline strips for 7 to 10 days T1: single strip T2: multiple strips	T1: +0.43, NR T2: +0.87, NR	T1: +0.44, NS T2: +0.48, NS

R, randomized; Non-R, nonrandomized; PL, placebo-controlled; NP, no placebo; DB, double-blind; SB, single blind; NB, not blinded; NR, not reported; N/A, not applicable because not one of the clinical measures used; NS, not significant.

*Defect and nondefect sites refer to, respectively, the mean of measurements from the buccal and lingual side versus measurements for all remaining parts of the tooth.

Table 7. Main Features and Findings on Probing Depth and Clinical Attachment Level: Trials of Systemic Minocycline

Author, Year	Randomization Placebo Blinded	Duration	Number Completing Treatment Control	Dosage and Mode	Treatment Group PD Reduction (mm) Level of Significance	Treatment Group CAL Gain (mm) Level of Significance
Ciancio et al., 1982[61]	R PL DB	10 weeks	N: 26 subjects T: 13 subjects C: 13 subjects	200 mg minocycline per day for 7 days	Data NR, NS	N/A
Atilla et al., 1996[62]	Non-R NP NR	6 weeks	N: 21 subjects T1: 5 (PD 4-5 mm) C1: 6 (PD 4-5 mm) T2: 5 (PD ≥ 6 mm) C2: 5 (PD ≥ 6 mm)	100 mg minocycline per day for 14 days	Initial PD 4-5 mm: -0.06, NS Initial PD ≥ 6 mm: +0.49, NS	N/A

R, randomized; Non-R, nonrandomized; PL, placebo-controlled; NP, no placebo; DB, double-blind; NR, not reported; N/A, not applicable because not one of the clinical measures used; NS, not significant.

Table 8. Main Features and Findings on Probing Depth and Clinical Attachment Level: Trials of Local Minocycline

Author, Year	Randomization Placebo Blinded	Duration	Number Completing Treatment Control	Dosage and Mode	Treatment Group PD Reduction (mm) Level of Significance	Treatment Group CAL Gain (mm) Level of Significance
van Steenberghe et al., 1993[63]	R PL DB	12 weeks	N: 81 subjects T: 42 subjects C: 39 subjects	2% minocycline ointment applied at baseline and weeks 2, 4, and 6	Initial PD ≥ 5 mm: +0.3, *P* = 0.0018 Initial PD ≥ 7 mm: +1.0, *P* = 0.0001	Initial PD ≥ 5 mm: 0.0, NS Initial PD ≥7 mm: +0.40, NS
Jones, et al., 1994[64]	R PL DB	26 weeks (6 months)	N: 17 subjects T: 11 subjects C: 6 subjects	1 mg microencapsulated minocycline injected into ≥5 mm pockets, single application	Data NR, NS	Data NR, NR
Graca et al., 1997[32]	R PL DB	12 weeks	N: 26 subjects T: 13 subjects C: 13 subjects	2% minocycline gel applied at baseline and weeks 2 and 4	+0.34, NS	+0.39, *P* < 0.05
Kinane and Radvar, 1999[53]	R NP DB	26 weeks (6 months)	N: 39 subjects T: 20 subjects C: 19 subjects	2% minocycline gel applied at baseline and weeks 2 and 4	+0.39, NS	+0.36, NS
van Steenberghe et al., 1999[65]	R PL DB	65 weeks (15 months)	N: 93 subjects T: 46 subjects C: 47 subjects	2% minocycline ointment applied at baseline week 2, and months 1, 3, 6, 9, and 12	Initial PD ≥ 5 mm: +0.77, *P* < 0.0001 Initial PD ≥7 mm: +1.10, *P* < 0.0001	Initial PD ≥5 mm: +0.49, *P* < 0.0001 Initial PD ≥7 mm: +0.43, *P* < 0.0001
Williams et al., 2001[66]	R PL DB	39 weeks (9 months)	N: 467 subjects T: 237 subjects C: 230 subjects	2% minocycline microspheres in polymer gel applied at baseline and months 3 and 6	+0.32, *P* < 0.001	Data NR, NR

Table 8. Main Features and Findings on Probing Depth and Clinical Attachment Level: Trials of Local Minocycline (continued)

Author, Year	Randomization Placebo Blinded	Duration	Number Completing Treatment Control	Dosage and Mode	Treatment Group PD Reduction (mm) Level of Significance	Treatment Group CAL Gain (mm) Level of Significance
Henderson et al., 2002[67]	R NP SB	26 weeks (6 months)	N: 15 subjects T: 15 subjects C: 15 subjects	1 mg microencapsulated minocycline, single application	+0.7, $P \leq 0.05$	+0.8, $P = 0.04$
Van Dyke et al., 2002[68]	R NP DB	26 weeks (6 months)	N: 22 subjects T: 12 subjects C: 10 subjects	1 mg microencapsulated minocycline, single application	+0.28, NS	+0.48, NS

R, randomized; Non-R, nonrandomized; PL, placebo-controlled; NP, no placebo; DB, double-blind; SB, single blind; NR, not reported; N/A, not applicable because not one of the clinical measures used; NS, not significant.

Table 9. Main Features and Findings on Probing Depth and Clinical Attachment Level: Trials of Systemic Metronidazole

Author, Year	Randomization Placebo Blinded	Duration	Number Completing Treatment Control	Dosage and Mode	Treatment Group PD Reduction (mm) Level of Significance	Treatment Group CAL Gain (mm) Level of Significance
Loesche et al., 1984[69]	R PL DB	30 weeks	N: 14 subjects T: 7 subjects C: 7 subjects	250 mg metronidazole 3xday for 7 days	Initial PD 4-6 mm: +0.14, NS Initial PD ≥ 7 mm: +1.64, *P* < 0.03	Initial PD 4-6 mm: +0.10, NS Initial PD ≥ 7 mm: +1.19, *P* = 0.05
Joyston-Bechal et al., 1986[71]	R PL DB	156 weeks (3 years)	N: 28 subjects T: 15 subjects C: 13 subjects	1% chlorhexidine gel for first 10 weeks, then 200 mg metronidazole: 1 at evening of 3rd visit + 3xday for 5 days; repeated 4 weeks later	+0.41, NS	N/A
Soder et al., 1990[72]	R PL DB	26 weeks (6 months)	N: 92 subjects T: 46 subjects C: 46 subjects	400 mg metronidazole 3xday for 7 days	+0.05, NR	N/A
Loesche et al., 1991[73]	R PL DB	52 weeks	N: 39 subjects T: 18 subjects C: 21subjects	250 mg metronidazole 3xday for 7 days	Initial PD ≤ 3 mm: -0.07, NS Initial PD 4-6 mm: -0.06, NS Initial PD ≥ 7 mm: +0.41, NS	Initial PD ≤ 3 mm: +0.10, NS Initial PD 4-6 mm: +0.13, NS Initial PD ≥ 7 mm: +0.32, NS

Table 9. Main Features and Findings on Probing Depth and Clinical Attachment Level: Trials of Systemic Metronidazole (continued)

Author, Year	Randomization Placebo Blinded	Duration	Number Completing Treatment Control	Dosage and Mode	Treatment Group PD Reduction (mm) Level of Significance	Treatment Group CAL Gain (mm) Level of Significance
Loesche et al., 1992[74]	R PL DB	104 weeks (2 years)	N: 33 subjects T: 15 subjects C: 18 subjects	250 mg metronidazole 3xday for 7 days	Initial PD ≤ 3 mm: -0.15, P = 0.08 Initial PD 4-6 mm: +0.47, *P* < 0.01 Initial PD ≥ 7 mm: +1.05, *P* < 0.01	Initial PD ≤ 3 mm: +0.37, P = 0.07 Initial PD 4-6 mm: +0.47, *P* < 0.01 Initial PD ≥ 7 mm: +0.66, NS
Noyan et al., 1997[75]	R NP NR	6 weeks	N: 10 subjects T: 5 subjects C: 5 subjects	250 mg metronidazole 3xday for 7 days, then SRP again	+0.60, NR	+0.41, NR
Palmer et al., 1998[76]	R NP SB	24 weeks	N: 58 subjects T: 31 subjects C: 27 subjects	200 mg metronidazole 3xday for 7 days	-0.06, NS	+0.16, NS
Rooney et al., 2002[70]	R PL DB	26 weeks	N: 31 subjects T: 16 subjects C: 15 subjects	200 mg metronidazole plus placebo 3xday for 7 days; plus 0.2% chlorhexidine irrigation	Initial PD ≥ 6 mm: Data NR, *P* < 0.05	Initial PD ≥ 6 mm: Data NR, NS

R, randomized; ; PL, placebo-controlled; NP, no placebo; DB, double-blind; SB, single blind; NR, not reported; N/A, not applicable because not one of the clinical measures used; NS, not significant.

Table 10. Main Features and Findings on Probing Depth and Clinical Attachment Level: Trials of Local Metronidazole

Author, Year	Randomization Placebo Blinded	Duration	Number Completing Treatment Control	Dosage and Mode	Treatment Group PD Reduction (mm) Level of Significance	Treatment Group CAL Gain (mm) Level of Significance
Aziz-Gandour and Newman 1986[77]	R PL DB	12 weeks	N: 16 subjects T: 210 surfaces C: 118 surfaces	0.05% metronidazole irrigation for 28 days	Data NR; $P < 0.01$	N/A
Moran et al., 1990[37]	R NP DB	12 weeks	N: 33 pockets T: 15 pockets C: 18 pockets	Acrylic strips impregnated with metronidazole	+0.9, NS	+0.3, NS
Noyan et al., 1997[75]	R NP NR	6 weeks	N: 10 subjects T: 5 subjects C: 5 subjects	25% metronidazole gel applied on days 0 and 7	+0.78, NS	+0.66, $P < 0.01$
Awartani and Zulqarnain 1998[28]	R NP SB	14 weeks	N: 12 subjects T: 360 sites C: 378 sites	25% metronidazole gel applied on days 0 and 7	-0.12, NS	N/A
Lie et al., 1998[34]	R NP DB	26 weeks (6 months)	N: 18 subjects T: 18 subjects C: 18 subjects	25% sustained release metronidazole gel after SRP sessions on days 0 and 7	Defect sites:* +0.5, NS Nondefect sites:* -0.1, NS	Defect sites:* +0.7, NS Nondefect sites:* 0.0, NS
Palmer et al, 1998[76]	R NP SB	24 weeks	N: 53 subjects T: 26 subjects C: 27 subjects	25% metronidazole gel subgingival application on days 0 and 7	Data NR, NS	-0.04, NS
Kinane and Radvar, 1999[53]	R NP SB	26 weeks (6 months)	N: 36 subjects T: 19 subjects C: 20 subjects	25% metronidazole gel 2xday applied on day 0 and 7	+0.22, NS	+0.004, NS
Riep et al., 1999[78]	R NP SB	13 weeks (3 months)	N: 29 subjects T: 29 subjects C: 29 subjects	25% metronidazole gel applied 5 times over 10 days	0.0, NS	+0.17, NS

Table 10. Main Features and Findings on Probing Depth and Clinical Attachment Level: Trials of Local Metronidazole

Author, Year	Randomization Placebo Blinded	Duration	Number Completing Treatment Control	Dosage and Mode	Treatment Group PD Reduction (mm) Level of Significance	Treatment Group CAL Gain (mm) Level of Significance
Al Mubarak et al., 2000[80]	R NP SB	13 weeks (90 days)	N: 14 subjects T: 14 subjects C: 14 subjects	25% metronidazole gel applied on days 0 and 7	+0.8, $P < 0.03$	N/A
Griffiths et al., 2000[79]	R NP SB	39 weeks (9 months)	N: 88 subjects T: 1,770 sites C: 1,780 sites	25% metronidazole gel 1xweek for 3 weeks	+0.5, $P < 0.001$	+0.4, $P < 0.001$
Stelzel and Flores-de-Jacoby, 2000[36]	R NP SB	37 weeks (9 months)	N: 59 subjects T: 59 subjects C: 59 subjects	25% metronidazole gel applied 2xday on days 0 and 7	+0.18, $P < 0.05$	+0.07, NS

R, randomized; ; PL, placebo-controlled; NP, no placebo; DB, double-blind; SB, single blind; NR, not reported; N/A, not applicable because not one of the clinical measures used; NS, not significant.

*Defect and nondefect sites refer to, respectively, the mean of measurements from the buccal and lingual side versus measurements for all remaining parts of the tooth.

Table 11. Main Features and Findings on Probing Depth and Clinical Attachment Level: Trials of Systemic Metronidazole plus Amoxicillin

Author, Year	Randomization Placebo Blinded	Duration	Number Completing Treatment Control	Dosage and Mode	Treatment Group PD Reduction (mm) Level of Significance	Treatment Group CAL Gain (mm) Level of Significance
Berglundh et al., 1998[81]	R PL NR	104 weeks	N: 16 subjects T: 8 subjects C: 8 subjects	250 mg metronidazole 3xday plus 375 mg amoxicillin 2xday for 2 weeks	+0.5, NR	+0.3, NR
Flemmig, Milian, et al., 1998[82]	R NP SB	52 weeks	N: 38 subjects T: 18 subjects C: 20 subjects	250 mg metronidazole plus 375 mg amoxicillin 3xday plus 0.06% chlorhexidine irrigation 1xday for 8 days	Data NR, NS	Data NR, NS
Winkel et al., 2001[83]	R PL DB	24 weeks	N: 49 subjects T: 23 subjects C: 26 subjects	250 mg metronidazole plus 375 mg amoxicillin 3xday for 7 days	+0.7, P < 0.05	+0.4, NS
Rooney et al., 2002[70]	R PL DB	26 weeks	N: 30 subjects T: 15 subjects C: 15 subjects	200 mg metronidazole plus 250 mg amoxicillin 3xday for 7 days; plus 0.2% chlorhexidine irrigation	Initial PD ≥ 6 mm: Data NR, *P* < 0.001	Initial PD ≥ 6 mm: Data NR, *P* < 0.05

R, randomized; PL, placebo-controlled; NP, no placebo; DB, double-blind; SB, single blind; NR, not reported; N/A, not applicable because not one of the clinical measures used; NS, not significant.

Table 12. Main Features and Findings on Probing Depth and Clinical Attachment Level: Trials of Local Chlorhexidine

Author, Year	Randomization Placebo Blinded	Duration	Number Completing Treatment Control	Dosage and Mode	Treatment Group PD Reduction (mm) Level of Significance	Treatment Group CAL Gain (mm) Level of Significance
Braatz et al., 1985[30]	R PL NR	24 weeks	N: 14 subjects T: 54 sites C: 52 sites	Irrigation with 2% chlorhexidine solution daily for 24 weeks	+0.3, NS	+0.2, NS
MacAlpine 1985[31]	R PL NR	24 weeks	N: 11 subjects T: 16 sites C: 16 sites	Irrigation with 2% chlorhexidine solution every 2 weeks for 24 weeks	+1.0, NS	+0.9, NS
Aziz-Gandour and Newman, 1986[77]	R PL DB	12 weeks	N: 12 subjects T: 147 surfaces C: 118 surfaces	Irrigation with 0.02% chlorhexidine solution 1xday for 28 days	Data NR, NS	N/A
Watts and Newman, 1986[84]	R PL DB	12 weeks	N: 11 subjects T: 128 sites C: 134 sites	Irrigation with 0.02% chlorhexidine solution 1xday for 28 days	Data NR, NS	N/A
Wennstrom et al., 1987[85]	R PL SB	52 weeks	N: 10 subjects T: 28 subjects C: 24 subjects	Irrigation with 0.2% chlorhexidine solution 3xweek	+0.1, NR	-0.1, NS
Southard et al., 1989[86]	R NP DB	15 weeks	N: 8 subjects T: 8 subjects C: 8 subjects	Irrigation with 2% chlorhexidine solution at day 0 then 1xweek for 3 weeks	-0.1, NS	+0.1, NS
Taggart et al., 1990[87]	NR PL NR	10 weeks	N: 10 subjects T: 10 subjects C: 10 subjects	Irrigation with 0.02% chlorhexidine solution	+0.1, NS	+0.1, NS

Table 12. Main Features and Findings on Probing Depth and Clinical Attachment Level: Trials of Local Chlorhexidine (continued)

Author, Year	Randomization Placebo Blinded	Duration	Number Completing Treatment Control	Dosage and Mode	Treatment Group PD Reduction (mm) Level of Significance	Treatment Group CAL Gain (mm) Level of Significance
Reynolds et al., 1992[88]	R PL DB	4 weeks (28 days)	N: 60 subjects T: 90 sites C: 90 sites	Irrigation with 0.12% chlorhexidine solution, 1 time	Data NR, NR	N/A
Shiloah and Patters, 1994[54]	R PL SB	4 weeks	N: 7 subjects T: 12 sites C: 12 sites	Irrigation with 0.12% chlorhexidine solution, 1 time	Data NR, NS	Data NR, NS
Oosterwaal et al., 1991[89]	R PL DB	36 weeks	N: 10 subjects T: 10 subjects C: 10 subjects	0.2% chlorhexidine gel applied 3x within 10 minutes after SRP	Data NR, NS	N/A
Unsal et al., 1994[59]	R NP NR	12 weeks	N: 15 subjects T: 7 subjects C: 8 subjects	1% chlorhexidine gel applied once	-0.25, NS	-0.34, NS
Soskolne et al., 1997[90]	R NP DB	26 weeks (6 months)	N: 94 subjects T: 94 subjects C: 94 subjects	2.5 mg chlorhexidine chip inserted into pockets 5-8 mm at day 0 and 3 months	+0.46, $P < 0.001$	+0.16, $P < 0.05$
Jeffcoat et al., 1998[91]	R PL DB	39 weeks (9 months)	N: 419 subjects T: 211 subjects C: 208 subjects	2.5 mg chlorhexidine chip inserted into pockets at baseline and months 3 and 6	+0.26, $P < 0.00056$	+0.20, $P < 0.012$
Heasman et al., 2001[92]	R NP SB	26 weeks (6 months)	N: 24 subjects T: 24 subjects C: 24 subjects	2.5 mg controlled release chlorhexidine chip	+0.33, $P = 0.05$	+0.28, $P = 0.048$
Azmak et al., 2002[93]	R NP SB	26 weeks (6 months)	N: 20 subjects T: 20 subjects C: 20 subjects	2.5 mg chlorhexidine chip in pockets	Data NR, NS	Data NR, NS

Table 12. Main Features and Findings on Probing Depth and Clinical Attachment Level: Trials of Local Chlorhexidine (continued)

Author, Year	Randomization Placebo Blinded	Duration	Number Completing Treatment Control	Dosage and Mode	Treatment Group PD Reduction (mm) Level of Significance	Treatment Group CAL Gain (mm) Level of Significance
Grisi et al., 2002[94]	R NP SB	39 weeks (9 months)	N: 19 subjects T: 10 subjects C: 9 subjects	2.5 mg chlorhexidine chip at day 0, 3 and 6 months	-0.2, NS	-0.4, NS
Quirynen et al., 2000[95]	Non-R NP NR	35 weeks (8 months)	N: 24 subjects T: 12 subjects C: 12 subjects	Combination of 1% chlorhexidine gel for brushing and subgingival irrigation + 0.2% chlorhexidine rinse + spray within 24 hours, then 0.2% rinse and spray 2xday for 60 days	Single-root: -0.1, NS Multi-root: -0.5, NS	Initial PD ≥7 mm: Single-root: -0.3, NS Multi-root: -0.3, NS Initial PD < 7 mm Data NR, NR

R, randomized; Non-R, nonrandomized; PL, placebo-controlled; NP, no placebo; DB, double-blind; SB, single blind; NR, not reported; N/A, not applicable because not one of the clinical measures used; NS, not significant.

Table 13. Main Features and Findings on Probing Depth and Clinical Attachment Level: Trials of Other Systemic Antibiotics

Author, Year	Randomization Placebo Blinded	Duration	Number Completing Treatment Control	Dosage and Mode	Treatment Group PD Reduction (mm) Level of Significance	Treatment Group CAL Gain (mm) Level of Significance
Chin Quee et al., 1987[96]	R PL DB	26 weeks (6 months)	N: 50 subjects T: 26 subjects C: 24 subjects	3 tablets (750,000 IU of spiramycin and 125 mg of metronidazole), 2xday for 14 days	Data NR, NS	Data NR, $P < 0.05$
Al-Joburi et al., 1989[45]	R PL DB	24 weeks	N: 52 subjects T: 28 subjects C: 24 subjects	500 mg spiramycin 2xday for 14 days	Initial PD ≤ 3 mm: +0.42, NS Initial PD 4-6 mm: -0.40, NS Initial PD ≥ 7 mm: -0.28, NS	Initial PD ≤ 3 mm: +0.92, NS Initial PD 4-6 mm: -0.22, NS Initial PD ≥ 7 mm: -0.08, NS
Bain et al., 1994[97]	R PL DB	24 weeks	N: 189 subjects T: 93 subjects C: 96 subjects	1,500,000 IU of spiramycin “500” capsules, 2xday for 14 days	+0.47, $P < 0.0075$	+0.29, NS
Haffajee et al., 1995[46]	R PL DB	43 weeks (10 months)	N: 21 subjects T: 10 subjects C: 11 subjects	250 mg amoxicillin with clavulanic acid 3xday for 30 days	+0.29, NS	Data NR, NS
Ng and Bissada, 1998[98]	R PL SB	24 weeks	N: 16 subjects T: 8 subjects C: 8 subjects	200 mg doxycycline on day 1 then 100 mg 1xday for 6 weeks	-0.6, NS	+1.3, $P \leq 0.05$

Table 13. Main Features and Findings on Probing Depth and Clinical Attachment Level: Trials of Other Systemic Antibiotics (continued)

Author, Year	Randomization Placebo Blinded	Duration	Number Completing Treatment Control	Dosage and Mode	Treatment Group PD Reduction (mm) Level of Significance	Treatment Group CAL Gain (mm) Level of Significance
Rooney et al., 2002[70]	R PL DB	26 weeks (6 months)	N: 31 subjects T: 16 subjects C: 15 subjects	250 mg amoxicillin and placebo (calcium lactate tablets 3xday for 7 days, plus 0.2% chlorhexidine rinse	Initial PD ≥ 6 mm: Data NR, $P < 0.05$	Initial PD ≥ 6 mm: Data NR, NR
Smith et al., 2002[99]	R PL DB	22 weeks	N: 44 subjects T: 23 subjects C: 21 subjects	500 mg azithromycin 1xday for 3 days at week 2	Initial PD 1-3 mm: +0.14, NS Initial PD 4-5 mm: +0.52, $P < 0.01$ Initial PD ≥ 6 mm: +0.87, $P < 0.05$	N/A

R, randomized; PL, placebo-controlled; DB, double-blind; SB, single blind; ; NR, not reported; N/A, not applicable because not one of the clinical measures used; NS, not significant.

Table 14. Main Features and Findings on Probing Depth and Clinical Attachment Level: Trials of Other Local Antibiotics

Author, Year	Randomization Placebo Blinded	Duration	Number Completing Treatment Control	Dosage and Mode	Treatment Group PD Reduction (mm) Level of Significance	Treatment Group CAL Gain (mm) Level of Significance
Kimura et al., 1991[100]	R PL NR	4 weeks	N: 27 subjects T: 27 subjects C: 27 subjects	Controlled-release ofloxacin insert applied 1x week for 2 weeks, then SRP again and inserts applied 1xweek for next 3 weeks	N/A	N/A
Eickholz et al., 2002[101]	R PL DB	26 weeks (6 months)	N: 108 subjects T: 108 subjects C: 108 subjects	15% doxycycline gel, 1 subgingival application	+0.44, *P* = 0.0066	+0.37, *P* = 0.038

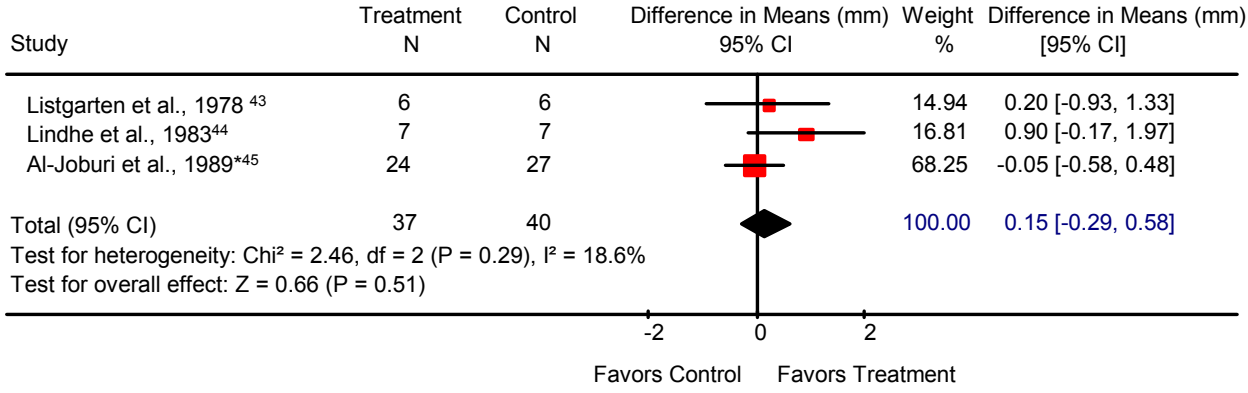
R, randomized; ; PL, placebo-controlled; ; DB, double-blind; NR, not reported; N/A, not applicable because not one of the clinical measures; NS, not significant

Table 15. Main Features and Findings on Probing Depth and Clinical Attachment Level: Trials of Other Antimicrobials

Author, Year	Randomization Placebo Blinded	Duration	Number Completing Treatment Control	Dosage and Mode	Treatment Group PD Reduction (mm) Level of Significance	Treatment Group CAL Gain (mm) Level of Significance
Wennstrom et al., 1987[85]	R PL SB	52 weeks	N: 10 subjects T: 10 subjects C: 10 subjects	3% hydrogen peroxide irrigation 3xweek for 2 weeks	+0.8, $P < 0.05$	+0.1, NS
Listgarten et al., 1989[103]	R PL DB	8 weeks	N: 40 subjects T: 20 subjects C: 20 subjects	7% tetrapotassium peroxydiphosphate irrigation 2xday for 8 weeks	+0.65, NS	+0.25, NS
Oosterwaal et al., 1991[89]	R PL DB	36 weeks	N: 10 subjects T: 10 subjects C: 10 subjects	T1:1.25% amine fluoride gel 3x within 10 minutes T2: 4% stannous fluoride gel 3x within 10 minutes	T1:Data NR, NS T2: Data NR, NS	T1: N/A T2: N/A
Furuichi et al., 1997[102]	R PL DB	2 weeks	N: 16 subjects T: 32 sites C: 32 sites	0.6% triclosan gel + 0.3% triclosan dentifrice 2xday for 2 weeks, repeated again after 1 week washout period	-0.1, NS	N/A
Rosling et al., 2001[104]	NR PL NR	676 weeks (13 years)	N: 150 subjects T: 58 subjects C: 92 subjects	0.1% povidone iodine solution	+0.6, NR	-0.59, NR

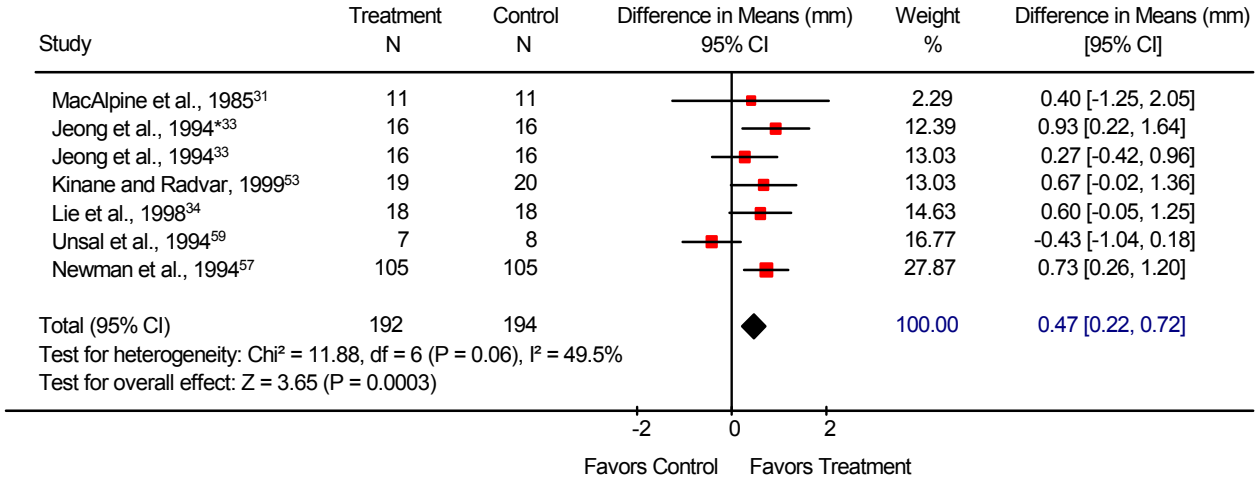
R, randomized; PL, placebo-controlled; DB, double-blind; SB, single blind; NR, not reported; N/A, not applicable because not one of the clinical measures used; NS, not significant.

Figure 3. Meta-analysis of Systemic Tetracycline and SRP vs. SRP Alone: Probing Depth



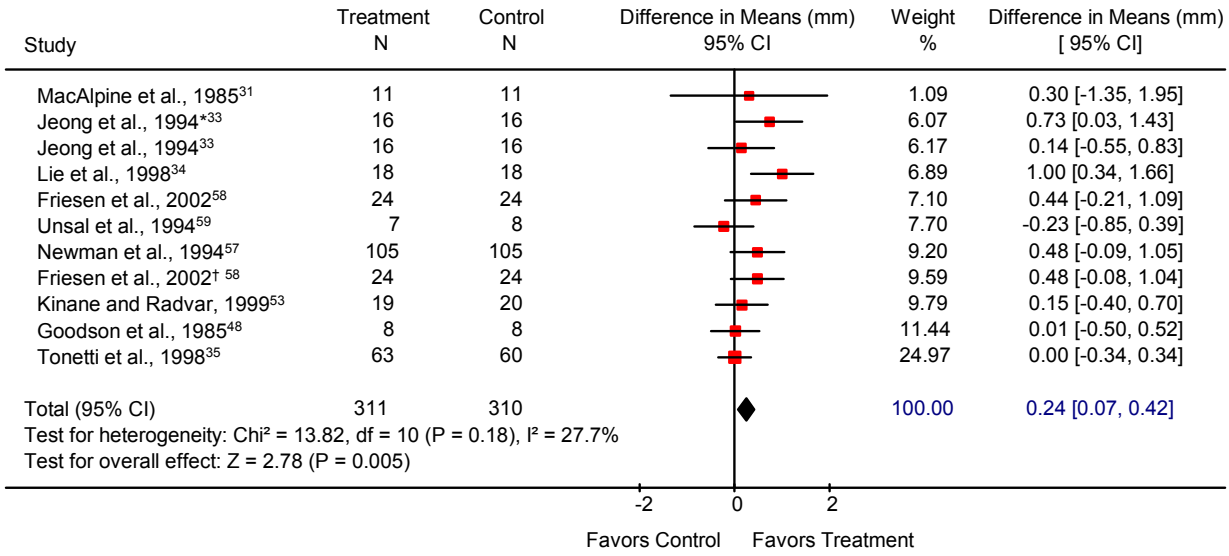
*Only subjects with initial PD ≥ 4 mm to ≤ 6 mm.

Figure 4. Meta-analysis of Local Tetracycline and SRP versus SRP Alone: Probing Depth



*Tetracycline gel with citric acid used as treatment.

Figure 5. Meta-analysis of Local Tetracycline and SRP versus SRP Alone: Clinical Attachment Level



*Tetracycline gel with citric acid used as treatment.
†Multiple tetracycline strips used as treatment.

Figure 6. Meta-analysis of Local Minocycline and SRP versus SRP Alone: Probing Depth

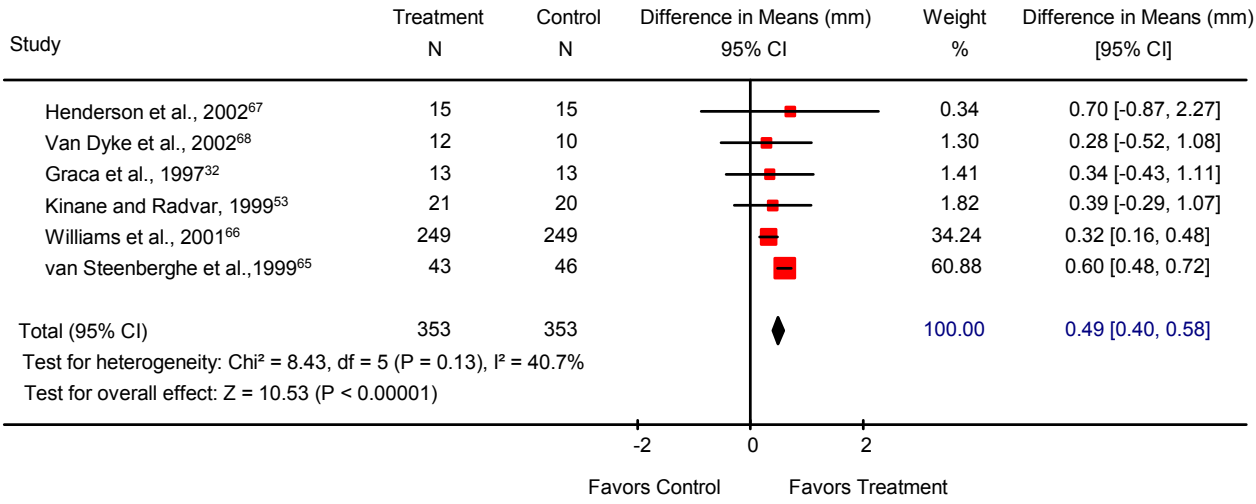


Figure 7. Meta-analysis of Local Minocycline and SRP versus SRP Alone: Clinical Attachment Level

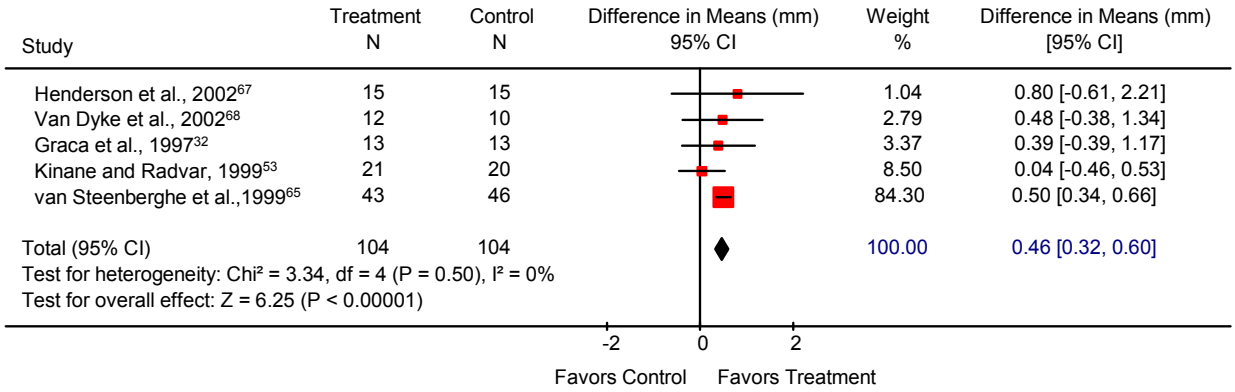


Figure 8. Meta-analysis of Local Metronidazole and SRP versus SRP Alone: Probing Depth

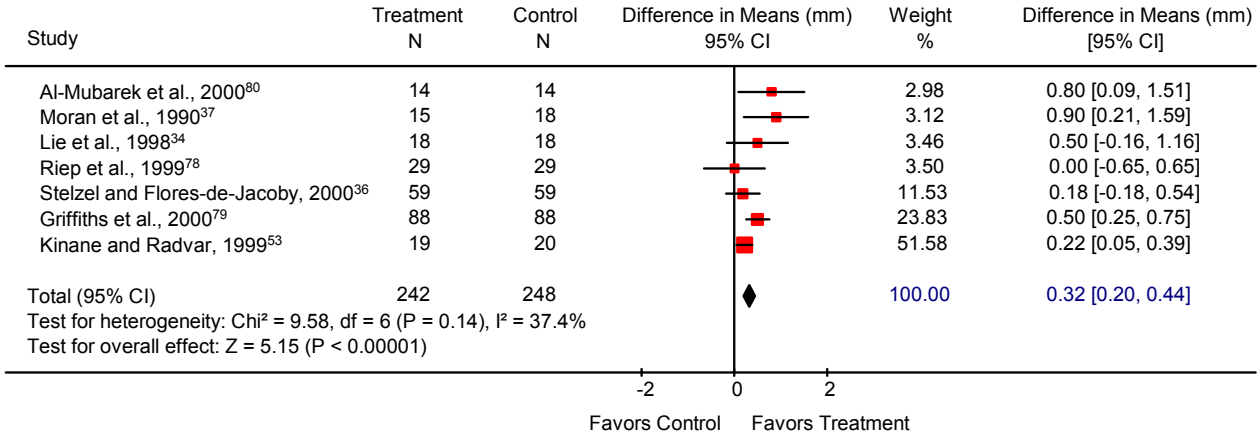


Figure 9. Meta-analysis of Local Metronidazole and SRP versus SRP Alone: Clinical Attachment Level

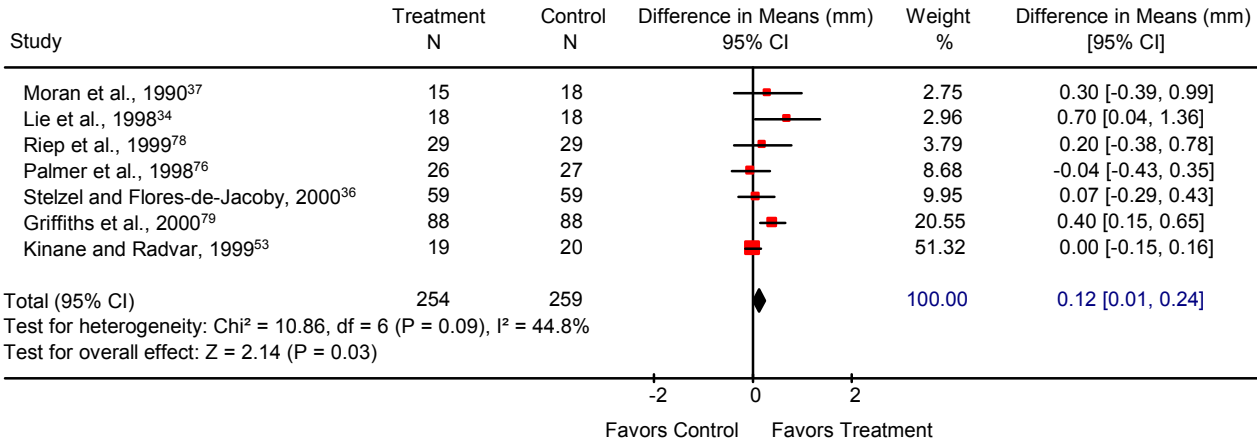


Figure 10. Meta-analysis of Local Chlorhexidine and SRP versus SRP Alone: Probing Depth

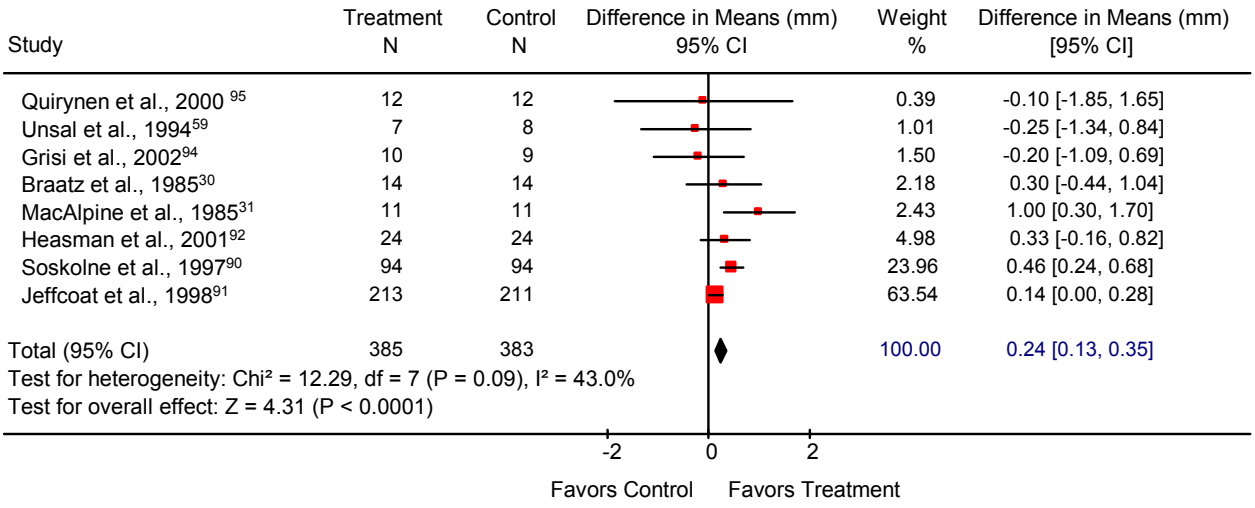
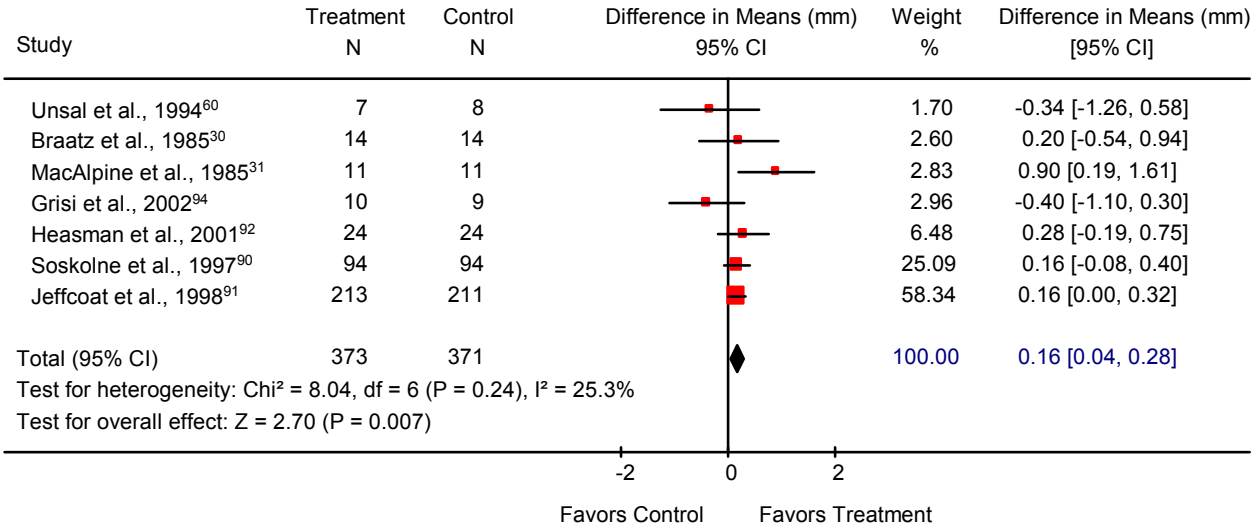


Figure 11. Meta-analysis of Local Chlorhexidine and SRP versus SRP Alone: Clinical Attachment Level



Chapter 4. Conclusions

Overview

The key question examined in this report was: How does the effectiveness of scaling and root planing therapy (SRP) by itself for the treatment of chronic periodontitis compare to SRP accompanied by adjunctive therapy at varying lengths of time? To focus the evaluation of effectiveness, we relied primarily upon two clinical measures – reduction in probing depth (PD) and gains in clinical attachment level (CAL) – and one specific microbial measure – percentage reduction of spirochetes.

A total of 70 studies (unduplicated) met our inclusion criteria for this evidence report. However, some of these studies had multiple arms involving different adjunctive treatments; therefore, we included some studies more than once in the synthesis (Chapter 3) and evidence tables (Chapter 7). We provide qualitative and descriptive information for all these studies in Chapter 3; in addition, we did a total of nine meta-analyses when we had three or more studies that provided appropriate data for a 6-month follow-up period (plus or minus 3 months).

The adjunctive therapies were all chemical antimicrobials, applied either locally or systemically, which we grouped into 11 separate categories: systemic and local tetracycline, systemic and local minocycline, systemic and local metronidazole, metronidazole in combination with amoxicillin (systemic), chlorhexidine (local), systemic and local other antibiotics, and other local antimicrobials. The populations, severity of periodontitis, types of teeth treated, number of teeth treated, and added supportive therapies used all differed from study to study. In addition, thoroughness of SRP also differed across studies; we accepted studies only when the investigators used the same SRP approach for both the treatment and control groups. Some of the studies performed modified Widman flaps as needed to gain better access for debridement of study teeth. The time periods covered for follow-up of the therapies also varied from only a couple of weeks to 13 years.

The studies demonstrated that, for virtually any length of follow-up period reported, SRP whether or not accompanied by an adjunctive therapy resulted in statistically and clinically significant PD reductions and CAL gains between the baseline and study endpoint measurements. Those data set a context within which to interpret our findings, but effects of SRP are generally well known and so that was not a question that we sought to examine.

Rather, as agreed by the sponsors (the National Institute for Dental and Craniofacial Research [NIDCR], the Agency for Healthcare Research and Quality [AHRQ]), our Technical Expert Advisory Group (see Chapter 1), and our clinical consultants and colleagues from the University of North Carolina and elsewhere, we set out to determine whether the available research findings on using chemical antimicrobial therapy with SRP made an *added* contribution beyond that of the SRP alone. In simple terms, this value is the result of subtracting the baseline-to-follow-up differences for the SRP-only (or SRP with placebo) groups from the baseline-to-follow-up differences for the experimental or treatment groups using SRP and adjunctive therapy, and we characterized this as the net PD reduction or net CAL gain in our discussion.

Summary of Results

Overall Comments

Table 16 summarizes our main findings, focusing on just the two clinical measures (PD and CAL) because those measures were far more commonly reported than changes in microbial environments (even changes in the percentages of spirochetes). We further focus in that table on just the number of "positive" studies – i.e., those that showed a statistically significant net PD reduction or net CAL gain favoring the adjunctive therapy in question. We specify the total number of studies and the number of positive studies (columns 1 and 3) and the range of effect sizes in millimeters for just those positive studies (columns 2 and 4). Finally, we recap the meta-analytic results, showing the overall estimated mean effect size in millimeters and the 95 percent confidence interval (CI) around that estimate (columns 2 and 4).

Across these 11 groupings of adjunctive therapies, we had a total of 84 intervention arms for PD reductions (recalling that some studies examined multiple types of antimicrobials). The two most commonly studied adjunctive therapies were local tetracycline (16) and chlorhexidine (17), followed by local metronidazole (11); least studied were systemic minocycline and the other local antibiotics (two each). Generally, investigators reported less frequently on gains in CAL, so we had only a total of 70 intervention arms; again, the commonly studied therapies were local tetracycline (16) and chlorhexidine (13), followed by local metronidazole and local minocycline (eight each), and the least studied were also systemic minocycline and other local antibiotics (two each).

We found it interesting to compare aggregate results (numbers of positive studies and percentages of total studies) for systemic and local therapies. Of the five categories of systemic therapies, we included 25 studies that measured PD reductions; of these, 7 (28 percent) reported a statistically significant net result favoring the adjunctive therapy (in this case metronidazole, metronidazole with amoxycillin, and various other systemic antibiotics). By contrast, of the six categories of local therapies, we included 60 studies with PD data; of these 16 (27 percent) reported a significant net result for the adjunctive therapy (mainly tetracycline and metronidazole).

For systemic therapies with CAL data, we included 19 studies; of these 6 (32 percent) reported net CAL gains favoring the adjunctive agent (tetracycline, metronidazole, and other systemic antibiotics). For the local treatments, we included 50 studies; of these, 11 (22 percent) had significant net gains (spread across all categories except the group of other antimicrobials).

In short, taking systemic and local applications together, tetracycline, metronidazole, and chlorhexidine were the most frequently studied therapies. PD reductions were measured slightly more often than CAL gains, but both were far more commonly reported than microbial changes. Some, but by no means all, investigators reported data by subgroups defined largely by baseline PD levels, but across those trials, the categories differed somewhat. For neither the systemic therapy studies nor the local therapy studies, taken as two groups, were more than about one-quarter to one-third reflective of statistically significant PD reductions or CAL gains.

Therapy-Specific Findings

Again referring mainly to Table 16, we summarize below the results from positive studies (as defined above) and our meta-analyses (i.e., the overall estimate of mean effect size and the 95 percent CI, with the number of studies in the meta-analyses noted in the text). Chapter 3 provides more details on both the qualitative and quantitative results.

Tetracycline

Systemic Tetracycline. Of the five studies of systemic tetracycline, all pointed in the direction of greater net improvement in PD, but none showed a significant difference. The mean effect size (three studies) was a nonsignificant 0.15 mm. Four of these studies reported on CAL gains, of which one had a significant 0.31 mm result favoring the adjunctive therapy. We did no meta-analysis on the CAL studies because one provided no quantitative data and two did not run the appropriate study period.

Local Tetracycline. For the locally delivered tetracycline (fibers, irrigation, gel, strips, ointment), the 16 studies included four with significant PD results ranging from 0.41 mm to 0.93 mm. The mean effect size (six studies) was 0.47 mm (95 percent CI, 0.22 to 0.72). Of these same 16 studies, two yielded significant CAL gains ranging from 0.15 mm to 0.48 mm. The mean effect size (nine studies) was 0.24 mm (95 percent CI, 0.07 to 0.42).

Taking a nearly half-millimeter of PD reduction as one that the practicing and academic dental community would likely regard as clinically meaningful, we would highlight this result for local tetracycline as providing consistent evidence supportive of the use of this particular therapy and modality. We are less certain that a CAL gain of 0.24 mm would be regarded as notable in clinical terms, but it does lend additional support to the conclusion that adjunctive local tetracycline confers some clinical benefit.

Minocycline

Systemic Minocycline. Only two studies involved systemic minocycline. Neither provided statistically significant results for either PD reduction or CAL gain. We did no meta-analyses on these trials.

Local Minocycline. Locally applied minocycline stands in some contrast to systemic minocycline. Eight studies tested minocycline in this modality (as ointment, gel, or microencapsulated powder). Overall, four of these studies had statistically significant net PD reductions ranging from 0.30 mm to 1.10 mm (the latter for patients with baseline PD of 7 mm or greater). The mean effect size (six studies) was 0.49 mm (95 percent CI of 0.40 to 0.58). The gain in CAL for the three studies reporting significant net gains ranged from 0.39 mm to 0.8 mm. The mean effect size (five studies) was 0.46 mm (95 percent CI, 0.32 – 0.60). Thus, as with local tetracycline, these nearly half-millimeter net improvements on the clinical measures might well be regarded as clinically meaningful.

Metronidazole

Systemic Metronidazole. Of the seven studies of systemically delivered metronidazole, most showed a pattern of greater net reduction in PD for at least some of their patient subgroups, but only two studies provided statistically significant results, with PD reductions ranging from 0.47 mm (for patients with baseline PD of 4 mm to 6 mm) to 1.64 mm (for patients with baseline PD of more than 6 mm). With respect to CAL gains, two of five studies reported significant net improvements for the adjunctive therapy, ranging from 0.47 mm to 1.19 mm (in both cases only for patients with relatively deep PD at baseline). We did not do meta-analytic estimates of the mean effect size for either of these measures because of lack of data or the length of the study.

Local Metronidazole. Four of the 11 studies of locally delivered metronidazole (irrigant, gel, strips) yielded significant net PD reductions ranging from 0.18 mm to 0.80 mm (one study did not report specific data). The mean effect size (seven studies) was 0.32 mm (95 percent CI, 0.20 to 0.44). The statistically significant CAL gains in two of the eight studies ranged between 0.40 mm and 0.66 mm; the mean effect size (seven studies) was only 0.12 mm (95 percent CI, 0.01 to 0.24). Thus, although both clinical measures appear to reflect statistically significant impacts of local metronidazole, the clinical importance of the CAL gains might be debated.

Metronidazole and Amoxicillin Combination

Of the four studies of this systemically given combination of drugs, one reported a statistically significant net PD reduction of 0.7 mm; none reported any data for significant CAL gains favoring the drug therapy. We did no meta-analyses of these studies because no more than two reported any specific data.

Chlorhexidine

Our review included 17 studies of locally administered chlorhexidine (irrigant, rinse, gel, chip). Many of the studies had small numbers of subjects but larger numbers of sites or pockets as the unit of analysis. Even so, only three of these trials (all using chlorhexidine chips) produced statistically significant PD reductions for the experimental groups, ranging from 0.26 mm to 0.46 mm. The mean effect size (eight studies) was 0.24 mm (95 percent CI, 0.13 mm to 0.35 mm).

CAL gains were generally lower: three studies with significant results ranging from 0.16 mm to 0.28 mm. The mean effect size (seven studies) was 0.16 mm (95 percent CI, 0.04 mm to 0.28 mm), practically speaking the same as for the reduction in PD.

The chlorhexidine results seem to point to about a one-fifth to a one-quarter millimeter of improvement in these clinical measures. These are statistically significant results, but we remain uncertain as to whether they should be considered clinically meaningful.

Other Systemic Antibiotics

The seven trials in the group of other systemic antibiotics (doxycycline, spiramycin, the combination of spiramycin and metronidazole, azithromycin, amoxicillin and clavulanic acid, and amoxicillin plus chlorhexidine rinse) were quite heterogeneous in size, duration, and other variables, and we were not able to combine any into a meta-analysis. Of these, three had reported statistically significant results for PD reductions, which ranged from 0.47 mm (for spiramycin capsules) to 0.87 mm (for azithromycin among patients with initial PD levels of 6 mm or greater). Two claimed significant results for CAL gains; only one gave specific data (a gain with doxycycline of 1.3 mm). Given the diversity of these therapies, modalities, and overall study designs, we believe caution is warranted in interpreting them as convincing evidence of effectiveness, especially in the light of the generally negative results for other, more commonly studied systemic antibiotics.

Other Local Antibiotics

Only two trials dealt with other local antibiotics (doxycycline gel and ofloxacin inserts), and only the one with doxycycline provided data showing a 0.44 mm PD reduction and a 0.37 mm CAL gain. These results are perhaps promising, as they come from a trial examining 108 treatment and 108 control sites, but they should also be interpreted in the more conservative context of multiple studies of more commonly used local adjunctive therapies.

Other Antimicrobials

Neither is it possible to say much about the collection of five studies (one with two experimental arms) grouped together as other antimicrobials (amine flouride gel, stannous fluoride gel, triclosan gel and dentifrice, hydrogen peroxide, povidone iodine, and tetrapotassium perioxydiphosophate), all of which are locally delivered. As regards PD reduction, one trial reported an 0.8 mm net reduction at 52 weeks for hydrogen peroxide; for CAL gains, no study had significant improvements favoring the treatment group. Given the appreciable heterogeneity across these studies, we did no meta-analyses on other antimicrobials. In the light of the level of improvements from adjunctive use of some local antibiotics, the PD findings for hydrogen peroxide may seem promising, but they are from only a single small study.

Concluding Comments

Several themes emerge from these findings. First, PD reductions seemed to be more frequently measured (and statistically significant) than CAL gains although the two are clearly related; whether this has any practical or clinical ramifications is debatable, however. Second, adjunctive local antibiotics appeared to have more impact than adunctive systemic antibiotics, measured in terms of net PD reductions or CAL gains relative to SRP alone. Third, judging from trials with statistically significant results based on either our qualitative synthesis or our meta-analyses, the major PD reductions were in the range of about one-quarter to one-half millimeter, and the major CAL gains in the range of about one-tenth to one-half millimeter. As noted earlier, we take no stand on what might be considered a clinically meaningful change, but note that if the dental community were to consider improvements in the neighborhood of 0.50 mm as clinically important, then some of the therapies studied here do fall into that domain.

Fourth, combining PD and CAL results suggests that local minocycline might be the most promising adjunctive therapy (meta-analysis estimates of 0.49 mm for PD reduction and 0.46 mm for CAL gain), followed by local tetracycline (estimates of 0.47 mm for PD reduction and 0.24 mm for CAL gain). Local metronidazole and chlorhexidine results are well below these levels.

Fifth, in the absence of statistical significance, or when the evidence base is very small in terms of overall numbers of studies, the question of whether the evidence for adjunctive treatment is meaningful in a clinical sense does not need to be addressed, except to say the available evidence does not support its use. On the basis of the literature reviewed in this report, some experts might reach this conclusion for systemic tetracycline, systemic minocycline, systemic metronidazole, metronidazole with amoxicillin, and the various other systemic or local antibiotics and antimicrobials; others might disagree.

Sixth, by and large, harms from these adjunctive therapies are relatively minor. We take note, however, of concerns about bacterial resistance from overuse of systemic antibiotics, and we would urge that the positive findings reported here be interpreted in terms of whether the PD or CAL improvements justify that risk (for the individual patient but, perhaps more importantly, over the population).

Seventh, other important factors – supportive and follow-up care as well as self-care – may well affect the long-term periodontal status of patients as much if not more than use of these adjuncts to SRP, perhaps especially for patients with relatively early or moderate periodontitis. We did not review any body of literature directly on this point, but some results of trials that we did review suggested that added effectiveness of adjunctive treatment was greater in circumstances of more severe periodontitis where supportive or self-care may be less well executed. These situations may include patients with refractory periodontitis or who have deep pockets, defects or furcation involvement, or circumstances in which modified Widman flap surgery is not done (which would enable proper debridement of otherwise hard-to-reach areas). Routine use of appropriate (i.e., efficacious) adjunctive therapies might arguably be reserved for patients such as these.

Eighth, we cannot say from the trials reviewed here now how long the added effects of adjunctive treatment last (regardless of whether we would conclude they are either statistically or clinically significant). The endpoints for these studies varied tremendously, and even trying to narrow the field for the meta-analysis to trials lasting 6 months required us to allow in results from trials lasting 3 months to 9 months. What seems to occur in these studies is that if the adjunctive treatment is to have a more positive clinical effect (e.g., reduce PD or increase CAL) than SRP alone, then that effect seems to appear within a few weeks (1 to 2 months). However, with time, the difference in effect between SRP alone and SRP with adjunctive therapy narrows. Nonetheless, at all time periods, the SRP with adjunctive therapy seems to be more effective than SRP only, even if the net differences are quite small and not statistically significant.

Finally, putting all these results into the context of the results of SRP alone is imperative. SRP alone seems to produce significant improvements in mean PD reductions or CAL gains in the range of 1.5 mm to 2 mm or more, clearly making it the standard for nonsurgical (and nonpharmacologic) treatment of chronic periodontitis. The improvements produced by adjunctive antimicrobials beyond those levels – i.e., approximately one-quarter to one-third of the impact of SRP alone – pose a difficult "value" question for clinicians and patients alike that goes quite beyond the question of what adjunctive antibiotics to use. For example, one can

question whether these improvements justify the added effort on the part of periodontists and dentists (and their staffs) or of patients or the likely added costs (either to dental insurance plans or to patients facing out-of-pocket payments). Moreover, as discussed in the next chapter, this literature on adjunctive therapies has enough drawbacks and gaps that a substantial research agenda remains before many of these issues can be resolved.

Table 16. Summary of Qualitative and Quantitative Results for Probing Depth and Clinical Attachment Level

	Probing Depth Reductions		Clinical Attachment Level Gains	
Adjunctive Therapy	**Number of Studies/ Number of Positive Studies***	**Effect Sizes (in mm): Range and Meta-Analytic Estimate (95% CI) †**	**Number of Studies/ Number of Positive Studies**	**Effect Sizes (in mm): Range and Meta-Analytic Estimate (95% CI)**
Tetracycline, systemic	5/0	Range: NA MA : 0.15 (-0.29 - 0.58)	5/1	Range: 0.31 MA: none done
Tetracycline, local	16/5	Range: 0.40-0.93 MA: 0.47 (0.22 - 0.72)	16/2	Range: 0.15 - 0.48 MA: 0.24 (0.07 - 0.42)
Minocycline, systemic	2/0	Range: NA MA: none done	0/0	Range: NA MA: none done
Minocycline, local	8/4	Range: 0.30‡ – 1.10§ MA: 0.49 (0.40 - 0.58)	8/3	Range: 0.39 – 0.80 MA: 0.46 (0.32 - 0.60)
Metronidazole, systemic	8/3**	Range: 0.47¶ – 1.64‖ MA: none done	6/2	Range: 0.47¶ – 1.19# MA: none done
Metronidazole, local	11/4**	Range: 0.18 – 0.80 MA: 0.32 (0.20 - 0.44)	8/2	Range: 0.40 – 0.66 MA: 0.12 (0.01 – 0.24)
Metronidazole with amoxicillin, systemic	4/2**	Range: 0.7 MA: none done	4/1**	Range: NR MA: none done
Chlorhexidine, local	17/3	Range: 0.26 – 0.46 MA: 0.24 (0.13 - 0.35)	13/3	Range: 0.16 – 0.28 MA: 0.16 (0.04 – 0.28)
Other antibiotics, systemic	7/3**	Range: 0.47 – 0.87†† MA: none done	6/2**	Range: 1.30 MA: none done
Other antibiotics, local	1/1	Range: 0.44 MA: none done	1/1	Range: 0.37 MA: none done
Other antimicrobials, local	5/1	Range: 0.8 MA: none done	4/0	Range: NA MA: none done

*Positive studies are defined as those showing statistically significant effects in favor of the adjunctive therapy as contrasted with scaling and root planing alone. For details on studies, see the specific text tables in Chapter 3 or evidence tables in Chapter 7.
†CI, confidence interval; MA, meta-analysis; mm, millimeters NA, Not applicable; NR, not reported.
‡ 0.30 mm PD reduction for baseline probing depths of 5 mm or greater.
§1.10 mm PD reduction for baseline probing depths of 7 mm or greater.
¶ 0.47 mm PD reduction and CAL gain for baseline probing depths of 4 mm to 6 mm.
‖ 1.64 mm PD reduction for baseline probing depths of more than 6 mm.
1.19 mm CAL gain for baseline probing depths of more than 6 mm.
** One of these studies did not report any specific data, only a significant difference.
†† 0.87 mm PD reduction for baseline probing depths of 6 mm or greater.

Chapter 5. Recommendations for Future Research

Clinical Issues Concerning Antimicrobials

Our recommendations for further research on the role of antimicrobials as adjuncts in the treatment of chronic periodontitis reflect several concerns. First, some issues remain for the specific key question of this evidence report, which dealt with the *added* effectiveness of particular antimicrobials when they are used as an adjunct to scaling and root planing (SRP), including whether any antimicrobials warrant further investigation in this regard. Second is the design and analysis of any future studies of this question, as the limitations of the existing literature are not trivial. Some of those limitations may relate to the actual reporting of the trials or other studies reviewed here, not the underlying design and conduct of the investigations per se. Moreover, the research reviewed in this evidence report provides a fairly broad range of expected effects of adjunctive antimicrobial use, but those effects remain far smaller in magnitude than the benefits achieved by SRP alone. A third topic, therefore, centers on the issue of what size difference between SRP alone and SRP with an adjunctive antimicrobial has clinical significance or relates to outcomes of particular meaning to patients and their dentists or periodontists.

We are limiting our consideration of future research directions or priorities to which antimicrobials, if any, warrant further examination in the context of use as adjuncts to SRP. We did not review literature relating to, for instance, antimicrobial use as an alternative to SRP, and we did not include every possible antimicrobial, in every possible modality, in this evidence report. Therefore, we do not comment further on any potential for new research in those areas. We also do not comment on research focused solely on the effectiveness of SRP per se, which appears to be well grounded in robust evidence accumulated over the years, as that was not a key question for this systematic review.

Types of Antimicrobials

Of all the medications we did review in this evidence report, three would seem to have had sufficient promise as SRP adjuncts to justify continued investigation: tetracycline, minocycline and perhaps chlorhexidine and metronidazole. We base this conclusion on those results that seem to show that these pharmaceuticals, in either local or systemic form, conferred at least some extra benefit that was statistically significant when used in conjunction with SRP. The main outcomes in which this benefit occurred tended to be reductions in probing depth (PD) or gains in clinical attachment level (CAL), not in reductions in the presence of bacterial agents (specifically spirochetes).

With respect to tetracycline, the evidence for effectiveness of the drug applied locally, measured as reductions in PD, appeared to be fairly consistently statistically significant in the literature we reviewed. Further investigations of locally administered minocycline and doxycycline, both tetracycline-like antibiotics, may also provide better insights into their utility as SRP adjuncts. Remaining issues include the magnitude of the PD reductions and how long those reductions persist. As for adjunctive chlorhexidine, the evidence appears to substantiate statistically significant improvements in terms of reduction in PD and gain in CAL; however, the improvements over SRP alone are very modest, and how long they persist without continued treatment also remains to be established. The third antimicrobial with sufficient evidence

appears to show fairly consistent, statistically significant differences between treatment and control groups in reducing PDs is metronidazole; by extension, metronidazole in combination with amoxicillin seems to produce similarly encouraging results.

Thus, we would be comfortable in encouraging additional research to document more clearly whether these positive directions are real for these particular antimicrobials, the size of the improvements, and the time periods over which such improvements last. Narrower questions involve whether such results are similar across patients with different initial PDs or other clinical characteristics or whether positive results tend to be observed more in patients with more severe chronic periodontitis (e.g., initial PDs of 6 mm or more).

By and large, too few studies provided enough information to permit a thorough review of the possible impacts of antimicrobials, *in the specific role of adjunctive therapy*, on the presence (or absence or elimination) of pathogenic bacterial species. On balance, we judge the important goals of SRP with or without adjunctive therapy to be improvements in clinical measures related to possible bone or tooth loss and in patient-oriented outcomes. Nonetheless, chronic periodontitis is an infectious disease or inflammatory process for which the putative causative organisms most important for initiating or sustaining the disease have not been definitively identified. Therefore, continuing to investigate what organisms are most important in chronic periodontitis and the effects of adjunctive antimicrobial use on them may still be an important step in well-designed future studies.

The remaining antimicrobials reviewed in this report might warrant additional research, but it would have to be designed, in the first instance, to establish whether they can be expected to deliver consistently statistically significant added benefits over SRP alone. All in all, we would recommend that the dental research community and funding agencies put higher priority on clarifying the impacts of the three main antimicrobials noted earlier, rather than continuing to mount research on agents that have not, to date, shown as much promise.

Clinical Significance of Potential Benefits

A critical gap in the evidence base assembled so far concerns what clinical meaning to attach to differences in PDs, CALs, or other measures between what is achieved with SRP alone and what is achieved with SRP and adjunctive antimicrobials. Much of this literature commented on "before and after" measures of PD, CAL, and the like *within* treatment and control groups; the studies often did not give their own results about the net differences *between* treatment and control groups at the close of the follow-up period (that is, the "differences between the differences"). Where those data were available, or where we could calculate them, we determined that these net differences were often relatively small, at least on average across patients with different baseline levels of PD.

Thus, even in the face of statistical significance, the dental field is left without a good sense for the clinical significance of these comparatively small net improvements. One problem is that large samples can produce statistically significant results that have little, if any, clinical significance or relevance for the typical practice of periodontology. For that reason, statistical significance should never be the sole criterion by which to interpret these research results. By extension, the dental community must consider clinical factors as well as have an appreciation of the value of these net changes in terms that relate to outcomes valued by patients (e.g., appearance, functioning, or pain).

Therefore, we recommend that, in future studies of these medications as adjuncts to SRP, more attention be given to what levels of improvement should be considered clinically significant. Such information is needed to help guide changes in actual dental practice. One useful step for researchers is to attempt to reach some consensus on what extent or range of expected improvement in PD or CAL should be the goal of the adjunctive treatment. In so doing, in conjunction with newer studies as suggested above, dental researchers might then be able to narrow the field of eligible antimicrobial agents even further, providing a better knowledge base for options in dental practice.

Other Research Questions

Our evidence report did not deal with issues of costs or cost-effectiveness of antimicrobials as adjuncts to SRP, partly for reasons of time and resource availability and partly for lack of solid evidence on effectiveness in the first place. The first priority, as suggested above, is to understand the marginal benefits of adjunctival medications over SRP alone and which ones provide clinically meaningful marginal benefits. At that point, however, questions of the marginal costs of those medications comes into play and, from that, questions of the relative cost-effectiveness of different medications become important. We would recommend, as future research begins to answer the first-order clinical questions, that data be collected to address the economic ramifications of the use of antimicrobials as adjuncts to SRP.

Some experts in the field noted the paucity of information on so-called patient-oriented outcomes in this research base. We would agree that more work needs to be done, once the clinical significance of the current measures of periodontal health is clarified, on correlating these with health status or quality-of-life measures that matter to patients. These might include domains involving pain, eating and nutrition, concerns about appearance, impacts on social interaction, as well as effects of the disease and treatment options on usual daily activities (e.g., days lost from work) and on their out-of-pocket costs of care.

At the outset, we aimed to use reduction or elimination of bacterial causative agents as an important outcome variable, but this proved problematic because of the variety of species that appeared in this literature, the variety of ways changes in the presence or absence of these species were reported, and the fact that commonly reported species are not considered by some experts as comprehensive enough. Thus, as a sidelight to research on the specific issues of adjunctive antimicrobial therapy might be further studies that focus on clarifying the broad range of bacterial agents culpable in chronic periodontitis and their relative significance in this disease process, the effectiveness of therapy in eliminating or at least suppressing these pathogens, and correlating results about specific bacterial species with results relating to changes in clinical measures such as PD or CAL.

Improving Study Design and Conduct

Chapter 3 noted many of the difficulties we encountered in identifying appropriate research articles that would meet our *a priori* inclusion criteria and then in reviewing the included material in any coherent and systematic way. We may thus have omitted some relevant literature from this report, but even more important is the likelihood that some of the research that we did include could not be fully used or was open to incorrect interpretations because of poor reporting practices, confusing study designs, underpowered studies, and poorly conducted investigations.

The reporting practices may be the easiest to correct in the future (even though analysis and reporting of the data from these types of studies seem to have improved in recent years). Several authoritative statements from international groups provide clear instructions on appropriate ways to report on systematic reviews (QUORUM[105]), randomized controlled trials (CONSORT[106]), and observational studies (MOOSE[107]). Authors and journal editors alike should take heed of these guidelines as a critical step in improving this literature overall.

Other guidance can come from the growing movement to grade the quality of individual articles that are included in reviews such as this one to begin with. Among the critical work now available is a lengthy report on systems to grade the quality of studies (i.e., articles) and rate the strength of evidence from the RTI-University of North Carolina Evidence-based Practice Center[39] and related methods of the US Preventive Services Task Force.[108]

Study design issues, such as randomization, allocation concealment, blinding, and similar elements, must be given more careful consideration. Randomization should be a standard for all trials in this area. Use of placebo controls, and not simply variation in treatment arms, will be another useful step for trials attempting to establish the efficacy of a given medication. Every effort should be made to blind (mask) all parties (subjects, treatment providers, and outcome examiners) to the group (treatment arm[s], control) to which the patients belong. This is necessary to reduce the possibility of bias, which past research suggests typically exaggerates the effect of the treatment over what is experienced in the control group. In keeping with the reporting standards noted above, investigators should report clearly on randomization, control groups, and level of blinding achieved in their studies.

In addition, the study sample should be large enough to have adequate power to detect a statistically significant and clinically desired difference. Many of the studies we reviewed had apparently reasonable effect sizes, but they were based on small samples with large variances and could not have reached statistical significance. The problem here may be two-fold: the size of the original samples and the possibility of attrition (especially for studies with very long follow-up periods) such that samples at completion of the study became too small to provide adequate power for the analyses. This latter issue may pose particular challenges for investigators who propose to carry out intention-to-treat analyses but have instead to rely on final data only on completers.

Study reports often were unclear as to the underlying denominators for results, sometimes reporting on persons enrolled but then presenting data on some other unit. Thus, researchers should make it clear what the unit of analysis is – persons, teeth, sites, or pockets – and on what basis their means and measures of variance have been calculated. Specifically, investigators should ensure that their reports specify the number of units on which the mean for each group has been calculated and the variance (either standard deviation or standard error). Without this or comparable information, they or others cannot easily include the results in meta-analyses.

In addition, when using split-mouth designs, analytic techniques that take into account the nesting of observations within subjects need to be used, and when tests of statistical significance between groups are performed on multiple groups, techniques that adjust for the true significance level need to be used and reported. It remains to be demonstrated whether split-mouth designs of local therapies can adequately control the contamination or spill-over effect to be able to measure the true difference between the test and control groups.

Researchers in this area need to establish what measures are most meaningful for reporting treatment effects. Reaching some consensus on core outcomes for studies would help immensely for future systematic reviews on these topics, because the sheer number of possible outcomes complicated our work. With the inputs from our technical expert panel and representatives of the sponsors of this review, we selected PD reduction and CAL gain as the targeted clinical outcomes for several reasons. They appeared fairly frequently and consistently in the literature over the period covered by our review. They are also meaningful measures for clinicians, who can take such measures themselves to monitor the effects of treatment on their own patients. In the more recent literature, however, we saw a move away from reporting outcomes in terms of these metrics to outcomes that are somewhat less easy to understand or to measure objectively and reliably. Among them are variables such as percentage changes in prognosis, shifts from one category of treatment to another (extraction or surgery to maintenance), and other measures involving time (e.g., period of noninfection, time to recurrence). Moreover, investigators would find that easily used and understood statistical techniques are more readily available for analysis of metric data than for the analysis of percentages. A consistent, agreed-upon set of "critical" outcome measures would foster better comparisons across research projects and with past research. If the field moves to some of these newer outcome variables, attention will need to be given to standardizing how they are defined and reported and developing ways to convey absolute results and variances.

Some observers have noted that this literature contains little about measurement error and how it might affect reported results. Among the concerns are ambiguities about the level of training of those doing the SRP, the extensiveness and thoroughness of the SRP, the level of training and standardization of persons collecting the clinical measures, inaccuracies in measuring PD or CAL (or level of pre-existing inflammation), reliability of measurements across multiple examiners, and similar factors subject to variability in assessment and reporting. Moreover, time devoted to SRP, which is now the best proxy for the thoroughness of SRP, is a relatively imprecise measure and does not, in any case, ensure that SRP treatment was comparable across studies, patients, teeth, surfaces, or sites. Among the suggestions for overcoming some of these problems, at least in research venues, is the use of fiber optic devices that permit visual inspection of root surfaces and determination of the thoroughness of subgingival calculus removal and the level of cleanliness and smoothness of the root surface. The idea is that teeth (or surfaces, etc.) would be considered eligible for entry into a trial only after they had met some basic standard of SRP success. Whether moving to such a direct measure of SRP performance in place of time spent on SRP would yield more reliable and valid results, given the presumed additional costs to the research project, is itself an empirical question.

Finally, investigators need to be clearer as to the underlying diagnoses for their subjects. This point concerns two sources of ambiguity for those involved with developing the evidence based on these questions. The first problem is the mix of terms different research teams used for what was apparently the same disease: sometimes periodontal disease, sometimes periodontitis, with several different adjectives (adult, chronic, severe, moderate, mild) used, sometimes alone and sometimes in combination. We made every effort to focus this review on chronic periodontitis in adults (and in particular to eliminate studies in which patients could have had refractory or aggressive periodontitis), but on occasion we needed to draw an inference as to whether chronic periodontitis was indeed the disorder in question. Greater standardization of disease descriptors and their definitions, at least for use by the research community, would be helpful.

The second issue concerned whether subjects were being treated for periodontitis for the first time or were being retreated for chronic periodontitis. This confusion reflected in part the unpredictable use of descriptors such as recurrent, persistent, or refractory; although refractory may have a generally well-understood meaning within the periodontal and dental research community, recurrent and persistent have less agreed-upon definitions or connotations. The current literature generally did not make clear whether persons receiving retreatment had unsuccessful earlier treatment or were simply being retreated after successful treatment at some time in the past (i.e., were on some form of maintenance schedule). If researchers are including "maintenance" patients in their trials, they should explain this decision. More generally, investigators need to be certain that they are including only the types of patients for whom positive results from the particular study would be applicable in everyday practice.

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Evidence Tables

*	Calculated by review team
A.a	Actinobacillus actinomycetemcomitans
ANCOVA	Analysis of Covariance
ANOVA	Analysis of Variance
API	Approximal plague index
Appts.	appointments
BANA.	Benxoyl-DL-Arginine-Naphthylamide test
B.f..	Bacteroides forsythus
B.g..	Bacteroids gingivalis
bid	Two times daily
B1	Bleeding
BL	Bone Loss
BOP/SBI	Bleeding on Probing
C	Control Group
C.r..	Campylobacter rectus
CAG	Chronic Atrophia Gastritis
CAL	Clinical Attachment Level/Loss
CDI	Cell-directed Inhibitors
CHX	Chlorhexidine
CIS	Simplified Calculus Index
CPITN.	Community Periodontal Index of Treatment Needs
Diff	Difference
E.c..	Eikenella corrodens
EDTA	Ethylenediaminetetracetic Acid
GCF	Gingival Crevicular Fluid
GI	Gingival Index or Gingivitis Index
GLM	General Linear Models
Grad.	Graduate Grp Group
HCI	Hydrochloride
Ind.	Index
JP	Juvenile Periodontitis
LAP	Localized Aggressive Peridontitis
LoA	Level of Attachment
max.	Maximum
Mg.	Milligram
MGI.	Modified Gingival Index
min.	Minute
mm	Millimeter
mg/ml.	Milligrams per milliliter
MMP-8	Metalloproteinas-8
Mo	Month
NA.	Not Applicable, measure not part of study
ng/ml.	nanogram per milliliter
NR	Not reported
NS	Not significant
P	Probability
PAL	Probing Attachment Level
PBI	Papilla Bleeding Index
PD	Probing Depth
PDI	Peridontal Disease Index
P.g.	Porphyromonas gingivalis
P.i.	Prevotella intermedia
PlI	Plaque Index
PD	Probing Depth Pocket
Pts	Patients
quad.	Quadrant
RCT	Randomized Controlled Trial
Rmg.	Remaining
RP	Root Planing
SBI	Sulcus Bleeding Index
SD	Standard Deviation
SDD	Subantimicrobial Dose Doxycycline
se	Standard Error
sig.	significance
SL	Stomelysin
SRP	Scaling and Root Planing
T	Treatment Group
TC	Triclosan
T.d.	Treponema denticola
TET	Tetracyline
tid	Three times daily
TIMP	Tissue Inhibitor of Metalloproteinases
Txt	Treatment
wk.	Week
w/w.	Weight percent
x.	Per
Yr	Year

Evidence Table 1a. Effectiveness of Systemic Tetracycline as an Adjunct to Scaling and Root Planing to Treat Chronic Periodontitis

Study Description	Study Design Characteristics	Disease Characteristics	Examiner Characteristics	Description of Scaling and Root Planing
Haffajee et al., 1995[46] **Study Period:** 43 weeks (10 months) **Study/Treatment Site:** Hospital Dental Clinic **Location:** USA **Patients Selected:** Originally 98 patients aged 14-71 with evidence of prior attachment loss, at least 20 teeth and at least 4 pockets >4 mm and 4 sites of LOA >3mm, no localized JP. From this pool, subjects exhibiting LOA >2.5 mm at = 1 sites anytime during 6 months observation period were admitted to study	**Design Type:** RCT **Subject/Site Allocation:** Random **Blinding:** Examiners and patients blind **Placebo:** Yes **Split-mouth:** No	**Severity:** Active disease, no rapidly progressing periodontal disease **Types of Teeth:** All excluding third molars **Widman flap:** Yes, at active sites and where PD > 4mm	**Number:** 1 **Trained:** NA **Assigned to Subjects:** Same examiner throughout study	**SRP performed:** Scaling and root planing by quadrant, approximate 10 day intervals, repeated during course of study every 3 months for 1 yr **Time spent on SRP:** NR

Evidence Table 1a. Effectiveness of Systemic Tetracycline as an Adjunct to Scaling and Root Planing to Treat Chronic Periodontitis (continued)

Eligible Study Groups and How Defined:	Study Group Characteristics	Compliance Monitoring	Baseline Measures	Time Interval(s)
Subject/Site allocation: 24 subjects, 6 sites per tooth T: 13 subjects C: 11 subjects **Dose, Mode, Schedule:** All rinsed with 0.12% chlorhexidine for 30 days T: SRP plus 250 mg tetracycline 3xday for 30 days C: SRP plus placebo (250 mg sucrose) 3xday for 30 days	**Age:** Mean All: 48 ± 12 Mean T: 44 ± 15 Mean C: 48 ± 11 **Gender:** All: 57% Male T: 62% Male C: 55% Male **Race/Ethnicity:** NR	NR	Before SRP	6 times (at baseline and 2, 4, 6, 8, and 10 months)

Evidence Table 1a. Effectiveness of Systemic Tetracycline as an Adjunct to Scaling and Root Planing to Treat Chronic Periodontitis (continued)

Study Description	Outcomes Assessed	Adverse Effects	Study Group Attrition and Reasons	Type of Analysis
Haffajee et al., 1995[46] (continued)	**Clinical Measurement:** BOP/SBI PD CAL GI **Radiographic Techniques:** NR **Microbiological Methods:** DNA probes and colony lifts for 14 taxa in 29 of 40 subjects **Subject Self Report:** NR	NR	NR	**Type of analysis reported:** Mann-Whitney and Kruskal-Wallis, change by site, averaged for individual, then averaged for group

Evidence Table 1a. Effectiveness of Systemic Tetracycline as an Adjunct to Scaling and Root Planing to Treat Chronic Periodontitis (continued)

	Outcomes Accessed			
	Attachment Level mm	Probing Depth mm	Spirochetes	
(N of Pts)	$\bar{x}$ (SD)	$\bar{x}$ (SD)	$\bar{x}$ % (SD)	Comments
Baseline:				Only baseline values presented in table. Change score mostly presented in bar graphs. Text presents change scores for PD, but not the associated SDs.
T: 13	3.6 (1.1)	3.8 (0.5)	NA	
C: 11	3.5 (1.2)	3.6 (0.5)	NA	
Final: 43 weeks (10 months)				
T: 13	NR	NR	NA	
C: 11	NR	NR	NA	**Quality Score:** 62; 46
Change:	Gain	Reduction		
T:	0.49 (NR)	0.75 (NR)	NA	
C:	NR	0.46 (NR)	NA	
Test:	Mann Whitney Test	Mann Whitney Test		
P value:	NS	NS		

Evidence Table 1a. Effectiveness of Systemic Tetracycline as an Adjunct to Scaling and Root Planing to Treat Chronic Periodontitis (continued)

Study Description	Study Design Characteristics	Disease Characteristics	Examiner Characteristics	Description of Scaling and Root Planing
Author and Year: Lindhe et al, 1983[44] **Study Period:** 50 weeks **Site of Study:** Dept of Periodontology, Univ of Gothenburg, Sweden **Location:** Gothenburg, Sweden **Patients Selected:** Referral patients with at least 20 teeth, and 4 pairs of diseased sites around contralateral premolars or incisors with = 6 mm PD and = 40% bone loss	**Design Type:** RCT **Subject/Site Allocation:** Random **Blinding:** Examiners and patients blind **Placebo:** Yes **Split-mouth:** Yes, for SRP No, for inter-vention	**Severity:** Advanced periodontitis **Types of Teeth:** Premolars and incisors **Widman flap:** No	**Number:** NR **Trained:** NR **Assigned to Subjects:** NR	**SRP performed:** Meticulous scaling under anesthesia (half mouth) requiring 2-4 visits during course of week **Time spent on SRP:** NR

Evidence Table 1a. Effectiveness of Systemic Tetracycline as an Adjunct to Scaling and Root Planing to Treat Chronic Periodontitis (continued)

Eligible Study Groups and How Defined:	Study Group Characteristics	Compliance Monitoring	Baseline Measures	Assessment Time Interval(s)
Subject/Site allocation: 14 subjects T: 7 subjects C: 7 subjects **Dose, Mode, Schedule:** T: SRP plus 250 mg tetracycline 4xday for 2 weeks, then 250 mg 1xday for 48 weeks C: SRP plus placebo	**Age:** Range: 37-52 **Gender Distribution:** Male: 6 Female: 8 **Race/Ethnicity:** NR	NR	Before SRP	5 exams (at baseline, 2, 10, 20, and 30 weeks)

Evidence Table 1a. Effectiveness of Systemic Tetracycline as an Adjunct to Scaling and Root Planing to Treat Chronic Periodontitis (continued)

Study Description	Outcomes Assessed	Adverse Effects	Study Group Attrition and Reasons	Type of Analysis
Lindhe et al, 1983[44] (continued)	**Clinical Measurement:** OHI GI BOP PD CAL **Radiographic Techniques:** NR **Microbiological Methods:** Subgingival plaque; % coccoids, rods, spirochetes **Subject Self Report:** NR	NR	NR	**Type of analysis reported:** Full participants only

Evidence Table 1a. Effectiveness of Systemic Tetracycline as an Adjunct to Scaling and Root Planing to Treat Chronic Periodontitis (continued)

	Outcomes Accessed			
	Attachment Level mm	Probing Depth mm	Spirochetes	
(N of Pts)	$\bar{x}$ (SD)	$\bar{x}$ (SD)	$\bar{x}$ % (SD)	Comments
Baseline:				The PD values and spirochetes were measured at each exam. The CAL values are change scores from baseline. Standard errors are shown rather than standard deviations. **Quality Score:** 70; 77
T: 7	7.1 (0.4)	7.5 (0.3 se)	48 (3 se)	
C: 7	7.4 (0.5)	7.7 (0.4 se)	37 (10 se)	
Final: 50 weeks				
T: 7	NR	4.4 (0.1 se)	0 (0 se)	
C: 7	NR	5.4 (0.2 se)	8 (8 se)	
Change:	Gain			
T:	1.7 (0.3 se)	3.1* (NR)	NR	
C:	1.4 (0.3 se)	2.3* (NR)	NR	
Test:	NR	NR		
P value:	NR	NR		

Evidence Table 1a. Effectiveness of Systemic Tetracycline as an Adjunct to Scaling and Root Planing to Treat Chronic Periodontitis (continued)

Study Description	Study Design Characteristics	Disease Characteristics	Examiner Characteristics	Description of Scaling and Root Planing
Author and Year: Listgarten et al., 1978[43] **Study Period:** 25 weeks **Site of Study:** Central Hospital **Location:** Sweden **Patients Selected:** Wait-listed patients for periodontal care, patients had at least 3 pairs of contralateral teeth with PD of = 5 mm and 50% bone loss	**Design Type:** RCT **Subject/Site Allocation:** Random **Blinding:** NR **Placebo:** No **Split-mouth:** Yes, for SRP No, for intervention	**Severity:** Severe chronic periodontitis **Types of Teeth:** NR **Widman flap:** NR	**Number:** NR **Trained:** NR **Assigned to Subjects:** NR	**SRPperformed:** Series of weekly scalings requiring 2 to 4 appts for 2 selected quadrants 2 additional scalings at weeks 15 and 22; not described in terms of intensity **Time spent on SRP:** NR

Evidence Table 1a. Effectiveness of Systemic Tetracycline as an Adjunct to Scaling and Root Planing to Treat Chronic Periodontitis (continued)

Eligible Study Groups and How Defined:	Study Group Characteristics	Compliance Monitoring	Baseline Measures	Assessment Time Interval(s)
Subject/Site allocation: 12 subjects T: 6 subjects C: 6 subjects **Dose, Mode, Schedule:** T: SRP plus 250mg tetracycline 4xday for 2 two-week periods, separated by 4 weeks C: SRP only	**Age:** Mean: 34 Range: 27 - 42 **Gender Distribution:** Male: 7 Female: 5 **Race/Ethnicity:** NR	NR	Before SRP	3 times (at baseline and weeks 8 and 25)

Evidence Table 1a. Effectiveness of Systemic Tetracycline as an Adjunct to Scaling and Root Planing to Treat Chronic Periodontitis (continued)

Study Description	Outcomes Assessed	Adverse Effects	Study Group Attrition and Reasons	Type of Analysis
Listgarten et al, 1978[43] (continued)	**Clinical Measurement:** Gingival fluid flow GI PI PD CAL **Radiographic Techniques:** NR **Microbiological Methods:** Microbial composition Histological data Electron microscopy data **Subject Self Report:** NR	NR	NR	**Type of analysis reported:** Full participants only

Evidence Table 1a. Effectiveness of Systemic Tetracycline as an Adjunct to Scaling and Root Planing to Treat Chronic Periodontitis (continued)

	Outcomes Accessed			
	Attachment Level mm	Probing Depth mm	Spirochetes	
(N of Pts)	$\bar{x}$ (SD)	$\bar{x}$ (SD)	$\bar{x}$ % (SD)	Comments
Baseline:				No statistical testing of change scores between groups. No data reported for CAL, text says "no detectable change occurred."
T: 6	NR	7.2 (0.5 se)	36.3 (5.2 se)	
C: 6	NR	7.0 (0.6 se)	34.8 (6.2 se)	
Final: 25 weeks				
T: 6	NR	4.8 (0.3 se)	6.5 (4.0 se)	**Quality Score:** 38; 31
C: 6	NR	4.8 (0.9 se)	6.3 (4.3 se)	
Change:				
T:	NR	2.4* (NR)	NR	
C:	NR	2.2* (NR)	NR	
Test:		NR		
P value:		NS		

Evidence Table 1a. Effectiveness of Systemic Tetracycline as an Adjunct to Scaling and Root Planing to Treat Chronic Periodontitis (continued)

Study Description	Study Design Characteristics	Disease Characteristics	Examiner Characteristics	Description of Scaling and Root Planing
Al-Joburi et al., 1989[45] **Study Period:** 24 weeks **Study/Treatment Site:** Several Universities **Location:** Canada **Patient Population:** Patients with = 2 sites with PD of = 7 mm, and at least 15 teeth	**Design Type:** RCT **Subject/Site Allocation:** Random **Blinding:** Examiners and patients blind **Placebo:** Yes **Split-mouth:** No	**Severity:** Advanced adult chronic periodontitis **Types of Teeth:** NR **Widman flap:** NR	**Number:** 2 **Trained:** NR **Assigned to Subjects:** Same examiner throughout study	**SRP performed:** Thorough scaling and root planing (intensive) completed in 2 visits, one week apart **Time spent:** 6 hours

Evidence Table 1a. Effectiveness of Systemic Tetracycline as an Adjunct to Scaling and Root Planing to Treat Chronic Periodontitis (continued)

Eligible Study Groups and How Defined:	Study Group Characteristics	Compliance Monitoring	Baseline Measures	Time Interval(s)
Subject/Site allocation: 96 enrolled in full study 79 completed full study 2 sites per subject 51 in relevant groups T: 27 completed C: 24 completed **Dose, Mode, Schedule:** T: SRP plus 250 mg tetracycline capsule 4xday for 14 days C: SRP plus placebo capsule 4xday for 14 days	**Age:** Mean: 46 ± 9 (full study) **Gender:** NR **Race/Ethnicity:** NR	Yes	Before SRP	5 times (at baseline and weeks 2, 8, 12, and 24)

Evidence Table 1a. Effectiveness of Systemic Tetracycline as an Adjunct to Scaling and Root Planing to Treat Chronic Periodontitis (continued)

Study Description	Outcomes Assessed	Adverse Effects	Study Group Attrition and Reasons	Type of Analysis
Al-Joburi et al., 1989[45] (continued)	**Clinical Measurement:** BOP/SBI PII PD CAL **Radiographic Techniques:** NR **Microbiological Methods:** Crevicular fluid microbiota Plaque microbiota **Subject Self Report:** NR	Yes, 1 subject excluded because of nausea	17 subjects excluded from full study: intercurrent but unrelated illness during the study which required taking antibiotics other than study medication (1); lost to follow-up (3); failed to take medication as prescribed (6); developed severe diarrhea (1)	**Type of analysis reported:** Full participants for these 2 study groups

Evidence Table 1a. Effectiveness of Systemic Tetracycline as an Adjunct to Scaling and Root Planing to Treat Chronic Periodontitis (continued)

	Outcomes Accessed			
	Attachment Level mm	Probing Pocket Depth mm	Spirochetes	
(N of Pts)	$\bar{x}$ (SD)	$\bar{x}$ (SD)	$\bar{x}$ (SD)	Comments
PD 1 to 3 mm:				The difference in the reduction in spirochetes between tetracycline group and SRP alone group was significant at 2 and 8 weeks
Baseline:				
T: NR	7.25 (0.46)	3.00 (0.00)	NR	
C: NR	7.50 (0.84)	3.00 (0.00)	NR	
Final: 24 weeks				
T: 27	7.06 (0.55)	2.88 (0.22)	NR	
C: 24	7.80 (0.82)	3.00 (0.16)	NR	% Spirochetes:
Change:				Baseline Final
T:	0.19 (NR)	0.12 (NR)		T: 26 (NR) 7 (NR)
C:	-0.30 (NR)	0.00 (NR)		C: 30 (NR) 11 (NR)
Test:				(P = 0.05)
P value:				
PD 4 to 5 mm:				**Quality Score:** 69; 62
Baseline:				
T:	9.06 (0.26)	5.21 (0.08)		
C:	9.11 (0.22)	5.25 (0.08)		
Final: 24 weeks				
T:	8.00 (0.27)	3.54 (0.14)		
C:	8.09 (0.21)	3.53 (0.12)		
Change:				
T:	1.06 (NR)	1.67 (NR)		
C:	1.02 (NR)	1.72 (NR)		
Test:	t-test	t-test		
P value:	NS	NS		
PD = 7 mm:				
Baseline:				
T:	10.58 (0.25)	7.40 (0.11)		
C:	10.75 (0.29)	7.60 (0.12)		
Final: 24 weeks				
T:	8.79 (0.26)	4.36 (0.21)		
C:	9.21 (0.34)	4.75 (0.24)		
Change:				
T:	1.99 (NR)	3.04 (NR)		
C:	1.54 (NR)	2.85 (NR)		
Test:	t-test	t-test		
P value:	NS	NS		

Evidence Table 1a. Effectiveness of Systemic Tetracycline as an Adjunct to Scaling and Root Planing to Treat Chronic Periodontitis (continued)

Study Description	Study Design Characteristics	Disease Characteristics	Examiner Characteristics	Description of Scaling and Root Planing
Ramberg et al., 2001[47] **Study Period:** 13 years (52 weeks of data reported) **Study/Treatment Site:** Department of Peridontology **Location:** Helsingborg, Sweden **Patient Population:** Adults referred to the clinic, with = 16 teeth (2 must be molars)	**Design Type:** Prospective clinical trial **Subject/Site Allocation:** No mention of how subjects were assigned to groups; age; and gender matched control **Blinding:** NR **Placebo:** Yes **Split-mouth:** No	**Severity:** Advanced periodontitis **Types of Teeth:** All teeth **Widman flap:** NR	**Number:** 2 **Trained:** NR **Assigned to Subjects:** NR	**SRP performed:** 4 to 6 sessions of non-surgical periodontal therapy under local anesthesia, during 3 week treatment interval. **Time spent:** 60 to 90 minutes

Evidence Table 1a. Effectiveness of Systemic Tetracycline as an Adjunct to Scaling and Root Planing to Treat Chronic Periodontitis (continued)

Eligible Study Groups and How Defined:	Study Group Characteristics	Compliance Monitoring	Baseline Measures	Time Interval(s)
Subject/Site allocation: 89 subjects T: 28 subjects C: 61 subjects **Dose, Mode, Schedule:** T: SRP plus 250 mg tetracycline tablet 4xday for 3 weeks and 0.2% chlorhexidine rinse 2xday C: SRP and 0.2% chlorhexidine rinse 2xday	**Age:** Mean: T: 41.2 C: 42.1 Range: T: 24-60 C: 23-66 **Gender:** T: Male: 16 Female: 19 C: Male: 38 Female: 42 **Race/Ethnicity:** NR	NR	Before SRP	4 times (at baseline and years 1, 3, 5, and 13)

Evidence Table 1a. Effectiveness of Systemic Tetracycline as an Adjunct to Scaling and Root Planing to Treat Chronic Periodontitis (continued)

Study Description	Outcomes Assessed	Adverse Effects	Study Group Attrition and Reasons	Type of Analysis
Ramberg et al., 2001[47] (continued)	**Clinical Measurement:** BOP PII PD all teeth, six sites/tooth CAL Number of teeth **Radiographic Techniques:** Bone Loss/Regeneration **Microbiological Methods:** NR **Subject Self Report:** NR	NR	Died (3), moved (18), withdrew from txt group (5)	**Type of analysis reported:** Full participants only

Evidence Table 1a. Effectiveness of Systemic Tetracycline as an Adjunct to Scaling and Root Planing to Treat Chronic Periodontitis (continued)

	Outcomes Accessed			
(N of Pts)	Attachment Level mm $\bar{x}$ (SD)	Probing Depth mm $\bar{x}$ (SD)	Spirochetes $\bar{x}$% (SD)	Comments
Baseline:				The mean individual PD value which was decreased between baseline and Year 1 had significantly increased between 5 and 12 years
T: 35	NR	4.2 (0.8)	NA	
C: 80	NR	3.9 (0.9)	NA	
Final: 52 weeks				
T: 28	NR	NR	NA	No sig difference in any measures reported for 3, 5, and 12 years
C: 61	NR	NR	NA	
Change: 52 weeks	Gain	Reduction		
T:	0.47 (0.6)	1.0 (0.8)	NA	**Quality Score:** 31; 23
C:	0.16 (0.5)	0.7 (0.7)	NA	
Test:	t-test	t-test		
P value:	< 0.001	NS		

Evidence Table 1b. Effectiveness of Local Tetracycline as an Adjunct to Scaling and Root Planing to Treat Chronic Periodontitis

Study Description	Study Design Characteristics	Disease Characteristics	Examiner Characteristics	Description of Scaling and Root Planing
Darhous et al., 1995[50] **Study Period:** 8 weeks **Study/Treatment Site:** Graduate Program University Clinic **Location:** Cairo, Egypt **Patient Population:** Adult patients with 4 to 7 mm PD	**Design Type:** Non-RCT **Subject/Site Allocation:** Unknown **Blinding:** NR **Placebo:** No **Split-mouth:** Yes	**Severity:** Moderate **Types of Teeth:** NR **Widman flap:** Always on all patients	**Number:** NR **Trained:** NR **Assigned to Subjects:** NR	**SRP performed:** NR; modified Widman flap for all sites **Time spent:** NR

Evidence Table 1b. Effectiveness of Local Tetracycline as an Adjunct to Scaling and Root Planing to Treat Chronic Periodontitis (continued)

Eligible Study Groups and How Defined:	Study Group Characteristics	Compliance Monitoring	Baseline Measures	Time Interval(s)
Subject/Site allocation: 7 subjects, 2 sites (quadrants) per subject T: 7 subjects C: 7 subjects **Dose, Mode, Schedule:** T: SRP plus irrigation with 100 mg/ml tetracycline HCl for 5 minutes C: SRP only	**Age:** Range: 35 to 65 **Gender:** NR **Race/Ethnicity:** NR	NA	Before SRP	3 times (at baseline and weeks 6 and 8)

Evidence Table 1b. Effectiveness of Local Tetracycline as an Adjunct to Scaling and Root Planing to Treat Chronic Periodontitis (continued)

Study Description	Outcomes Assessed	Adverse Effects	Study Group Attrition and Reasons	Type of Analysis
Darhous et al., 1995[50] (continued)	**Clinical Measurement:** PII PD CAL GI Gingival fluid flow **Radiographic Techniques:** NR **Microbiological Methods:** Plaque microbiota **Subject Self Report:** NR	NR	NR	**Type of analysis reported:** Full participants only

Evidence Table 1b. Effectiveness of Local Tetracycline as an Adjunct to Scaling and Root Planing to Treat Chronic Periodontitis (continued)

	Outcomes Accessed			
	Attachment Level mm	Probing Depth mm	Spirochetes	
(N of Pts)	$\bar{x}$ (SD)	$\bar{x}$ (SD)	$\bar{x}$ % (SD)	Comments
Baseline:				Tetracycline irrigation gave less bacterial counts than the control group right after irrigation, however, after 2 weeks the bacterial counts increased again and were insignificantly different in the 2 groups
T: 7	6.54 (0.18)	5.54 (0.67)	NA	
C: 7	6.53 (0.16)	5.73 (0.24)	NA	
Final: 8 weeks				
T: 7	3.45 (0.25)	1.82 (0.69)	NA	
C: 7	5.24 (0.21)	3.05 (0.24)	NA	
Change:				**Quality Score:** 31; 31
T:	3.09 (0.35)	3.72 (0.40)	NA	
C:	1.29 (0.31)	2.68 (0.24)	NA	
Test:	NR	NR		
P value:	NR	NR		

Evidence Table 1b. Effectiveness of Local Tetracycline as an Adjunct to Scaling and Root Planing to Treat Chronic Periodontitis (continued)

Study Description	Study Design Characteristics	Disease Characteristics	Examiner Characteristics	Description of Scaling and Root Planing
Drisko et al., 1995[49] **Study Period:** 52 weeks **Study/Treatment Site:** Dental Center and 2 universities **Location:** Eastman Dental Center; Minneapolis, MN University of MN Kansas City, MO University of Missouri-Kansas USA **Patient Population:** Adult patients with 1-2 teeth with = 5 mm PD and BOP. 46% were new to perio therapy, 54% were maintenance patients Approximately equal distribution between 3 centers	**Design Type:** RCT **Subject/Site Allocation:** Random **Blinding:** Examiners blind **Placebo:** No **Split-mouth:** Yes	**Severity:** NR **Types of Teeth:** NR **Widman flap:** NR	**Number:** 3 (1 at each center) **Trained:** Calibration (gold standard) **Assigned to Subjects:** Same examiner throughout study	**SRP performed:** Scaling and root planing under local anesthesia. Scaling could also occur after 10 days at fiber removal visit **Time spent:** 5 minutes on each tooth

Evidence Table 1b. Effectiveness of Local Tetracycline as an Adjunct to Scaling and Root Planing to Treat Chronic Periodontitis (continued)

Eligible Study Groups and How Defined:	Study Group Characteristics	Compliance Monitoring	Baseline Measures	Time Interval(s)
Subject/Site allocation: 122 (116 completed) T: 116 sites C: 116 sites **Dose, Mode, Schedule:** T: SRP plus 17 mg tetracycline HCl fiber, removed at 10 days C: SRP only	**Age:** Mean: 45.1 Range: 25 to 73 **Gender:** Male: 68 Female: 54 **Race/Ethnicity:** NR	Yes	Before SRP	6 times (at baseline and months 1, 3, 6, 9, and 12)

Evidence Table 1b. Effectiveness of Local Tetracycline as an Adjunct to Scaling and Root Planing to Treat Chronic Periodontitis (continued)

Study Description	Outcomes Assessed	Adverse Effects	Study Group Attrition and Reasons	Type of Analysis
Drisko et al., 1995[49] (continued)	**Clinical Measurement:** BOP/SBI PII PD CAL **Radiographic Techniques:** NR **Microbiological Methods:** NR **Subject Self Report:** Subject Satisfaction	Yes, 12 adverse events: severe gingival redness, tongue pigmentation, glossitis, periodontal abscess, lymphadenopathy, oral candidiasis	Poor compliance or unrelated illness (4); oral candidiasis (1); periodontal abscess 6 months after treatment (1)	**Type of analysis reported:** Full participants only

Evidence Table 1b. Effectiveness of Local Tetracycline as an Adjunct to Scaling and Root Planing to Treat Chronic Periodontitis (continued)

	Outcomes Accessed			
(N of Pts)	Attachment Level mm $\bar{x}$ (SD)	Probing Depth mm $\bar{x}$ (SD)	Spirochetes $\bar{x}$ % (SD)	Comments
Baseline:				There were no clinically significant differences in probing depth nor in clinical attachment level in the 2 groups of subjects at any of the examination intervals
T:	NR	4.94 (NR)	NA	
C:	NR	4.96 (NR)	NA	
Final: 52 weeks				
T: 116	NR	NR	NA	**Quality Score:** 62; 62
C: 116	NR	NR	NA	
Change:				
T:	NR	NR	NA	
C:	NR	NR	NA	
Test:	NR	NR		
P value:	NS	NS		

Evidence Table 1b. Effectiveness of Local Tetracycline as an Adjunct to Scaling and Root Planing to Treat Chronic Periodontitis (continued)

Study Description	Study Design Characteristics	Disease Characteristics	Examiner Characteristics	Description of Scaling and Root Planing
Friesen et al., 2002[58]	**Design Type:** RCT	**Severity:** NR	**Number:** NR	**SRP performed:** Local anesthesia
Study Period: 26 weeks (6 months)	**Subject/Site Allocation:** Random site within subject	**Types of Teeth:** Both	**Trained:** Standardization	**Time spent:** Minimum of 5 minutes per tooth
Study/Treatment Site: Graduate Program University Clinic	**Blinding:** Examiners blind	**Widman flap:** NR	**Assigned to Subjects:** NR	
Location: USA	**Placebo:** No			
Patient Population: Adult patients with 4 non-adjacent teeth with 6-10 mm PD and BOP	**Split-mouth:** Yes			

Evidence Table 1b. Effectiveness of Local Tetracycline as an Adjunct to Scaling and Root Planing to Treat Chronic Periodontitis (continued)

Eligible Study Groups and How Defined:	Study Group Characteristics	Compliance Monitoring	Baseline Measures	Time Interval(s)
Subject/Site allocation: 28 subjects enrolled 24 completed 3 sites/subject T1: 24 sites T2: 24 sites C: 24 sites **Dose, Mode, Schedule:** T1: SRP plus single 13.5mg tetracycline strip inserted in pocket for 7 to 10 days T2: SRP plus multiple 13.5mg tetracycline strips for 7 to 10 days C: SRP only	**Age:** Mean: 43.6 Range: 26 to 69 **Gender:** Male: 13 Female: 15 **Race/Ethnicity:** NR	NA	Before SRP	4 times (at baseline and months 1, 3, and 6)

Evidence Table 1b. Effectiveness of Local Tetracycline as an Adjunct to Scaling and Root Planing to Treat Chronic Periodontitis (continued))

Study Description	Outcomes Assessed	Adverse Effects	Study Group Attrition and Reasons	Type of Analysis
Friesen et al., 2002[58] (continued)	**Clinical Measurement:** BOP/SBI PII PD CAL GI **Radiographic Techniques:** NR **Microbiological Methods:** NR **Subject Self Report:** NR	Bitter taste	Lost to follow-up (3), removed due to antibiotic use (1)	**Type of analysis reported:** Intent to treat

Evidence Table 1b. Effectiveness of Local Tetracycline as an Adjunct to Scaling and Root Planing to Treat Chronic Periodontitis (continued)

		Outcomes Assessed			
		Attachment Level mm	Probing Depth mm	Spirochetes	
(N of Pts)		$\bar{x}$ (SD)	$\bar{x}$ (SD)	$\bar{x}$ % (SD)	Comments
T1 (Single Strip):					Single and multiple fiber treatments resulted in a statistically significant reduction in probing depths (*P* = 0.333) compared to the scaling and untreated group, but the groups were not tested individually (one by one). **Quality Score:** 46; 38
Baseline:					
T:	24	NR	6.26 (0.95)	NA	
C:	24	NR	6.60 (1.10)	NA	
Final: 26 weeks					
T:	24	NR	NR	NA	
C:	24	NR	NR	NA	
Change:		Gain	Reduction		
T:	24	0.31 (0.92)	1.41 (NR)	NA	
C:	24	- 0.13 (0.71)	0.98 (NR)	NA	
Test:		ANOVA	ANOVA		
P value:		NS	NR		
T2 (Multiple Strip):					
Baseline:					
T:	24	NR	6.58 (1.23)	NA	
C:	24	NR	6.60 (1.10)	NA	
Final: 26 weeks					
T:	24	NR	NR	NA	
C:	24	NR	NR	NA	
Change:		Gain	Reduction		
T:		0.35 (0.68)	1.85 (NR)	NA	
C:		-0.13 (0.71)	0.98 (NR)	NA	
Test:		ANOVA	ANOVA		
P value:		NS	NR		

Evidence Table 1b. Effectiveness of Local Tetracycline as an Adjunct to Scaling and Root Planing to Treat Chronic Periodontitis (continued)

Study Description	Study Design Characteristics	Disease Characteristics	Examiner Characteristics	Description of Scaling and Root Planing
Author and Year: Goodson et al., 1985[48]	**Design Type:** RCT	**Severity:** Currently active	**Number:** 1	**SRP performed:** Scaling on day of fiber placement and again on day of fiber removal (day 10)
Study Period: 52 weeks	**Subject/Site Allocation:** Random	**Types of Teeth:** NR, all in quadrant?	**Trained:** NA	**Time spent on SRP:** Minimum of 45 min/quad
Site of Study: NR	**Blinding:** Examiner blind	**Widman flap:** No	**Assigned to Subjects:** Same examiner throughout the study	
Location: NR (US authors)	**Placebo:** No			
Patients Selected: Patients with currently active periodontal disease and attachment loss of = 2 mm at = 1 sites	**Split-mouth:** Yes			

Evidence Table 1b. Effectiveness of Local Tetracycline as an Adjunct to Scaling and Root Planing to Treat Chronic Periodontitis (continued)

Eligible Study Groups and How Defined:	Study Group Characteristics	Compliance Monitoring	Baseline Measures	Assessment Time Interval(s)
Subject/Site allocation: 10 subjects 4 quadrants/subject T: 9 teeth (96 sites) C: 9 teeth (91 sites) **Dose, Mode, Schedule:** T: SRP plus 25% tetracycline fibers for 10 days C: SRP only at baseline and day 10	**Mean Age:** NR **Gender Distribution:** Male: NR Female: NR **Race/Ethnicity:** NR	NA	Before SRP	6 times (at baseline and months 1, 3, 6, 9, and 12)

Evidence Table 1b. Effectiveness of Local Tetracycline as an Adjunct to Scaling and Root Planing to Treat Chronic Periodontitis (continued)

Study Description	Outcomes Assessed	Adverse Effects	Study Group Attrition and Reasons	Type of Analysis
Goodson et al., 1985[48] (continued)	**Clinical Measurement:** PD CAL **Radiographic Techniques:** NR **Microbiological Methods:** NR **Subject Self Report:** NR	NR	NR	**Type of analysis reported:** All who completed treatment

Evidence Table 1b. Effectiveness of Local Tetracycline as an Adjunct to Scaling and Root Planing to Treat Chronic Periodontitis (continued)

	Outcomes Accessed			
	Attachment Level mm	Probing Depth mm	Spirochetes	
(N of Pts)	$\bar{x}$ (SD)	$\bar{x}$ (SD)	$\bar{x}$ % (SD)	Comments
Baseline:				CAL reported differently in 2 tables. Difference not clear. PD reported only in highly summarized version, not included here.
T: NR	NR	NR	NA	
C: NR	NR	NR	NA	
Final: 52 weeks				
T: 96 sites	NR	NR	NA	**Quality Score:** 38; 31
C: 91 sites	NR	NR	NA	
Change: n=9	Gain for initial PD of > 3 mm			
T:	1.19 (0.14 se)	NR	NA	
C:	0.85 (0.15 se)	NR	NA	
Test:	ANOVA			
P value:	NS			
Change: n=7	Gain for initial PD of > 6 mm			
T:	2.04 (0.32 se)	NR	NA	
C:	1.71 (0.45 se)	NR	NA	
Test:	ANOVA			
P value:	NS			

Evidence Table 1b. Effectiveness of Local Tetracycline as an Adjunct to Scaling and Root Planing to Treat Chronic Periodontitis (continued)

Study Description	Study Design Characteristics	Disease Characteristics	Examiner Characteristics	Description of Scaling and Root Planing
Jeong et al., 1994[33] **Study Period:** 12 weeks **Study/Treatment Site:** NR **Location:** NR **Patient Population:** Adult patients with 1 tooth in each quadrant with 4-6 mm PD	**Design Type:** RCT **Subject/Site Allocation:** Random (quadrant within subject) **Blinding:** NR **Placebo:** No **Split-mouth:** Yes	**Severity:** Moderate **Types of Teeth:** Single-rooted teeth **Widman flap:** NR	**Number:** 1 **Trained:** NA **Assigned to Subjects:** Same examiner throughout study	**SRP performed:** Thorough root planing at baseline, previous receipt of supragingival scaling **Time spent:** 5 minutes each tooth

Evidence Table 1b. Effectiveness of Local Tetracycline as an Adjunct to Scaling and Root Planing to Treat Chronic Periodontitis (continued)

Eligible Study Groups and How Defined:	Study Group Characteristics	Compliance Monitoring	Baseline Measures	Time Interval(s)
Subject/Site allocation: 16 subjects T1: 16 teeth T2: 16 teeth C: 16 teeth **Dose, Mode, Schedule:** T1: SRP plus 5% tetracycline HCI gel, 1 application T2: SRP plus 5% tetracycline HCI plus citric acid in gel, 1 application C: SRP only	**Age:** Mean: NR Range: 28 to 58 **Gender:** Male: 6 Female: 10 **Race/Ethnicity:** NR	NA	Unclear	5 times (at baseline and weeks 2, 4, 8, and 12)

Evidence Table 1b. Effectiveness of Local Tetracycline as an Adjunct to Scaling and Root Planing to Treat Chronic Periodontitis (continued)

Study Description	Outcomes Assessed	Adverse Effects	Study Group Attrition and Reasons	Type of Analysis
Jeong et al., 1994[33] (continued)	**Clinical Measurement:** SBI PII Tooth Mobility CAL PD **Radiographic Techniques:** NR **Microbiological Methods:** Plaque microbiota (% motile rods and spirochetes) **Subject Self Report:** NR	NR	NR	**Type of analysis reported:** Full participants only

Evidence Table 1b. Effectiveness of Local Tetracycline as an Adjunct to Scaling and Root Planing to Treat Chronic Periodontitis (continued)

	Outcomes Assessed			
(N of Pts)	Attachment Level mm $\bar{x}$ (SD)	Probing Depth mm $\bar{x}$ (SD)	Spirochetes $\bar{x}$ % (SD)	Comments
T1 (Tetracycline)				
Baseline:				
T: 16	5.06 (0.95)	4.94 (0.77)	8.7 (9.9)	
C: 16	5.07 (1.03)	4.67 (0.62)	7.2 (9.9)	
Final: 12 weeks				
T: 16	3.31 (1.01)	3.00 (0.73)	1.7 (5.7)	
C: 16	3.46 (0.74)	3.00 (0.65)	2.4 (5.0)	
Change:				
T:	1.75* (NR)	1.94* (NR)	7.0* (NR)	
C:	1.61* (NR)	1.67* (NR)	4.8* (NR)	
Test:	NR	NR	NR	
P value:	NS	NS	NR	
T2 (Tetracycline and Citric Acid)				Significant decrease in probing depth was noted after 12 weeks in tetracycline and citric acid group compared to the other groups
Baseline:				
T: 16	5.27 (0.73)	5.07 (0.7)	10.7 (13.4)	
C: 16	5.07 (1.03)	4.67 (0.62)	7.2 (9.9)	
Final: 12 weeks				No difference between groups for CAL change
T: 16	2.93 (0.96)	2.47 (0.74)	4.0 (8.5)	
C: 16	3.46 (0.74)	3.0 (0.65)	2.4 (5.0)	**Quality Score:** 38; 46
Change:				
T:	2.34* (NR)	2.60* (NR)	6.7* (NR)	
C:	1.61* (NR)	1.67* (NR)	4.8* (NR)	
Test:	NR	NR	NR	
P value:	NS	< 0.05NR	NR	

Evidence Table 1b. Effectiveness of Local Tetracycline as an Adjunct to Scaling and Root Planing to Treat Chronic Periodontitis (continued)

Study Description	Study Design Characteristics	Disease Characteristics	Examiner Characteristics	Description of Scaling and Root Planing
Kinane and Radvar 1999[53] **Study Period:** 26 weeks (6 months) **Study/Treatment Site:** Dental Hospital, Dental Clinic **Location:** Glasgow, Scotland **Patient Population:** Patients with persistent pockets that did not respond to SRP with = 4 pockets with =5 mm PD and BOP	**Design Type:** RCT **Subject/Site Allocation:** Random **Blinding:** Examiner blind **Placebo:** No **Split-mouth:** No	**Severity:** Severe, persistent pockets not responding to SRP **Types of Teeth:** NR **Widman flap:** NR	**Number:** 1 **Trained:** NA **Assigned to Subjects:** Same examiner throughout study	**SRP performed:** SRP under local anesthesia **Time spent:** NR

Evidence Table 1b. Effectiveness of Local Tetracycline as an Adjunct to Scaling and Root Planing to Treat Chronic Periodontitis (continued)

Eligible Study Groups and How Defined:	Study Group Characteristics	Compliance Monitoring	Baseline Measures	Time Interval(s)
Subject/Site allocation: 39 subjects, 4 sites/subject T: 19 subjects C: 20 subjects **Dose, Mode, Schedule:** T: SRP plus 25% tetracycline fibers, removed after 10 days C: SRP only	**Age:** Mean: 45 ± 6.4 **Gender:** Male: 29 Female: 50 **Race/Ethnicity:** NR	NA	Before SRP	4 times (at baseline, 6 weeks and months 3 and 6)

Evidence Table 1b. Effectiveness of Local Tetracycline as an Adjunct to Scaling and Root Planing to Treat Chronic Periodontitis (continued)

Study Description	Outcomes Assessed	Adverse Effects	Study Group Attrition and Reasons	Type of Analysis
Kinane and Radvar 1999[53] (continued)	**Clinical Measurement:** BOP/SBI PII PD CAL GI Supperation **Radiographic Techniques:** NR **Microbiological Methods:** NR **Subject Self Report:** NR	Yes, found none	1 subject dropped from control, reason not given	**Type of analysis reported:** All with any follow-up Analysis adjusted: GLM, baseline value as continuous covariate

Evidence Table 1b. Effectiveness of Local Tetracycline as an Adjunct to Scaling and Root Planing to Treat Chronic Periodontitis (continued)

	Outcomes Accessed			
(N of Pts)	Attachment Level mm $\bar{x}$ (SD)	Probing Depth mm $\bar{x}$ (SD)	Spirochetes $\bar{x}$ % (SD)	Comments
Baseline:				The probing depth reduction at all time points was significantly greater in the SRP plus tetracycline fiber group than the SRP alone group ($P < 0.01$)
T: 19	NR	5.402 (0.141 se)	NA	
C: 20	NR	5.480 (0.175 se)	NA	
Final: 26 weeks				
T: 19	NR	NR	NA	This is a follow-up study
C: 20	NR	NR	NA	
Change:	Gain	Reduction		**Quality Score:** 54; 62
T:	0.687 (0.138 se)	1.38 (0.166 se)	NA	
C:	0.537 (0.143 se)	0.711 (0.188 se)	NA	
Test:	GLM	GLM		
P value:	NS	= 0.008		

Evidence Table 1b. Effectiveness of Local Tetracycline as an Adjunct to Scaling and Root Planing to Treat Chronic Periodontitis (continued)

Study Description	Study Design Characteristics	Disease Characteristics	Examiner Characteristics	Description of Scaling and Root Planing
Lie et al., 1998[34] **Study Period:** 26 weeks **Study/Treatment Site:** University of Bergen, Department of Peridontology **Location:** Bergen, Norway **Patient Population:** Patients with untreated PD = 5 mm and BOP	**Design Type:** RCT **Subject/Site Allocation:** Random **Blinding:** Examiner and patients blind **Placebo:** No **Split-mouth:** Yes	**Severity:** Moderate to severe **Types of Teeth:** Single-rooted **Widman flap:** NR	**Number:** 1 **Trained:** NA **Assigned to Patients:** Same examiner throughout study	**SRP performed:** Sonic instrument and curets, 2 sessions, 1 week apart **Time spent:** NR

Evidence Table 1b. Effectiveness of Local Tetracycline as an Adjunct to Scaling and Root Planing to Treat Chronic Periodontitis (continued)

Eligible Study Groups and How Defined:	Study Group Characteristics	Compliance Monitoring	Baseline Measures	Time Interval(s)
Subject/Site allocation: 18 subjects T: 18 sites C: 18 sites **Dose, Mode, Schedule:** T: SRP plus application of 3% tetracycline ointment after each SRP session, 1 week apart C: SRP only	**Age:** Range: 36 to 77 **Gender:** NR **Race/Ethnicity:** NR	NA	NR	3 times (at baseline and months 3 and 6)

Evidence Table 1b. Effectiveness of Local Tetracycline as an Adjunct to Scaling and Root Planing to Treat Chronic Periodontitis (continued)

Study Description	Outcomes Assessed	Adverse Effects	Study Group Attrition and Reasons	Type of Analysis
Lie et al., 1998[34] (continued)	**Clinical Measurement:** BOP/SBI PD CAL **Radiographic Techniques:** NR **Microbiological Methods:** NR **Patient Self Report:** NR	NR	NR	**Type of analysis reported:** Full participants only

Evidence Table 1b. Effectiveness of Local Tetracycline as an Adjunct to Scaling and Root Planing to Treat Chronic Periodontitis (continued)

	Outcomes Accessed			
(N of Pts)	Attachment Level mm $\bar{x}$ (SD)	Probing Depth mm $\bar{x}$ (SD)	Spirochetes $\bar{x}$ (SD)	Comments
Defect Sites				There were no significant differences between the effects following topical application of the tetracycline ointment. Scaling and root planing alone appeared as effective as the drug augmented regiment *P.g.* was significantly reduced in the treatment group. **Quality Score:** 62; 62
Baseline:				
T: 18 sites	13.8 (2.5)	5.2 (1.5)	NA	
C: 18 sites	13.4 (1.8)	5.1 (1.2)	NA	
Final: 26 weeks				
T: 18 sites	12.6 (2.0)	3.5 (1.6)	NA	
C: 18 sites	13.2 (1.5)	4.0 (1.4)	NA	
Change:				
T:	1.2* (NR)	1.7* (NR)	NA	
C:	0.2* (NR)	1.1* (NR)	NA	
Test:	ANOVA	ANOVA		
P value:	NS	NS		
Nondefect Sites				
Baseline:				
T:	13.1 (2.3)	3.1 (0.6)		
C:	12.8 (1.6)	3.2 (1.1)		
Final: 26 weeks				
T:	12.5 (1.3)	2.7 (0.9)		
C:	12.4 (1.5)	2.5 (0.9)		
Change:				
T:	0.6* (NR)	0.4* (NR)		
C:	0.4 *(NR)	0.7* (NR)		
Test:	NR	NR		
P value:	NS	NS		

Evidence Table 1b. Effectiveness of Local Tetracycline as an Adjunct to Scaling and Root Planing to Treat Chronic Periodontitis (continued)

Study Description	Study Design Characteristics	Disease Characteristics	Examiner Characteristics	Description of Scaling and Root Planing
Author and Year: MacAlpine et al., 1985[31] **Study Period:** 24 weeks **Site of Study:** NR **Location:** NR (Swedish and US authors) **Patients Selected:** Patients with = 6 mm PD demonstrated by loss of attachment BOP and subgingival calculus	**Design Type:** Clinical trial **Subject/Site Allocation:** Assignment method not reported **Blinding:** NR **Placebo:** Yes **Split-mouth:** Yes	**Severity:** Generalized chronic periodontitis **Types of Teeth:** Single root **Widman flap:** No	**Number:** 1 **Trained:** NA **Assigned to Subjects:** Same examiner throughout study	**SRP performed:** Supra and subgingival instrumentation under local anesthesia **Time spent on SRP:** NR

Evidence Table 1b. Effectiveness of Local Tetracycline as an Adjunct to Scaling and Root Planing to Treat Chronic Periodontitis (continued)

Eligible Study Groups and How Defined:	Study Group Characteristics	Compliance Monitoring	Baseline Measures	Assessment Time Interval(s)
Subject/Site allocation: 11 subjects 4 or 8 sites per subject T: 16 sites C: 16 sites **Dose, Mode, Schedule:** T: SRP plus subgingival irrigation with tetracycline solution 50mg/ml every 2 weeks for 22 weeks C: SRP plus saline irrigation, every 2 weeks for 22 weeks	**Age:** Range: 25-67 **Gender Distribution:** Males: 2 Females: 9 **Race/Ethnicity:** NR	NA	Before SRP	4 times (at baseline, and weeks 8, 16, and 24)

Evidence Table 1b. Effectiveness of Local Tetracycline as an Adjunct to Scaling and Root Planing to Treat Chronic Periodontitis (continued)

Study Description	Outcomes Assessed	Adverse Effects	Study Group Attrition and Reasons	Type of Analysis
MacAlpine et al., 1985[31] (continued)	**Clinical Measurement:** BOP Plaque PD CAL **Radiographic Techniques:** NR **Microbiological Methods:** Plaque microbiota (% spirochetes) **Subject Self Report:** NR	NR	NR	**Type of analysis reported:** All who completed treatment

Evidence Table 1b. Effectiveness of Local Tetracycline as an Adjunct to Scaling and Root Planing to Treat Chronic Periodontitis (continued)

		Outcomes Accessed			
		Attachment Level mm	Probing Depth mm	Spirochetes	
	(N of Pts)	$\bar{x}$ (SD)	$\bar{x}$ (SD)	$\bar{x}$ % (SD)	Comments
Tetracycline vs Saline					**Quality Score:** 38; 38
Baseline:					
T:	16	NR	7.5 (0.5)	36 (NR)	
C:	16	NR	7.4 (0.6)	39 (NR)	
Final: 24 weeks					
T:	16	NR	4.6 (1.3)	1 (NR)	
C:	16	NR	4.9 (1.8)	4 (NR)	
Change:		Gain	Reduction		
T:		1.1 (1.4)	2.9 (NR)		
C:		0.8 (1.4)	2.5 (NR)		
Test:		NR	NR		
P value:		NS	NR		

Evidence Table 1b. Effectiveness of Local Tetracycline as an Adjunct to Scaling and Root Planing to Treat Chronic Periodontitis (continued)

Study Description	Study Design Characteristics	Disease Characteristics	Examiner Characteristics	Description of Scaling and Root Planing
Minabe et al., 1991[52] **Study Period:** 8 weeks **Study/Treatment Site:** Hospital dental clinic **Location:** Yokosuka, Kanagawa, Japan **Patient Population:** Adults attending hospital dental clinic	**Design Type:** RCT **Subject/Site Allocation:** Random **Blinding:** NR **Placebo:** No **Split-mouth:** Yes	**Severity:** Generalized periodontitis **Types of Teeth:** Teeth bifurcated (molars) with furcation involvement **Widman flap:** NR	**Number:** NR **Trained:** NR **Assigned to Subjects:** NR	**SRP performed:** Single episode of supra- and ultrasonic subgingival root planing performed under local anesthesia **Time spent:** NR

Evidence Table 1b. Effectiveness of Local Tetracycline as an Adjunct to Scaling and Root Planing to Treat Chronic Periodontitis (continued)

Eligible Study Groups and How Defined:	Study Group Characteristics	Compliance Monitoring	Baseline Measures	Time Interval(s)
Subject/Site allocation: 16 subjects provided 46 total teeth, randomly allocated to 4 groups, only two groups included here T: 10 sites C: 8 sites **Dose, Mode, Schedule:** T: SRP plus tetracycline-immobilized cross-linked collagen film administered at 1 week intervals at 4 times C: SRP only	**Age:** Mean: 46 Range: NR **Gender:** Male: 8 Female: 8 **Race/Ethnicity:** NR	NA	Before SRP	4 times (at baseline and weeks 4, 6, and 8)

Evidence Table 1b. Effectiveness of Local Tetracycline as an Adjunct to Scaling and Root Planing to Treat Chronic Periodontitis (continued)

Study Description	Outcomes Assessed	Adverse Effects	Study Group Attrition and Reasons	Type of Analysis
Minabe et al., 1991[52] (continued)	**Clinical Measurement:** BOP PII PD CAL GI **Radiographic Techniques:** NR **Microbiological Methods:** Density of micro-organisms in periodontal pocket **Subject Self Report:** NR	NR	NR	**Type of analysis reported:** Full participants only

Evidence Table 1b. Effectiveness of Local Tetracycline as an Adjunct to Scaling and Root Planing to Treat Chronic Periodontitis (continued)

	Outcomes Accessed				
	(N of Pts)	Attachment Level mm $\bar{x}$ (SD)	Probing Depth mm $\bar{x}$ (SD)	Spirochetes $\bar{x}$ % (SD)	Comments
Baseline:					No sig difference between treatments at any test period for PD or CAL or spirochetes.
T:	10	7.4 (2.22)	6.60 (1.71)	16.65 (14.1)	
C:	8	7.81 (2.33)	6.03 (1.13)	10.55 (9.96)	
Final: 8 weeks					Only reported PD and CAL for 4 weeks, (graphic presentation shows little difference from 8 weeks):
T:	10	NR	NR	2.39 (3.4)	
C:	8	NR	NR	3.93 (5.89)	
Change:					CAL: T: 5.4 (1.85) C: 7.0 (1.36) PD : T: 3.8 (0.79) C: 4.25 (0.71)
T:		NR	2.7 (NR)	NR	
C:		NR	2.0 (NR)	NR	
Test:		Mann Whitney U	Mann Whitney U	Mann Whitney U	
P value:		NS	NS	NS	**Quality Score:** 23 ; 23

Evidence Table 1b. Effectiveness of Local Tetracycline as an Adjunct to Scaling and Root Planing to Treat Chronic Periodontitis (continued)

Study Description	Study Design Characteristics	Disease Characteristics	Examiner Characteristics	Description of Scaling and Root Planing
Newman et al., 1994[57] **Study Period:** 26 weeks (6 months) **Study/Treatment Site:** 7 private dental practices **Location:** USA **Patient Population:** Periodontal maintenance patients receiving regular supportive periodontal therapy. Pts had sites in 2 quadrants with 5-8 mm PD and BOP	**Design Type:** Randomized in blocks of 4 such that 2 subjects within the block received control treatment in site with lower teeth and experimental treatment in the site with the higher tooth number **Subject/Site Allocation:** Random **Blinding:** Examiners blind **Placebo:** No **Split-mouth:** Yes	**Severity:** Localized recurrent periodontitis in maintenance patients **Types of Teeth:** Molars, pre-molars, cuspids, incisors **Widman flap:** NR	**Number:** 7 **Trained:** Calibration (gold standard) **Assigned to Subjects:** Same examiner throughout study	**SRP performed:** Full mouth ultrasonic scaling and root planing in accepted mechanical procedure for treating periodontitis **Time spent:** NR

Evidence Table 1b. Effectiveness of Local Tetracycline as an Adjunct to Scaling and Root Planing to Treat Chronic Periodontitis (continued)

Eligible Study Groups and How Defined:	Study Group Characteristics	Compliance Monitoring	Baseline Measures	Time Interval(s)
Subject/Site allocation: 113 subjects started 105 completed 2 teeth/subject T: 105 sites C: 105 sites **Dose, Mode, Schedule:** T: SRP plus 12.1 cm of tetracycline HCl fiber applied for 10 days C: SRP only	**Age:** Mean: 51.0 **Gender:** Male: 56 Female: 49 **Race/Ethnicity:** NR	Yes	After SRP	4 times (at baseline and months 1, 3, and 6)

Evidence Table 1b. Effectiveness of Local Tetracycline as an Adjunct to Scaling and Root Planing to Treat Chronic Periodontitis (continued)

Study Description	Outcomes Assessed	Adverse Effects	Study Group Attrition and Reasons	Type of Analysis
Newman et al., 1994[57] (continued)	**Clinical Measurement:** BOP/SBI PD CAL Recession Oral soft tissue **Radiographic Techniques:** NR **Microbiological Methods:** Plaque microbiota **Subject Self Report:** NR	NR	Moved or could not complete the study due to unrelated illness (6); undated tooth fracture (1); data recording errors (1)	**Type of analysis reported:** All with any follow-up

Evidence Table 1b. Effectiveness of Local Tetracycline as an Adjunct to Scaling and Root Planing to Treat Chronic Periodontitis (continued)

	Outcomes Accessed				
		Attachment Level mm	Probing Depth mm	Spirochetes	
	(N of Pts)	$\bar{x}$ (SD)	$\bar{x}$ (SD)	$\bar{x}$ % (SD)	Comments
Baseline:					Fiber therapy significantly enhanced the effectiveness of SRP
T:	NR	7.77 (2.17)	6.46 (1.01)	NA	
C:	NR	7.55 (2.19)	6.31 (1.20)	NA	
					Quality Score: 69; 69
Final: (26 weeks)					
T:	105 (sites)	NR	NR	NA	
C:	105 (sites)	NR	NR	NA	
Change:		Gain	Reduction		
T:		1.56 (0.145 se)	1.81 (0.121 se)	NA	
C:		1.08 (0.145 se)	1.08 (0.121 se)	NA	
Test:		ANCOVA	ANCOVA		
P value:		< 0.05	< 0.01		

Evidence Table 1b. Effectiveness of Local Tetracycline as an Adjunct to Scaling and Root Planing to Treat Chronic Periodontitis (continued)

Study Description	Study Design Characteristics	Disease Characteristics	Examiner Characteristics	Description of Scaling and Root Planing
Nylund and Egelberg, 1990[51] **Study Period:** 52 weeks **Site of Study:** NR **Location:** NR **Patients Selected:** Patients with loss of attachment, BOP, subgingival calculus, and 2+ molars with furcation involvement. No perio treatment for 3 years	**Design Type:** Clinical trial **Subject/Site Allocation:** NR **Blinding:** Examiner not blinded **Placebo:** Yes **Split-mouth:** Yes	**Severity:** Generalized periodontitis **Types of Teeth:** Molars with furcation involvement **Widman flap:** No	**Number:** 1 **Trained:** NR **Assigned to Subjects:** Same examiner throughout study	**SRP performed:** Single episode of crown and root debridement under local anesthesia using sonic, ultrasonic and various had instruments **Time spent on SRP:** 6-9 minutes/tooth

Evidence Table 1b. Effectiveness of Local Tetracycline as an Adjunct to Scaling and Root Planing to Treat Chronic Periodontitis (continued)

Eligible Study Groups and How Defined:	Study Group Characteristics	Compliance Monitoring	Baseline Measures	Assessment Time Interval(s)
Subject/Site allocation: 20 subjects T: 20 subjects (65 teeth) C: 20 subjects (58 teeth) **Dose, Mode, Schedule:** T: SRP plus irrigation with 50mg/ml tetracycline solution once every two weeks for 3 months C: SRP plus irrigation with saline once every two weeks for 3 months	**Mean Age:** NR **Gender Distribution:** NR **Race/Ethnicity:** NR	NA	Before SRP	7 times (at baseline, and months 1, 2, 3, 6, 9, and 12)

Evidence Table 1b. Effectiveness of Local Tetracycline as an Adjunct to Scaling and Root Planing to Treat Chronic Periodontitis (continued)

Study Description	Outcomes Assessed	Adverse Effects	Study Group Attrition and Reasons	Type of Analysis
Nylund and Egelberg, 1990[51] (continued)	**Clinical Measurement:** PD CAL Plaque BOP **Radiographic Techniques:** NR **Microbiological Methods:** NR **Subject Self Report:** NR	NR	NR	**Type of analysis reported:** All who completed treatment; t-tests on site data for subgroups of sites by baseline PD and furcation grade

Evidence Table 1b. Effectiveness of Local Tetracycline as an Adjunct to Scaling and Root Planing to Treat Chronic Periodontitis (continued)

	Outcomes Accessed				
		Attachment Level mm	Probing Depth mm	Spirochetes	
	(N of Pts)	$\bar{x}$ (SD)	$\bar{x}$ (SD)	$\bar{x}$ % (SD)	Comments
Baseline:					All data reported in graphs. No significant differences found between treatment and control for any subgroup (by baseline PD or furcation grade) at any time point **Quality Score:** 15; 23
T:	65 teeth	NR	NR	NA	
C:	58 teeth	NR	NR	NA	
Final:					
T:	NR	NR	NR	NA	
C:	NR	NR	NR	NA	
Change:					
T:		NR	NR	NA	
C:		NR	NR	NA	
Test:		NR	NR		
P value:		NS	NS		

Evidence Table 1b. Effectiveness of Local Tetracycline as an Adjunct to Scaling and Root Planing to Treat Chronic Periodontitis (continued)

Study Description	Study Design Characteristics	Disease Characteristics	Examiner Characteristics	Description of Scaling and Root Planing
Shiloah and Patters, 1994[54] **Study Period:** 4 weeks (1 month) **Study/Treatment Site:** Graduate Program University Clinic **Location:** USA **Patient Population:** Adults with = 5 non-adjacent sites with = 5 mm PD and attachment loss	**Design Type:** RCT **Subject/Site Allocation:** Random sites within subjects **Blinding:** Examiner blind **Placebo:** Yes **Split-mouth:** Yes	**Severity:** Moderate to severe chronic adult periodontitis **Types of Teeth:** Both **Widman flap:** NR	**Number:** 1 **Trained:** Calibration (Gold standard) **Assigned to Subjects:** Same examiner throughout study	**SRP performed:** SRP of entire dentition performed with ultrasonic scaler and Gracey curettes under local anesthesia **Time spent:** 4 to 7 hours per subject over several visits

Evidence Table 1b. Effectiveness of Local Tetracycline as an Adjunct to Scaling and Root Planing to Treat Chronic Periodontitis (continued)

Eligible Study Groups and How Defined:	Study Group Characteristics	Compliance Monitoring	Baseline Measures	Time Interval(s)
Subject/Site allocation: 7 subjects (1 or 2 teeth per subject) T: 12 sites C: 12 sites **Dose, Mode, Schedule:** T: SRP plus 5% aqueous tetracycline, 2 cc irrigation/site, 1 application C: SRP plus saline irrigation	**Age:** Mean: 49.5 Range: 33 to 65 **Gender:** Male: 2 Female: 5 **Race/Ethnicity:** NR	NA	Before SRP	3 times (at baseline, week 1 and month 1)

Evidence Table 1b. Effectiveness of Local Tetracycline as an Adjunct to Scaling and Root Planing to Treat Chronic Periodontitis (continued)

Study Description	Outcomes Assessed	Adverse Effects	Study Group Attrition and Reasons	Type of Analysis
Shiloah and Patters, 1994[54] (continued)	**Clinical Measurement:** PII GI PD CAL Gingival Fluid Flow **Radiographic Techniques:** NR **Microbiological Methods:** Bacterial DNA probes for *A.a., P.g.,* and *P.i.* **Subject Self Report:** NR	NR	NR	**Type of analysis reported:** Full participants only

Evidence Table 1b. Effectiveness of Local Tetracycline as an Adjunct to Scaling and Root Planing to Treat Chronic Periodontitis (continued)

	Outcomes Accessed			
(N of Pts)	Attachment Level mm $\bar{x}$ (SD)	Probing Depth mm $\bar{x}$ (SD)	Spirochetes $\bar{x}$ % (SD)	Comments
Baseline:				Data presented by figures only (bar charts) PD reduced 1-2mm, and CAL gained approx 1 mm in control and treatment groups.
T:	NR	NR	NA	
C:	NR	NR	NA	
Final: 4 weeks				
T: 12 sites	NR	NR	NA	Microbial outcomes: Not sig for *P.g., A.a.*
C: 12 sites	NR	NR	NA	
Change:				Numbers of bacteria by type per site were also reduced in control and treatment groups, with no sig differences between groups.
T:	NR	NR	NA	
C:	NR	NR	NA	
Test:	ANOVA	ANOVA		
P value:	NS	NS		
				Quality Score: 54; 54

Evidence Table 1b. Effectiveness of Local Tetracycline as an Adjunct to Scaling and Root Planing to Treat Chronic Periodontitis (continued)

Study Description	Study Design Characteristics	Disease Characteristics	Examiner Characteristics	Description of Scaling and Root Planing
Tonetti et al., 1998[35] **Study Period:** 26 weeks (6 months) **Study/Treatment Site:** Multicenter, 6 Private Periodontal Practices **Location:** Italy **Patient Population:** Patients participating in regular periodontal supportive periodontal care programs, and presenting with at least 1 mandibular Class II furcation with persistent BOP, in maintenance care	**Design Type:** RCT **Subject/Site Allocation:** Random **Blinding:** Examiners blind **Placebo:** No **Split-mouth:** No	**Severity:** NR **Types of Teeth:** Molars with furcation involvement **Widman flap:** NR	**Number:** 6, 1 per center **Trained:** Standardi-zation **Assigned to Subjects:** Same examiner throughout the study	**SRP performed:** Using sonic and hand instruments **Time spent:** Minimum of 3 minutes

Evidence Table 1b. Effectiveness of Local Tetracycline as an Adjunct to Scaling and Root Planing to Treat Chronic Periodontitis (continued)

Eligible Study Groups and How Defined:	Study Group Characteristics	Compliance Monitoring	Baseline Measures	Time Interval(s)
Subject/Site allocation: 127 subjects enrolled 123 completed T: 63 subjects C: 60 subjects **Dose, Mode, Schedule:** T: SRP plus tetracycline fibers containing 25% w/w tetracycline HCl crystals dispersed into a copolymer of ethylene and vinyl-acetate fiber in place for 10 ± 3 days C: SRP only	**Age:** Mean: 49.7 (± 9.2) **Gender:** Male: 69 Female: 56 **Race/Ethnicity:** NR	Yes	Before SRP	3 times (at baseline and months 3 and 6)

Evidence Table 1b. Effectiveness of Local Tetracycline as an Adjunct to Scaling and Root Planing to Treat Chronic Periodontitis (continued)

Study Description	Outcomes Assessed	Adverse Effects	Study Group Attrition and Reasons	Type of Analysis
Tonetti et al., 1998[35] (continued)	**Clinical Measurement:** BOP/SBI PD CAL **Radiographic Techniques:** NR **Microbiological Methods:** Plaque microbiota **Subject Self Report:** NR	7 subjects exhibited adverse events consisting of periodontal abscesses	Root fracture (1), abcess developed at experimental sites (3)	**Type of analysis reported:** Full participants only

Evidence Table 1b. Effectiveness of Local Tetracycline as an Adjunct to Scaling and Root Planing to Treat Chronic Periodontitis (continued)

		Outcomes Accessed			
		Attachment Level mm	Probing Depth mm	Spirochetes	
	(N of Pts)	$\bar{x}$ (SD)	$\bar{x}$ (SD)	$\bar{x}$ % (SD)	Comments
Baseline:					Test treatment resulted in a 0.5 mm greater reduction of PD than the control at 3 months, the improvement was highly significant but its duration did not extend until the 6 months evaluation. No differences were observed in terms of changes in CAL
T:	66	8.0 (2.0)	6.3 (1.6)	NA	
C:	61	8.1 (2.3)	5.8 (1.7)	NA	
Final: 26 weeks (6 months)					
T:	63	7.1 (0.13 se)	5.0 (1.5)	NA	
C:	60	7.1 (0.14 se)	4.9 (1.4)	NA	
Change:		Gain	Reduction		
T:		0.9* (NR)	1.3* (NR)	NA	**Quality Score:** 69; 69
C:		1.0* (NR)	0.9* (NR)	NA	
Test:		ANOVA	ANOVA		
P value:		NS	NS		

Evidence Table 1b. Effectiveness of Local Tetracycline as an Adjunct to Scaling and Root Planing to Treat Chronic Periodontitis (continued)

Study Description	Study Design Characteristics	Disease Characteristics	Examiner Characteristics	Description of Scaling and Root Planing
Trombelli et al., 1996[55] **Study Period:** 8 weeks (60 days) **Study/Treatment Site:** Department of Periodontology, University of Ferrara, School of Dentistry **Location:** Ferrara, Italy **Patient Population:** Adults referred for treatment with at least 3 non-molar teeth in same arch, sites having = 5 mm PD	**Design Type:** RCT **Subject/Site Allocation:** Random **Blinding:** Examiners blind **Placebo:** No **Split-mouth:** Yes	**Severity:** Adult advanced periodontitis **Types of Teeth:** Single-rooted teeth **Widman flap:** NR	**Number:** NR **Trained:** NR **Assigned to Subjects:** NR	**SRP performed:** Supragingival and subgingival ultrasonic scaling **Time spent:** NR

Evidence Table 1b. Effectiveness of Local Tetracycline as an Adjunct to Scaling and Root Planing to Treat Chronic Periodontitis (continued)

Eligible Study Groups and How Defined:	Study Group Characteristics	Compliance Monitoring	Baseline Measures	Time Interval(s)
Subject/Site allocation: 12 subjects with 63 sites T1: 20 sites T2: 24 sites C: 19 sites **Dose, Mode, Schedule:** T1: SRP plus irrigation with 100 mg/ml tetracycline solution, 15 ml delivered subgingivally, 1 application for 4 minutes T2: SRP plus vinyl acetate fibers with 25% tetracycline HCl by weight positioned in pockets and packed with blunt instrument. Removed after 10 days C: SRP only	**Age:** Mean: 41.8 Range: 27 to 63 **Gender:** Male: 4 Female: 8 **Race/Ethnicity:** NR	NA	Before SRP	3 times (at baseline, and days 30 and 60)

Evidence Table 1b. Effectiveness of Local Tetracycline as an Adjunct to Scaling and Root Planing to Treat Chronic Periodontitis (continued)

Study Description	Outcomes Assessed	Adverse Effects	Study Group Attrition and Reasons	Type of Analysis
Trombelli et al., 1996[55] (continued)	**Clinical Measurement:** BOP PII PD CAL GI Recession depth O'Leary Plaque Control Record **Radiographic Techniques:** NR **Microbiological Methods:** NR **Subject Self Report:** NR	NR	NR	**Type of analysis reported:** NR

Evidence Table 1b. Effectiveness of Local Tetracycline as an Adjunct to Scaling and Root Planing to Treat Chronic Periodontitis (continued)

	Outcomes Accessed			
	Attachment Level mm	Probing Depth mm	Spirochetes	
(N of Pts)	$\bar{x}$ (SD)	$\bar{x}$ (SD)	$\bar{x}$ % (SD)	Comments
<u>T1 (Irrigation with Tetracycline):</u>				For PD, the 2 treatments differed from SRP alone (*P* = 0.011).
Baseline:				
T: (20 sites)	6.3 (1.9 se)	5.8 (0.9 se)	NA	
C: (19 sites)	6.3 (1.2 se)	6.1 (1.3 se)	NA	
Final: 8 weeks				For CAL, there is no significant difference btw treatment groups and control (*P* = 0.121)
T:	4.7 (1.7 se)	3.6 (1.9 se)	NA	
C:	4.9 (1.9 se)	4.3 (1.9 se)	NA	
Change:				**Quality Score:** 38 ; 46
T:	1.8* (NR)	2.2* (NR)	NA	
C:	1.4* (NR)	1.8* (NR)	NA	
Test:	ANOVA	ANOVA		
P value:	NS	NS		
<u>T2 (Tetracycline Fibers):</u>				
Baseline:				
T: (24 sites)	7.3 (1.8 se)	6.1 (1.1 se)	NA	
C: (19 sites)	6.3 (1.2 se)	6.1 (1.3 se)	NA	
Final: 8 weeks				
T:	5.5 (2.4 se)	3.8 (1.4 se)	NA	
C:	4.9 (1.9 se)	4.3 (1.9 se)	NA	
Change:				
T:	1.6* (NR)	2.3* (NR)	NA	
C:	1.4* (NR)	1.8* (NR)	NA	
Test:	ANOVA	ANOVA		
P value:	NS	NS		

Evidence Table 1b. Effectiveness of Local Tetracycline as an Adjunct to Scaling and Root Planing to Treat Chronic Periodontitis (continued)

Study Description	Study Design Characteristics	Disease Characteristics	Examiner Characteristics	Description of Scaling and Root Planing
Unsal et al., 1994[59] **Study Period:** 12 weeks **Study/Treatment Site:** Department of Peridontology, Faculty of Dentistry **Location:** University of Ankara, Turkey **Patient Population:** Adult patients referred to clinic for treatment of periodontal disease, with = 3 teeth in each quadrant with 2 sites having periodontal disease = 4 mm, BOP, and radiographic evidence bone loss	**Design Type:** RCT **Subject/Site Allocation:** Random **Blinding:** NR **Placebo:** No **Split-mouth:** No	**Severity:** Moderate to advanced periodontitis **Types of Teeth:** NR **Widman flap:** NR	**Number:** NR **Trained:** NR **Assigned to Subjects:** NR	**SRP performed:** All subjects received hand and ultrasonic scaling and root planing; selected sites were mechanically debrided with hand instruments **Time spent:** NR

Evidence Table 1b. Effectiveness of Local Tetracycline as an Adjunct to Scaling and Root Planing to Treat Chronic Periodontitis (continued)

Eligible Study Groups and How Defined:	Study Group Characteristics	Compliance Monitoring	Baseline Measures	Time Interval(s)
Subject/Site allocation: 22 subjects invited 15 subjects in relevant 2 groups T: 7 (99 sites) C: 8 (110 teeth) **Dose, Mode, Schedule:** T: SRP plus 40% tetracycline HCI (w/w) in white petroleum, single application of paste C: SRP only	**Age:** Mean: 42 Range: 30 to 57 **Gender:** Male: 10 Female: 12 **Race/Ethnicity:** NR	NR	Before SRP	2 times (at baseline and at week 12)

Evidence Table 1b. Effectiveness of Local Tetracycline as an Adjunct to Scaling and Root Planing to Treat Chronic Periodontitis (continued)

Study Description	Outcomes Assessed	Adverse Effects	Study Group Attrition and Reasons	Type of Analysis
Unsal et al., 1994[59] (continued)	**Clinical Measurement:** Bleeding index PII PD CAL GI/GI-S Position of gingival margin **Radiographic Techniques:** NR **Microbiological Methods:** NR **Subject Self Report:** NR	None were reported	NR	**Type of analysis reported:** Intent to treat.

Evidence Table 1b. Effectiveness of Local Tetracycline as an Adjunct to Scaling and Root Planing to Treat Chronic Periodontitis (continued)

	Outcomes Accessed			
	Attachment Level mm	Probing Depth mm	Spirochetes	
(N of Pts)	$\bar{x}$ (SD)	$\bar{x}$ (SD)	$\bar{x}$ % (SD)	Comments
Baseline:				For both PD and CAL, the control experienced NS better outcomes than the tetracycline group
T: 7 (99 teeth)	3.10 (1.21)	4.25 (0.85)	NA	
C: 8 (110 teeth)	3.66 (1.22)	5.14 (1.45)	NA	
Final: 12 weeks				**Quality Score:** 38; 46
T: 7	2.29 (0.96)	2.85 (0.55)	NA	
C: 8	2.62 (1.24)	3.31 (0.73)	NA	
Change:				
T:	0.81 (0.69)	1.40 (0.32)	NA	
C:	1.04 (0.16)	1.83 (0.54)	NA	
Test:	ANOVA	ANOVA		
P value:	NS	NS		

Evidence Table 1b. Effectiveness of Local Tetracycline as an Adjunct to Scaling and Root Planing to Treat Chronic Periodontitis (continued)

Study Description	Study Design Characteristics	Disease Characteristics	Examiner Characteristics	Description of Scaling and Root Planing
Yalcin et al., 1999[56] **Study Period:** 7 weeks **Study/Treatment Site:** Health Department Clinic **Location:** Istanbul, Turkey **Patient Population:** Patients with = 2 sites in each of 4 quadrants with pocket depths of = 5 mm	**Design Type:** RCT **Subject/Site Allocation:** Random **Blinding:** Examiners blind **Placebo:** No **Split-mouth:** Yes	**Severity:** Moderate to advanced periodontitis never treated **Types of Teeth:** Both single and multi-root teeth **Widman flap:** NR	**Number:** 1 examiner performed clinical measure-ments 1 examiner did SRP 1 examiner placed fibers **Trained:** NR **Assigned to Subjects:** NR	**SRP performed:** NR **Time spent:** NR

Evidence Table 1b. Effectiveness of Local Tetracycline as an Adjunct to Scaling and Root Planing to Treat Chronic Periodontitis (continued)

Eligible Study Groups and How Defined:	Study Group Characteristics	Compliance Monitoring	Baseline Measures	Time Interval(s)
Subject/Site allocation: 17 subjects T: 221 sites C: 191 sites **Dose, Mode, Schedule:** T: SRP plus slow-release tetracycline fibers placed subgingivally for 10 days C: SRP only	**Age:** Range: 25 to 52 **Gender:** Male: 9 Female: 8 **Race/Ethnicity:** NR	NA	Before SRP	4 times (at baseline and weeks 1, 3, and 7)

Evidence Table 1b. Effectiveness of Local Tetracycline as an Adjunct to Scaling and Root Planing to Treat Chronic Periodontitis (continued)

Study Description	Outcomes Assessed	Adverse Effects	Study Group Attrition and Reasons	Type of Analysis
Yalcin et al., 1999[56] (continued)	**Clinical Measurement:** BOP/SBI PII PD CAL GI Oral soft tissue examined to assess adverse effects **Radiographic Techniques:** NR **Microbiological Methods:** NR **Subject Self Report:** NR	Oral candidiasis (1); severe gingival redness on quadrants treated with fibers (2)	NR	**Type of analysis reported:** All with any follow-up

Evidence Table 1b. Effectiveness of Local Tetracycline as an Adjunct to Scaling and Root Planing to Treat Chronic Periodontitis (continued)

	Outcomes Accessed			
(N of Pts)	Attachment Level mm $\bar{x}$ (SD)	Probing Depth mm $\bar{x}$ (SD)	Spirochetes $\bar{x}$ % (SD)	Comments
Baseline:				Tetracycline fiber treatment as adjunct to SRP is effective in regard to probing depth and bleeding on probing **Quality Score:** 62; 69
T: 210 (sites) CAL 221 (sites) PD	5.12 (2.53)	4.71 (2.34)	NA	
C: 179 (sites) CAL 191 (sites) PD	5.25 (2.59)	4.55 (2.37)	NA	
Final: 7 weeks				
T: NR	NR	NR	NA	
C: NR	NR	NR	NA	
Change:	Gain	Reduction		
T:	0.95 (0.132 se)	1.45 (0.14 se)	NA	
C:	0.75 (0.158 se)	1.04 (.0148 se)	NA	
Test:	ANCOVA	ANCOVA		
P value:	NS	= 0.047		

Evidence Table 2a. Effectiveness of Systemic Minocycline as an Adjunct to Scaling and Root Planing to Treat Chronic Periodontitis

Study Description	Study Design Characteristics	Disease Characteristics	Examiner Characteristics	Description of Scaling and Root Planing
Atilla et al., 1996[62] **Study Period:** 8 weeks **Study/Treatment Site:** NR **Location:** Turkey **Patient Population:** Adult patients with minimum of 20 natural teeth and PD = 4 mm	**Design Type:** Parallel non-randomized clinical trial **Subject/Site Allocation:** Patients with PD = 4 to 5 mm in one group, patients with PD = 6 mm in another group **Blinding:** NR **Placebo:** No **Split-mouth:** No	**Severity:** Moderate to severe periodontitis **Types of Teeth:** NR **Widman flap:** NR	**Number:** NR **Trained:** NR **Assigned to Subjects:** Clinical measure-ments were determined by the same periodontist	**SRP performed:** Non-surgical periodontal SRP **Time spent:** 2 or more appointments

Evidence Table 2a. Effectiveness of Systemic Minocycline as an Adjunct to Scaling and Root Planing to Treat Chronic Periodontitis (continued)

Eligible Study Groups and How Defined:	Study Group Characteristics	Compliance Monitoring	Baseline Measures	Time Interval(s)
Subject/Site allocation: 21 subjects T1: 5 subjects (PD 4-5mm) T2: 5 subjects (PD = 6 mm) C1: 6 subjects (PD 4-5 mm) C2: 5 subjects (PD = 6 mm) **Dose, Mode, Schedule:** T1 and 2: SRP plus 100 mg minocycline 1xday for 14 days C1 and 2: SRP only	**Age:** Mean: 44 ± 5.87 Range: 37 to 52 **Gender:** Male: 12 Female: 9 **Race/Ethnicity:** NR	NA	Before SRP	2 times (at baseline and 8 weeks)

Evidence Table 2a. Effectiveness of Systemic Minocycline as an Adjunct to Scaling and Root Planing to Treat Chronic Periodontitis (continued)

Study Description	Outcomes Assessed	Adverse Effects	Study Group Attrition and Reasons	Type of Analysis
Atilla et al., 1996[62] (continued)	**Clinical Measurement:** BOP/SBI PD Level of neutral proteasse activity Counting of epithelial cells in saliva Number of sites with PD of 4 to 5 mm or = 6mm **Radiographic Techniques:** NR **Microbiological Methods:** NR **Subject Self Report:** NR	NR	NR	**Type of analysis reported:** Full participants only

Evidence Table 2a. Effectiveness of Systemic Minocycline as an Adjunct to Scaling and Root Planing to Treat Chronic Periodontitis (continued)

	Outcomes Accessed				
	(N of Pts)	Attachment Level mm $\bar{x}$ (SD)	Probing Depth mm $\bar{x}$ (SD)	Spirochetes $\bar{x}$ % (SD)	Comments
T1: PD 4 to 5 mm					Systemic minocycline therapy might be useful as an adjunct to non-surgical therapy in the presence of deep pockets, especially for reinfected cases **Quality Score:** 31; 38
Baseline:					
T:	5	NA	3.11 (0.32)	NA	
C:	6	NA	3.26 (0.47)	NA	
Final: 6 weeks					
T:	5	NA	1.67 (0.52)	NA	
C:	6	NA	1.76 (0.52)	NA	
Change:					
T:		NA	1.44* (NR)	NA	
C:		NA	1.50* (NR)	NA	
Test:			NR		
P value:			NS		
T2: PD = 6 mm					
Baseline:					
T:	5	NA	4.17 (0.34)	NA	
C:	5	NA	4.19 (0.30)	NA	
Final: 6 weeks					
T:	5	NA	1.94 (0.42)	NA	
C:	5	NA	2.45 (0.59)	NA	
Change:					
T:		NA	2.23* (NR)	NA	
C:		NA	1.74* (NR)	NA	
Test:			NR		
P value:			NS		

Evidence Table 2a. Effectiveness of Systemic Minocycline as an Adjunct to Scaling and Root Planing to Treat Chronic Periodontitis (continued)

Study Description	Study Design Characteristics	Disease Characteristics	Examiner Characteristics	Description of Scaling and Root Planing
Author and Year: Ciancio, et al., 1982[61] **Study Period:** 10 weeks **Site of Study:** Dept of Periodontology and Periodontal Disease Clinical Research Center, State University of New York at Buffalo **Location:** Buffalo, NY **Patients Selected:** Adults with PD = 5 mm and a gingival inflammatory index of = 1	**Design Type:** RCT **Subject/Site Allocation:** Random **Blinding:** Examiner and subjects blind **Placebo:** Yes **Split-mouth:** Yes	**Severity:** Moderate to severe periodontitis **Types of Teeth:** Ramfjord teeth (molars, premolars, incisors) **Widman flap:** No	**Number:** 1 **Trained:** NR **Assigned to Subjects:** Same examiner throughout study	**SRP performed:** Mechanical debridement by hand performed by 2 dental hygienists to mimic common practice **Time spent on SRP:** 45-60 min on average for 2 quadrants

Evidence Table 2a. Effectiveness of Systemic Minocycline as an Adjunct to Scaling and Root Planing to Treat Chronic Periodontitis (continued)

Eligible Study Groups and How Defined:	Study Group Characteristics	Compliance Monitoring	Baseline Measures	Assessment Time Interval(s)
Subject/Site allocation: 26 subjects T: 13 subjects C: 13 subjects **Dose, Mode, Schedule:** T: SRP plus 200 mg minocycline 1xday for 7days C: SRP plus placebo	**Age:** Range 35-65 **Gender Distribution:** NR **Race/Ethnicity:** NR	NR	Before SRP	6 times (at baseline, and days 7, 14, 35, 49, and 70)

Evidence Table 2a. Effectiveness of Systemic Minocycline as an Adjunct to Scaling and Root Planing to Treat Chronic Periodontitis (continued)

Study Description	Outcomes Assessed	Adverse Effects	Study Group Attrition and Reasons	Type of Analysis
Ciancio et al., 1982[61] (continued)	**Clinical Measurement:** PD GI PI **Radiographic Techniques:** NR **Microbiological Methods:** Plaque microbiota: % spirochetes, coccoid cells, non-motile rods, filaments and motile rods, gram stain, colonial and cellular morphology **Subject Self Report:** NR	Vertigo in 2 subjects in treatment group, though not severe enough to affect walking	NR	**Type of analysis reported:** Intent to treat

Evidence Table 2a. Effectiveness of Systemic Minocycline as an Adjunct to Scaling and Root Planing to Treat Chronic Periodontitis (continued)

	Outcomes Accessed			
	Attachment Level mm	Probing Depth mm	Spirochetes	
(N of Pts)	$\bar{x}$ (SD)	$\bar{x}$ (SD)	$\bar{x}$ % (SD)	Comments
Baseline:				No PD data reported for baseline or final exam. Results stated as "no significant changes in any study group during the experimental period"
T: 13	NA	NR	29 (NR)	
C: 13	NA	NR	25 (NR)	
Final: 10 weeks				
T: 13	NA	NR	12 (NR)	The treatment resulted in a marked and long-lasting decrease in the proportion of spirochetes
C: 13	NA	NR	15 (NR)	
Change:				
T:	NA	NR	17* (NR)	
C:	NA	NR	10* (NR)	**Quality Score:** 62; 69
Test:		NR	NR	
P value:		NS	NR	

Evidence Table 2b. Effectiveness of Local Minocycline as an Adjunct to Scaling and Root Planing to Treat Chronic Periodontitis

Study Description	Study Design Characteristics	Disease Characteristics	Examiner Characteristics	Description of Scaling and Root Planing
Author and Year: Graca et al., 1997[32] **Study Period:** 12 weeks **Site of Study:** United Medical and Dental Schools of Guy's and St. Thomas' Hospitals **Location:** London, England **Patients Selected:** Adults with 2 pockets 5-10 mm on separate teeth with attachment loss > 4 mm and radiographic evidence of bone loss and BOP	**Design Type:** RCT **Subject/Site Allocation:** Paired according to smoking, gender, age. If more than 6 teeth met criteria (PD = 5-10 mm) then selection was random **Blinding:** Examiner and patients blind **Placebo:** Yes **Split-mouth:** NR	**Severity:** Moderate to advanced periodontitis **Types of Teeth:** NR **Widman flap:** NR	**Number:** 1 **Trained:** NR **Assigned to Subjects:** Same examiner throughout study	**SRP performed:** 2-6 teeth per patient were planed under local anesthesia using hand and ultrasonic instruments **Time spent on SRP:** NR

Evidence Table 2b. Effectiveness of Local Minocycline as an Adjunct to Scaling and Root Planing to Treat Chronic Periodontitis (continued)

Eligible Study Groups and How Defined:	Study Group Characteristics	Compliance Monitoring	Baseline Measures	Assessment Time Interval(s)
Subject/Site allocation: 30 subjects enrolled 26 completed, 2 to 6 teeth per subject T: 13 subjects C: 13 subjects **Dose, Mode, Schedule:** T: SRP plus 2% minocycline gel applied at baseline, and weeks 2 and 4 C: SRP plus placebo gel	**Age:** Range: 25 to 50 **Gender Distribution:** Males: 6 Females: 20 **Race/Ethnicity:** White: 16	NA	Before SRP	3 times (at baseline, and weeks 6 and 12)

Evidence Table 2b. Effectiveness of Local Minocycline as an Adjunct to Scaling and Root Planing to Treat Chronic Periodontitis (continued)

Study Description	Outcomes Assessed	Adverse Effects	Study Group Attrition and Reasons	Type of Analysis
Graca et al., 1997[32] (continued)	**Clinical Measurement:** PII BOP CAL PD **Radiographic Techniques:** NR **Microbiological Methods:** NR **Subject Self Report:** NR	Root sensitivity	2 pairs lost: systemic antibiotics (1); inability to keep appointments (1)	**Type of analysis reported:** Full participants only Matched pairs

Evidence Table 2b. Effectiveness of Local Minocycline as an Adjunct to Scaling and Root Planing to Treat Chronic Periodontitis (continued)

	Outcomes Accessed			
	Attachment Level mm	Probing Depth mm	Spirochetes	
(N of Pts)	$\bar{x}$ (SD)	$\bar{x}$ (SD)	$\bar{x}$ % (SD)	Comments
				Quality Score: 69; 69
Baseline:				
T: 13	6.86 (1.04)	5.93 (0.48)	NA	
C: 13	6.83 (0.73)	5.74 (0.35)	NA	
Final: 12 weeks				
T: 13	4.91 (0.72)	3.29 (0.49)	NA	
C: 13	5.27 (0.76)	3.44 (0.47)	NA	
Change:				
T:	1.95* (NR)	2.64* (NR)	NA	
C:	1.56* (NR)	2.30* (NR)	NA	
Test:	ANCOVA	ANCOVA		
P value:	<0.05	NS		

Evidence Table 2b. Effectiveness of Local Minocycline as an Adjunct to Scaling and Root Planing to Treat Chronic Periodontitis (continued)

Study Description	Study Design Characteristics	Disease Characteristics	Examiner Characteristics	Description of Scaling and Root Planing
Author and Year: Henderson et al., 2002[67] **Study Period:** 26 weeks (6 months) **Site of Study:** Department of Oral Rehabilitation, School of Dentistry, University of Otago **Location:** New Zealand **Patients Selected:** Adult patients with = 2 pairs of adjacent 6-9 mm pockets and = 3 mm loss of attachment, located in adjacent teeth in an interproximal space, on opposite sides of the mouth	**Design Type:** RCT **Subject/Site Allocation:** Random **Blinding:** Examiners blind **Placebo:** No **Split-mouth:** Yes	**Severity:** Moderate to advanced chronic periodontitis **Types of Teeth:** NR **Widman flap:** NR	**Number:** NR **Trained:** NR **Assigned to Patients:** NR	**SRP performed:** Single episode of full mouth ultrasonic and hand instrumentation under local anesthetic **Time spent on SRP:** 90 minutes

Evidence Table 2b. Effectiveness of Local Minocycline as an Adjunct to Scaling and Root Planing to Treat Chronic Periodontitis (continued)

Eligible Study Groups and How Defined:	Study Group Characteristics	Compliance Monitoring	Baseline Measures	Assessment Time Interval(s)
Subject/Site allocation: 15 subjects One of 2 teeth per subject received treatment, adjacent tooth or opposite side (remote) served as controls, remotes used for control in this report T: 15 subjects C: 15 subjects **Dose, Mode, Schedule:** T: SRP plus a single application of 1 mg minocycline C: SRP only	**Mean Age:** Mean: 46.3 Range: 35 to 69 **Gender Distribution:** Male: 7 Female: 8 **Race/Ethnicity:** NR	NR	Before SRP	3 times (at baseline, and months 3 and 6

Evidence Table 2b. Effectiveness of Local Minocycline as an Adjunct to Scaling and Root Planing to Treat Chronic Periodontitis (continued)

Study Description	Outcomes Assessed	Adverse Effects	Study Group Attrition and Reasons	Type of Analysis
Henderson et al., 2002[67] (continued)	**Clinical Measurement:** PD CAL BOP PII BI Soft tissue appearance **Radiographic Techniques:** NR **Microbiological Methods:** NR **Patient Self Report:** NR	No adverse events were reported by completers	NR	**Type of analysis reported:** Full participants only

Evidence Table 2b. Effectiveness of Local Minocycline as an Adjunct to Scaling and Root Planing to Treat Chronic Periodontitis (continued)

	Outcomes Accessed			
(N of Pts)	Attachment Level mm $\bar{x}$ (SD)	Probing Depth mm $\bar{x}$ (SD)	Spirochetes $\bar{x}$ (SD)	Comments
Baseline:				Statistically significant differences in pocket depths were found between groups over the six months of the study but the *P* value was not reported
T:	NR	6.7 (1.0)	NA	
C:	NR	7.1 (1.0)	NA	
Final: 26 weeks (6 months)				
T:	NR	4.3 (1.4)	NA	**Quality Score:** 54; 54
C:	NR	5.2 (1.2)	NA	
Change:				
T:	2.1 (1.5)	2.5 (1.4)	NA	
C:	1.3 (1.3)	1.8 (1.7)	NA	
Test:	NR	NR		
P value:	0.04	= 0.05		

Evidence Table 2b. Effectiveness of Local Minocycline as an Adjunct to Scaling and Root Planing to Treat Chronic Periodontitis (continued)

Study Description	Study Design Characteristics	Disease Characteristics	Examiner Characteristics	Description of Scaling and Root Planing
Author and Year: Jones et al., 1994[64] **Study Period:** 26 weeks (6 months) **Site of Study:** University of Texas Health Science Center **Location:** San Antonio, Texas, USA **Patients Selected:** Adults with at least 2 sites on different teeth in 1 quadrant with PD > 7 mm and presence of *P.g., P.i. or A.a.* microbial species.	**Design Type:** RCT **Subject/Site Allocation:** Random assignment to 4 groups All sites = 5 mm in the most diseased quadrant received treatment, other quadrants not treated **Blinding:** Examiners and patients blind **Placebo:** Yes **Split-mouth:** No	**Severity:** Moderate to advanced periodontitis **Types of Teeth:** 3rd molars and abutment teeth excluded **Widman flap:** NR	**Number:** NR **Trained:** NR **Assigned to Subjects:** NR	**SRP performed:** NR **Time spent on SRP:** NR

Evidence Table 2b. Effectiveness of Local Minocycline as an Adjunct to Scaling and Root Planing to Treat Chronic Periodontitis (continued)

Eligible Study Groups and How Defined:	Study Group Characteristics	Compliance Monitoring	Baseline Measures	Assessment Time Interval(s)
Subject/Site allocation: 26 subjects enrolled 17 completed T: 11 subjects C: 6 subjects **Dose, Mode, Schedule:** T: SRP plus microencapsulated minocycline HCL powder in a biodegradable controlled-release system, injected into = 5 mm pockets, 1 application C: SRP plus saline subgingival irrigation for 30 seconds	**Mean Age:** NR **Gender Distribution:** NR **Race/Ethnicity:** NR	NA	Before SRP	4 times (at baseline, and months 1, 3 and 6) CAL also recorded at month 5

Evidence Table 2b. Effectiveness of Local Minocycline as an Adjunct to Scaling and Root Planing to Treat Chronic Periodontitis (continued)

Study Description	Outcomes Assessed	Adverse Effects	Study Group Attrition and Reasons	Type of Analysis
Jones et al., 1994[64] (continued)	**Clinical Measurement:** CAL PD PII GI BOP **Radiographic Techniques:** NR **Microbiological Methods:** Anaerobic cultures (*A.a., P.g., P.i., E.c., C.r.*) DNA probe Monoclonal antibodies **Subject Self Report:** NR	No untoward reactions were observed	No reasons given, but 9 were lost	**Type of analysis reported:** Full participants only Sites averaged across each subject and then averaged across subjects to create group mean Any site with = 2 mm attachment loss was eliminated from analysis

Evidence Table 2b. Effectiveness of Local Minocycline as an Adjunct to Scaling and Root Planing to Treat Chronic Periodontitis (continued)

	Outcomes Accessed			
	Attachment Level mm	Probing Depth mm	Spirochetes	
(N of Pts)	$\bar{x}$ (SD)	$\bar{x}$ (SD)	$\bar{x}$ % (SD)	Comments
Baseline:				Presented actual data for baseline but not for final. Instead just showed figures (bar graphs) which depicted the amount of change. Can not interpolate data from records.
T:	10.93 (1.5)	6.12 (0.63)	NA	
C:	10.77 (1.22)	5.56 (0.95)	NA	
Final: 26 weeks				
T: 11	NR	NR	NA	
C: 6	NR	NR	NA	**Quality Score:** 46; 46
Change:				
T:	NR	NR	NA	
C:	NR	NR	NA	
Test:	Duncans Multiple Range Test	Duncans Multiple Range Test		
P value:	NS	NS		

Evidence Table 2b. Effectiveness of Local Minocycline as an Adjunct to Scaling and Root Planing to Treat Chronic Periodontitis (continued)

Study Description	Study Design Characteristics	Disease Characteristics	Examiner Characteristics	Description of Scaling and Root Planing
Author and Year: Kinane and Radvar 1999[53] **Study Period:** 26 weeks (6 months) **Site of Study:** Peridontal Department of the Glasgow Dental Hospital **Location:** Glasgow, Scotland **Patients Selected:** Patients with pockets that did not respond to SRP; at least 4 pockets > 5 mm and BOP that did not respond to SRP	**Design Type:** Parallel RCT **Subject/Site Allocation:** Random **Blinding:** Examiner blind **Placebo:** No **Split-mouth:** No	**Severity:** Chronic periodontitis with persistent pockets **Types of Teeth:** Sites with furcation lesions excluded **Widman flap:** NR	**Number:** 1 **Trained:** NR **Assigned to Subjects:** Same examiner throughout study	**SRP performed:** Scaling and root planing under local anesthesia **Time spent on SRP:** NR

Evidence Table 2b. Effectiveness of Local Minocycline as an Adjunct to Scaling and Root Planing to Treat Chronic Periodontitis (continued)

Eligible Study Groups and How Defined:	Study Group Characteristics	Compliance Monitoring	Baseline Measures	Assessment Time Interval(s)
Subject/Site allocation: 41 subjects T: 21 subjects C: 20 subjects **Dose, Mode, Schedule:** T: SRP plus 2% minocycline gel at baseline and weeks 2 and 4 C: SRP only	**Age:** Mean: 45 (± 6.4) **Gender Distribution:** Males: 50 Females: 29 **Race/Ethnicity:** NR	NR	Before SRP	3 times (at baseline, 6 weeks, and 6 months)

Evidence Table 2b. Effectiveness of Local Minocycline as an Adjunct to Scaling and Root Planing to Treat Chronic Periodontitis (continued)

Study Description	Outcomes Assessed	Adverse Effects	Study Group Attrition and Reasons	Type of Analysis
Kinane and Radvar 1999[53] (continued)	**Clinical Measurement:** PD BOP/SBI PII CAL MGI Supperation **Radiographic Techniques:** NR **Microbiological Methods:** NR **Subject Self Report:** NR	Examined for adverse signs but none reported	Control: reason not given (1); Treatment group: reason not given (1)	**Type of analysis reported:** Full participants only Analysis adjusted: GLM, baseline as continuous covariate

Evidence Table 2b. Effectiveness of Local Minocycline as an Adjunct to Scaling and Root Planing to Treat Chronic Periodontitis (continued)

	Outcomes Accessed			
	Attachment Level mm	Probing Depth mm	Spirochetes	
(N of Pts)	$\bar{x}$ (SD)	$\bar{x}$ (SD)	$\bar{x}$ % (SD)	Comments
Baseline:				This is a follow-up study
T: 21	NR	5.58 (0.15 se)	NA	
C: 20	NR	5.48 (0.18 se)	NA	**Quality Score:** 54; 62
Final: 26 weeks				
T: 21	NR	NR	NA	
C: 20	NR	NR	NA	
Change:	Gain	Reduction		
T:	0.57 (0.11 se)	1.10 (0.16 se)	NA	
C:	0.54 (0.14 se)	0.71 (0.19 se)	NA	
Test:	GLM	GLM		
P value:	NS	NS		

Evidence Table 2b. Effectiveness of Local Minocycline as an Adjunct to Scaling and Root Planing to Treat Chronic Periodontitis (continued)

Study Description	Study Design Characteristics	Disease Characteristics	Examiner Characteristics	Description of Scaling and Root Planing
Author and Year: Van Dyke et al, 2002[68]	**Design Type:** RCT	**Severity:** Moderate to severe peridontitis	**Number:** NR	**SRP performed:** NR
Study Period: 26 weeks (6 months)	**Subject/Site Allocation:** Random	**Types of Teeth:** No third molars	**Trained:** NR	**Time spent on SRP:** NR
Site of Study: NR	**Blinding:** Examiners and patients blind	**Widman flap:** NR	**Assigned to Patients:** NR	
Location: NR	**Placebo:** No			
Patients Selected: Adult patients with = 2 teeth having 1 site with PD = 6 mm and prostaglandin E_2 levels > 66.2 nt/ml in gingival crevicular fluid	**Split-mouth:** No			

Evidence Table 2b. Effectiveness of Local Minocycline as an Adjunct to Scaling and Root Planing to Treat Chronic Periodontitis (continued)

Eligible Study Groups and How Defined:	Study Group Characteristics	Compliance Monitoring	Baseline Measures	Assessment Time Interval(s)
Subject/Site allocation: 50 subjects recruited for full study (2 teeth per subject per treatment group) 22 completed T: 12 subjects (77 sites) C: 10 subjects (53 sites) **Dose, Mode, Schedule:** T: SRP plus 1 mg microencapsulated minocycline C: SRP and saline	**Mean Age:** NR **Gender Distribution:** Male: NR Female: NR **Race/Ethnicity:** NR	NR	Before SRP	4 times (at baseline, 1, 3 and 6 months)

Evidence Table 2b. Effectiveness of Local Minocycline as an Adjunct to Scaling and Root Planing to Treat Chronic Periodontitis (continued)

Study Description	Outcomes Assessed	Adverse Effects	Study Group Attrition and Reasons	Type of Analysis
Van Dyke et al., 2002[68] (continued)	**Clinical Measurement:** PD CAL BI PI GI **Radiographic Techniques:** NR **Microbiological Methods:** NR **Patient Self Report:** NR	Treatment group: black hairy tongue and abscesses at study sites unrelated to study drug (1), rhinitis (1); 1 subject in control group reported myalgia and granulo-matous lesion	7 sites in 2 subjects in treatment group not evaluable due to insufficient baseline PD	**Type of analysis reported:** Intent to treat

Evidence Table 2b. Effectiveness of Local Minocycline as an Adjunct to Scaling and Root Planing to Treat Chronic Periodontitis (continued)

	Outcomes Accessed			
	Attachment Level mm	Probing Depth mm	Spirochetes	
(N of Pts)	$\bar{x}$ (SD)	$\bar{x}$ (SD)	$\bar{x}$ (SD)	Comments
Baseline:				Substantially greater reductions in PD and CAL gains at each post treatment point versus control
T:	11.01 (NR)	6.86 (NR)	N/A	
C:	11.11 (NR)	6.53 (NR)	N/A	
Final: 26 weeks (6 months)				Difference between treatments in sites with = 5 mm and < 6 mm PD were highly significant ($P < 0.01$) at time points
T: 12	NR	NR	N/A	
C: 10	NR	NR	N/A	
Change:				
T:	1.02 (0.26 se)	1.94 (0.21 se)	N/A	
C:	0.54 (0.18 se)	1.66 (0.20 se)	N/A	For sites with PD > 6 mm no statistical significant differences between treatment groups
Test:	NR	NR		
P value:	NS	NS		
				Quality Score: 46; 46

Evidence Table 2b. Effectiveness of Local Minocycline as an Adjunct to Scaling and Root Planing to Treat Chronic Periodontitis (continued)

Study Description	Study Design Characteristics	Disease Characteristics	Examiner Characteristics	Description of Scaling and Root Planing
Author and Year: van Steenberghe et al., 1993[63] **Study Period:** 12 weeks **Site of Study:** 4 Universities **Location:** Belgium **Patients Selected:** Adults with at least 1 PD with = 5 mm and attachment loss = 3 mm in at least 1 site per quadrant; and radiographic evidence of alveoler bone loss	**Design Type:** RCT **Subject/Site Allocation:** Random **Blinding:** Examiners and patients blind **Placebo:** Yes **Split-mouth:** No	**Severity:** Moderate to severe chronic periodontitis **Types of Teeth:** NR **Widman flap:** NR	**Number:** I at each site **Trained:** Yes, experienced thorough discussion prior and during trial minimized diffs in clinical procedures **Assigned to Subjects:** Same examiner throughout study	**SRP performed:** SRP using hand instruments were performed at all surfaces of tested teeth **Time spent on SRP:** Max 3 minutes/tooth and 15/quad

Evidence Table 2b. Effectiveness of Local Minocycline as an Adjunct to Scaling and Root Planing to Treat Chronic Periodontitis (continued)

Eligible Study Groups and How Defined:	Study Group Characteristics	Compliance Monitoring	Baseline Measures	Assessment Time Interval(s)
Subject/Site allocation: 103 subjects enrolled 81 subjects completed T: 42 subjects C: 39 subjects **Dose, Mode, Schedule:** T: SRP plus 2% minocycline ointment applied at baseline, and weeks 2, 4, and 6 C: SRP plus placebo at baseline, and weeks 2, 4, and 6	**Age:** Mean: 48.7 **Gender Distribution:** Males: 41 Females: 62 **Race/Ethnicity:** NR	NA	Before SRP	5 times (at baseline, and weeks 2, 4, 6, and 12)

Evidence Table 2b. Effectiveness of Local Minocycline as an Adjunct to Scaling and Root Planing to Treat Chronic Periodontitis (continued)

Study Description	Outcomes Assessed	Adverse Effects	Study Group Attrition and Reasons	Type of Analysis
van Steenberghe et al., 1993[63] (continued)	**Clinical Measurement:** BOP PII GI GCF PD CAL **Radiographic Techniques:** NR **Microbiological Methods:** DNA Probe assay **Subject Self Report:** NR	T: 17% gingival abcesses, diarrhea, gingival edema, echy-mosis, upset stomach C: 12% gingival abcesses, mouth ulceration and pain	22 subjects not included because of: lack of baseline data (4); failed to return (14); lost to follow-up (3); antibiotic use (1)	**Type of analysis reported:** Full participants only

Evidence Table 2b. Effectiveness of Local Minocycline as an Adjunct to Scaling and Root Planing to Treat Chronic Periodontitis (continued)

	Outcomes Accessed			
(N of Pts)	Attachment Level mm $\bar{x}$ (SD)	Probing Depth mm $\bar{x}$ (SD)	Spirochetes $\bar{x}$ % (SD)	Comments
PD = 5 m				Difference in PAL 0.8 mm in each group, not significant, *P* = 0.58
Baseline:				
T:	NR	5.9 (NR)	NA	
C:	NR	5.9 (NR)	NA	
				Microbial outcomes assessed: No data, but stated significant changes in *P.g., A.a.,* and *P.I.* at weeks 6 and 12
Final: 12 weeks				
T: 42 (897 sites)	NR	4.2 (NR)	NA	
C: 39 (745 sites)	NR	4.5 (NR)	NA	
Change:				
T:	0.8 (NR)	1.7 (NR)	NA	Reduction in bacterial counts were associated with an improvement in clinical parameters
C:	0.8 (NR)	1.4 (NR)	NA	
Test:	t-test	t-test		
P value:	NS	= 0.0018		
				Quality Score: 69; 77
PD = 7 mm				
Baseline:				
T:	NR	7.5 (NR)	NA	
C:	NR	7.8 (NR)	NA	
Final: 12 weeks				
T: 28 (151 sites)	NR	4.4 (NR)	NA	
C: 24 (140 (sites)	NR	5.7 (NR)	NA	
Change:				
T:	1.3 (NR)	3.1 (NR)	NA	
C:	0.9 (NR)	2.1 (NR)	NA	
Test:	t-test	t-test		
P value:	NS	=0.0001		

Evidence Table 2b. Effectiveness of Local Minocycline as an Adjunct to Scaling and Root Planing to Treat Chronic Periodontitis (continued)

Study Description	Study Design Characteristics	Disease Characteristics	Examiner Characteristics	Description of Scaling and Root Planing
Author and Year: van Steenberghe et al., 1999[65] **Study Period:** 65 weeks (15 months) **Site of Study:** 6 university centers **Location:** Belgium, Sweden, The Netherlands, United Kingdom **Patients Selected:** Patients with = 1 approximal PD of > 5 mm attachment loss of = 3 mm, and radiographic evidence of alveolar bone loss in at least 1 site per quadrant	**Design Type:** RCT **Subject/Site Allocation:** Random **Blinding:** Examiners and patients blind **Placebo:** Yes **Split-mouth:** No	**Severity:** Moderate to severe chronic periodontitis **Types of Teeth:** NR **Widman flap:** NR	**Number:** 1/center (6 centers) **Trained:** Yes **Assigned to Subjects:** NR	**SRP performed:** Both supra and subgingival hand scaling under local anesthesia (if necessary); repeated at 6 and 12 months. **Time spent on SRP:** Maximum 15 min/quad

Evidence Table 2b. Effectiveness of Local Minocycline as an Adjunct to Scaling and Root Planing to Treat Chronic Periodontitis (continued)

Eligible Study Groups and How Defined:	Study Group Characteristics	Compliance Monitoring	Baseline Measures	Assessment Time Interval(s)
Subject/Site allocation: 104 subjects enrolled 93 completed T: 46 subjects C: 47subjects **Dose, Mode, Schedule:** T: SRP plus 2% minocycline ointment applied at baseline, 2 wks, 1, 3, 6, 9, and 12 months C: SRP plus placebo applied at baseline, 2 wks, 3, 6, 9, and 12 months	**Age:** Enrollees: Mean: 46 Range: 34 to 64 **Gender Distribution:** Males: 50% Males: 43 Females: 50 **Race/Ethnicity:** NR	NR	Before SRP	7 times (at baseline, and months 1, 3, 6, 9, 12, and 15) Additional microbiological sampling at week 2.

Evidence Table 2b. Effectiveness of Local Minocycline as an Adjunct to Scaling and Root Planing to Treat Chronic Periodontitis (continued)

Study Description	Outcomes Assessed	Adverse Effects	Study Group Attrition and Reasons	Type of Analysis
van Steenberghe et al., 1999[65] (continued)	**Clinical Measurement:** BOP PII PD CAL GI BI **Radiographic Techniques:** Full mouth intra-oral radiography **Microbiological Methods:** DNA/RNA Probe (P.i. and microbiological) **Subject Self Report:** NR	T: 11 C: 14 Minor clinical adverse reactions (e.g., redness) 3 in of treatment group reported abcesses	6 treatment and 5 control subjects excluded because they did not have a valid baseline evaluation, invalid post-baseline visits, improper randomiza-tions, plus other reasons not listed for 2 subjects	**Type of analysis reported:** Full participants only

Evidence Table 2b. Effectiveness of Local Minocycline as an Adjunct to Scaling and Root Planing to Treat Chronic Periodontitis (continued)

	Outcomes Accessed			
(N of Pts)	Attachment Level mm $\bar{x}$ (SD)	Probing Depth mm $\bar{x}$ (SD)	Spirochetes $\bar{x}$ % (SD)	Comments
PD = 5 mm				Microbial outcomes assessed:
Baseline:				
T: 46	NR	6.5 (NR)	NA	
C: 47	NR	6.3 (NR)	NA	Statistically significant greater reductions in P.g., T.d., and C.r. from baseline. For P.i. and A.a. the changes were not significant. F.n. and E.c. changes were not significant.
Final: 65 weeks				
T: (PD) (1241 sites)	NR	4.6 (NR)	NA	
C: (PD) (1275 sites)	NR	5.1 (NR)	NA	
Change:	Gain			
T: (CAL) 45 (1.231 sites)	0.9 (NR)	1.9 (NR)	NA	**Quality Score:** 85; 92
C: (CAL) 45 (1.275 sites)	0.5 (NR)	1.2 (NR)	NA	
Test:	t-test	t-test		
P value:	0.0001	0.0001		
PD = 7 mm				
Baseline:				
T:	NR	8.1 (NR)	NA	
C:	NR	7.7 (NR)	NA	
Final: 65 weeks				
T: 36 (334 sites)	NR	5.3 (NR)	NA	
C: 35 (284 sites)	NR	6.0 (NR)	NA	
Change:	Gain			
T:	1.4 (NR)	2.8 (NR)	NA	
C:	1.0 (NR)	1.7 (NR)	NA	
Test:	t-test	t-test		
P value:	0.0001	0.0001		

Evidence Table 2b. Effectiveness of Local Minocycline as an Adjunct to Scaling and Root Planing to Treat Chronic Periodontitis (continued)

Study Description	Study Design Characteristics	Disease Characteristics	Examiner Characteristics	Description of Scaling and Root Planing
Author and Year: Williams et al., 2001[66] **Study Period:** 39 weeks (9 months) **Site of Study:** 18 centers at Universities **Location:** USA **Patients Selected:** Adult patients with at least 4 teeth with 6-9 mm PD with BOP	**Design Type:** RCT **Subject/Site Allocation:** Random but stratified for smoking and study center **Blinding:** Examiners and patients blind **Placebo:** Yes **Split-mouth:** No	**Severity:** Moderate to advanced periodontitis **Types of Teeth:** NR **Widman flap:** NR	**Number:** 1 per site **Trained:** Trained and calibrated **Assigned to Subjects:** Same examiner throughout study	**SRP performed:** Full mouth, local anesthesia if needed **Time spent on SRP:** No limit on time

Evidence Table 2b. Effectiveness of Local Minocycline as an Adjunct to Scaling and Root Planing to Treat Chronic Periodontitis (continued)

Eligible Study Groups and How Defined:	Study Group Characteristics	Compliance Monitoring	Baseline Measures	Assessment Time Interval(s)
Subject/Site allocation: 498 subjects enrolled 467 completed T: 249/237 subjects C: 249/230 subjects **Dose, Mode, Schedule:** T: SRP plus 1 mg of 2% minocycline microspheres in 3 mg of polymer applied in all sites with pockets = 5 mm at baseline and months 3 and 6 C: SRP plus 3 mg of placebo polymer	**Age:** Mean: T: 49.1 C: 47.2 Range: 27-79 **Gender Distribution:** Male: 54.8% **Race/Ethnicity:** White: 76%	NA	Before SRP	5 times (at baseline, 1, 3, 6, and 9 months)

Evidence Table 2b. Effectiveness of Local Minocycline as an Adjunct to Scaling and Root Planing to Treat Chronic Periodontitis (continued)

Study Description	Outcomes Assessed	Adverse Effects	Study Group Attrition and Reasons	Type of Analysis
Williams et al., 2001[66] (continued)	**Clinical Measurement:** PD CAL BOP **Radiographic Techniques:** NR **Microbiological Methods:** NR **Subject Self Report:** NR``	T: 68% C: 72% Most common: headache, dental infection, increased perio-dontitis, tooth sensitivity, tooth caries, dental pain, gingivitis, stomatitis	NR	**Type of analysis reported:** Intent to treat (All sites with PD = 5 mm at baseline were included)

Evidence Table 2b. Effectiveness of Local Minocycline as an Adjunct to Scaling and Root Planing to Treat Chronic Periodontitis (continued)

	Outcomes Accessed			
	Attachment Level mm	Probing Depth mm	Spirochetes	
(N of Pts)	$\bar{x}$ (SD)	$\bar{x}$ (SD)	$\bar{x}$ % (SD)	Comments
Baseline:				CAL: Changes not reported for any group
T:	5.39 (1.43)	5.8 (0.4)	NA	Change for PD = 6 mm: T: 1.46 (0.09 se) C: 1.05 (0.10 se) *P* = 0.01
C:	5.38 (1.38)	5.9 (0.5)	NA	
Final: 39 weeks				Change for PD = 7 mm: T: 1.99 (0.31 se) C: 0.98 (0.29 se) *P* = 0.06
T: 237	NR	NR	NA	
C: 230	NR	NR	NA	
Change:		Reduction		**Quality Score:** 92; 92
T:	NR	1.32 (0.04 se)	NA	
C:	NR	1.00 (0.04 se)	NA	
Test:		ANCOVA/GLM		
P value:		< 0.001		

Evidence Table 3a. Effectiveness of Systemic Metronidazole as an Adjunct to Scaling and Root Planing to Treat Chronic Periodontitis

Study Description	Study Design Characteristics	Disease Characteristics	Examiner Characteristics	Description of Scaling and Root Planing
Joyston-Bechal et al., 1986[71] **Study Period:** 156 weeks (3 years) **Study/Treatment Site:** Hospital dental clinic **Location:** London, England **Patient Population:** Patients from a previous study invited for follow-up study 3 years later	**Design Type:** RCT **Subject/Site Allocation:** Random **Blinding:** Examiners and patients blind **Placebo:** Yes **Split-mouth:** No	**Severity:** Moderate, severe **Types of Teeth:** Teeth 16, 21, 24, 36, 41, and 44 **Widman flap:** NR	**Number:** NR **Trained:** NR **Assigned to Subjects:** NR	**SRP performed:** Scaling and oral hygiene **Time spent:** NR

Evidence Table 3a. Effectiveness of Systemic Metronidazole as an Adjunct to Scaling and Root Planing to Treat Chronic Periodontitis (continued)

Eligible Study Groups and How Defined:	Study Group Characteristics	Compliance Monitoring	Baseline Measures	Time Interval(s)
Subject/Site allocation: 28 subjects of the original 45 subjects in earlier study T: 15 subjects C: 13 subjects **Dose, Mode, Schedule:** T: SRP plus 1% chlorhexidine gel for the first 10 weeks; at the end of 2 weeks, they began 200 mg metronidazole, 1 that evening and 3xday for 5 days; repeated 4 weeks later; SRP as needed at 4 week intervals until week 10. Over the next 3 years, SRP given 2xyear as needed C: SRP with placebo; 1 tablet that evening and 3xday for 5 days; repeated 4 weeks later; SRP as needed at 4 week intervals until week 10. Over the next 3 years, got SRP 2xyear as needed	**Age:** NR **Gender:** NR **Race/Ethnicity:** NR	NR	NR	2 times (at baseline and 156 weeks)

Evidence Table 3a. Effectiveness of Systemic Metronidazole as an Adjunct to Scaling and Root Planing to Treat Chronic Periodontitis (continued)

Study Description	Outcomes Assessed	Adverse Effects	Study Group Attrition and Reasons	Type of Analysis
Joyston-Bechal et al., 1986[71] (continued)	**Clinical Measurement:** BOP/SBI PII PD Gingival bleeding Calculus **Radiographic Techniques:** NR **Microbiological Methods:** NR **Subject Self Report:** NR	NR	NR	**Type of analysis reported:** All who completed follow-up

Evidence Table 3a. Effectiveness of Systemic Metronidazole as an Adjunct to Scaling and Root Planing to Treat Chronic Periodontitis (continued)

	Outcomes Accessed			
	Attachment Level mm	Probing Depth mm	Spirochetes	
(N of Pts)	$\bar{x}$ (SD)	$\bar{x}$ (SD)	$\bar{x}$ % (SD)	Comments
Baseline:				There were no significant differences between test and control groups in mean PD. However, when T and C were subdivided into severity groups, the shallower pockets differed by treatment group (P = 0.027) but the deeper did not (P = 0.89). These results are different from the original 22 week study where deeper pockets benefited more from metronidazole. **Quality Score:** 38; 31
T: 15	NA	3.61 (NR)	NA	
C: 13	NA	3.61 (NR)	NA	
Final: 156 weeks				
T: 15	NA	2.58 (NR)	NA	
C: 13	NA	2.99 (NR)	NA	
Change:		Reduction		
T: 15	NA	1.03 (NR)	NA	
C: 13	NA	0.62 (NR)	NA	
Test:		t-test		
P value:		0.214		

Evidence Table 3a. Effectiveness of Systemic Metronidazole as an Adjunct to Scaling and Root Planing to Treat Chronic Periodontitis (continued)

Study Description	Study Design Characteristics	Disease Characteristics	Examiner Characteristics	Description of Scaling and Root Planing
Loesche et al., 1984[69] **Study Period:** 30 weeks **Study/Treatment Site:** University of Michigan, School of Dentistry **Location:** Ann Arbor, MI **Patient Population:** Patients with multiple sites of periodontal bone loss, BOP, and an anaerobic periodontal infection assigned to groups depending on initial severity of condition	**Design Type:** RCT **Subject/Site Allocation:** Random **Blinding:** Examiner and patients blind **Placebo:** Yes **Split-mouth:** No	**Severity:** Moderate to advanced periodontitis, multiple sites with bone loss and infection **Types of Teeth:** Both **Widman flap:** NR	**Number:** 1 **Trained:** NA **Assigned to Subjects:** Same examiner throughout study	**SRP performed:** Mechanical debridement (meticulous root surface debridement) **Time spent:** NR

Evidence Table 3a. Effectiveness of Systemic Metronidazole as an Adjunct to Scaling and Root Planing to Treat Chronic Periodontitis (continued)

Eligible Study Groups and How Defined:	Study Group Characteristics	Compliance Monitoring	Baseline Measures	Time Interval(s)
Subject/Site allocation: 14 subjects T: 7 subjects C: 7 subjects **Dose, Mode, Schedule:** T: SRP plus 250 mg metronidazole 3xday for 7 days starting at first session of root scaling C: SRP and placebo tablets 3xday for 7 days	**Age:** NR **Gender:** NR **Race/Ethnicity:** NR	All subjects reported that they used the entire supply of medication	NR	4 times (at baseline and weeks 2, 15, and 30)

Evidence Table 3a. Effectiveness of Systemic Metronidazole as an Adjunct to Scaling and Root Planing to Treat Chronic Periodontitis (continued)

Study Description	Outcomes Assessed	Adverse Effects	Study Group Attrition and Reasons	Type of Analysis
Loesche et al., 1984[69] (continued)	**Clinical Measurement:** PD CAL **Radiographic Techniques:** NR **Microbiological Methods:** Bacteriological sampling, anaerobic count of agar colonies dark field microscopy **Subject Self Report:** NR	Metallic taste	Unknown number of subjects that did not return for clinical examinations of PD and CAL	**Type of analysis reported:** Full participants only, though the bacteriological analysis used all available data

Evidence Table 3a. Effectiveness of Systemic Metronidazole as an Adjunct to Scaling and Root Planing to Treat Chronic Periodontitis (continued)

Outcomes Accessed					
	(N of Pts)	Attachment Level mm $\bar{x}$ (SD)	Probing Depth mm $\bar{x}$ (SD)	Spirochetes $\bar{x}$ % (SD)	Comments
					Microbial Outcomes:
Baseline:					P.g.
T:	NR	5.4 (NR)	5.2 (NR)	37.8 (NR)	Baseline: Final:
C:	NR	5.0 (NR)	6.2 (NR)	31.7 (NR)	T: 5.9 T: 0.9
					C: 5.8 C: 2.0
Final: 15 to 30 weeks					
T:	NR	NR	NR	19.6 (NR)	The treatment group had significant and sustained reduction of certain anaerobic organisms, such as *B.g.* and large spirochetes
C:	NR	NR	NR	31.2 (NR)	
PD 4 to 6 mm or 4-6 mm Attachment Loss:					
Change:		Gain	Reduction		
T:	NR	0.38	1.19 (NR)	NR	
C:	NR	0.28	1.05 (NR)	NR	
Test:		t-test	t-test		**Quality Score:** 46; 46
P value:		NS	NS		
PD 6+ mm:					
Change:		Gain	Reduction		
T:	NR	1.42 (NR)	3.19 (NR)	NR	
C:	NR	0.23 (NR)	1.55 (NR)	NR	
Test:		t-test	t-test		
P value:		0.05	0.03		

Evidence Table 3a. Effectiveness of Systemic Metronidazole as an Adjunct to Scaling and Root Planing to Treat Chronic Periodontitis (continued)

Study Description	Study Design Characteristics	Disease Characteristics	Examiner Characteristics	Description of Scaling and Root Planing
Loesche et al., 1991[73] **Study Period:** 52 weeks **Study/Treatment Site:** Graduate Periodontal University Clinic **Location:** USA **Patient Population:** Adult patients with deep pocketing and radiographic evidence bone loss about one or more teeth per jaw quadrant, spirochete infection in 2 quadrants	**Design Type:** RCT **Subject/Site Allocation:** Random **Blinding:** Examiners and patients blind **Placebo:** Yes **Split-mouth:** No	**Severity:** Advanced periodontitis **Types of Teeth:** Disto lingual sites not included **Widman flap:** NR	**Number:** 15 graduate students provided treatment, clinician did pre and post exam **Trained:** Used standard procedures **Assigned to Subjects:** Same examiner at each treatment planning assessment	**SRP performed:** Rigorous debridement of the root surfaces of teeth that had 3 mm of probing depth and occlusal adjustment of the teeth if necessary **Time spent:** 3 to 8 clinic visits

Evidence Table 3a. Effectiveness of Systemic Metronidazole as an Adjunct to Scaling and Root Planing to Treat Chronic Periodontitis (continued)

Eligible Study Groups and How Defined:	Study Group Characteristics	Compliance Monitoring	Baseline Measures	Time Interval(s)
Subject/Site allocation: 50 subjects started 39 completed T: 18 subjects C: 21 subjects **Dose, Mode, Schedule:** T: SRP plus 250 mg metronidazole tablets 3xday for 1 week C: SRP plus placebo tablets for 1 week	**Age:** T: 47.9 ± 9.2 C: 48.3 ± 11.5 **Gender:** Males: 20 (T: 9; C: 11) Females: 19 (T: 9, C: 10) **Race/Ethnicity:** NR	All subjects reported taking the medication as instructed except for 1 who stopped taking meds after 4 days because of a "leg cramp"	Before SRP	4 times (at baseline, weeks 4 to 6, and 2 annual visits)

Evidence Table 3a. Effectiveness of Systemic Metronidazole as an Adjunct to Scaling and Root Planing to Treat Chronic Periodontitis (continued)

Study Description	Outcomes Assessed	Adverse Effects	Study Group Attrition and Reasons	Type of Analysis
Loesche et al., 1991[73]	**Clinical Measurement:** BOP/SBI PD CAL Root topography Nature of bony defect Adequacy of access for thorough root instrumentation **Radiographic Techniques:** Bone Loss/Regeneration **Microbiological Methods:** Plaque microbiota, total anaerobic count, dark field microscopy	No complaints about medication	Of the original 50, losses were due to pts not returning for treatment, moved from community, or refused treatment (no numbers reported)	**Type of analysis reported:** All who completed follow-up

Evidence Table 3a. Effectiveness of Systemic Metronidazole as an Adjunct to Scaling and Root Planing to Treat Chronic Periodontitis (continued)

Outcomes Accessed					
	(N of Pts)	Attachment Level mm $\bar{x}$ (SD)	Probing Depth mm $\bar{x}$ (SD)	Spirochetes $\bar{x}$ % (SD)	Comments
Baseline:					Microbial Outcomes: Baseline: Final:
T:	18	NR	NR	52.6 (4.1)	*P.g.* *P.g.*
C:	21	NR	NR	59.1 (2.5)	T: 0.5 (0.2) T: 0.5 (0.5) C: 3.0 (2.1) C: 0.2 (0.1)
Final: 52 weeks					
T:	18	NR	NR	NR	*A.a.* *A.a.*
C:	21	NR	NR	NR	T: < 0.01 T: < 0.01 C: < 0.01 C: < 0.01
PD 4-6 mm (23 – 74 sites)					
Change:		Gain	Reduction		Metronidazole had a significant effect on the site specific reduction of spirochetes. 90% of sites in the treatment group and 64% in control had decrease in the percentage of spirochetes ($P < 0.05$)
T:	17	0.40 (NR)	0.75 (NR)	NR	
C:	19	0.27 (NR)	0.81 (NR)	NR	
Test:		ANOVA	ANOVA		
P value:		NS	NS		
PD 7+ mm (1-47 sites)					
Change:					
T:	17	0.86 (NR)	1.91 (NR)	NR	
C:	19	0.54 (NR)	1.50 (NR)	NR	No significant differences between the treatment groups were observed for CAL or PD.
Test:		ANOVA	ANOVA		
P value:		NS	NS		
					Quality Score: 54; 46

Evidence Table 3a. Effectiveness of Systemic Metronidazole as an Adjunct to Scaling and Root Planing to Treat Chronic Periodontitis (continued)

Study Description	Study Design Characteristics	Disease Characteristics	Examiner Characteristics	Description of Scaling and Root Planing
Loesche et al., 1992[74] **Study Period:** 104 weeks (2 years) **Study/Treatment Site:** Graduate Periodontal Clinic **Location:** NR **Patient Population:** Adult patients with deep pocketing and bone loss about 1 or more teeth per jaw quadrant (at least 4 such teeth per patient) with 20% + spirochetes	**Design Type:** RCT **Subject/Site Allocation:** Random **Blinding:** Examiners and patients blind **Placebo:** Yes **Split-mouth:** No	**Severity:** Advanced adult periodontitis **Types of Teeth:** NR **Widman flap:** NR	**Number:** NR **Trained:** NR **Assigned to Subjects:** Same examiner for each treatment planning session; examiner not involved in evaluation of data	**SRP performed:** Rigorous debridement of root surfaces of teeth that had 3 mm or more PD and occlusal adjustment of teeth if necessary by 2 grad students **Time spent:** NR

Evidence Table 3a. Effectiveness of Systemic Metronidazole as an Adjunct to Scaling and Root Planing to Treat Chronic Periodontitis (continued)

Eligible Study Groups and How Defined:	Study Group Characteristics	Compliance Monitoring	Baseline Measures	Time Interval(s)
Subject/Site allocation: 33 subjects completed T: 15 subjects C: 18 subjects **Dose, Mode, Schedule:** T: SRP plus 250 mg metronidazole 3xday for 1 week after SRP C: SRP with placebo (3xday for 1 week)	**Age:** NR **Gender:** Males: 17 Females: 16 **Race/Ethnicity:** NR	All subjects reported taking the medication as instructed	Before SRP	5 times (at baseline, 4-6 weeks, then annually for 2 years)

Evidence Table 3a. Effectiveness of Systemic Metronidazole as an Adjunct to Scaling and Root Planing to Treat Chronic Periodontitis (continued)

Study Description	Outcomes Assessed	Adverse Effects	Study Group Attrition and Reasons	Type of Analysis
Loesche et al., 1992[74] (continued)	**Clinical Measurement:** BOP/SBI PD CAL Root topography Nature of bony defect Adequacy of access for thorough root instrumentation **Radiographic Techniques:** Bone Loss/Regeneration **Microbiological Methods:** Anaerobic count of agar colonies **Subject Self Report:** NR	Metallic taste	Non-return for treatments; moved from community, or deceased	**Type of analysis reported:** Full participants only (with exception of 1 subject who completed the bacteriological analysis but wouldn't return for clinical exam)

Evidence Table 3a. Effectiveness of Systemic Metronidazole as an Adjunct to Scaling and Root Planing to Treat Chronic Periodontitis (continued)

	Outcomes Accessed			
	Attachment Level mm	Probing Depth mm	Spirochetes	
(N of Pts)	$\bar{x}$ (SD)	$\bar{x}$ (SD)	$\bar{x}$% (SD)	Comments
PD = 3 mm (39-121 sites) per subject				Microbial Outcomes:
Baseline:				Baseline: Final:
T:	NR	NR	NA	*P.g.* *P.g.*
C:	NR	NR	NA	T: 0.1 (0.2) T: < 0.1 (0.1)
Final: 104 weeks				C: 0.4 (1.4) C: < 0.1 (0.1)
T:	NR	NR	NA	*A.a.* *A.a.*
C:	NR	NR	NA	T: < 0.1 (0.1) T: < 0.1 (0.1)
Change:	Gain	Reduction		C: 0.3 (1.1) C: < 0.1 (0.1)
T:	0.04 (NR)	0.05 (NR)	NA	The clinical improvements in the metronidazole group were associated with significantly lower proportions of spirochetes. These findings indicate that systemic metronidazole, when given after the root surface debridement is completed, leads to additional treatment benefits including a reduced need for surgery.
C:	-0.33 (NR)	0.20 (NR)	NA	
Test:	ANOVA	ANOVA		
P value:	0.07	0.08		
PD4 – 6 mm (16-69 sites) per subject				
Baseline:				
T:	NR	NR	NA	
C:	NR	NR	NA	
Final: 104 weeks				
T:	NR	NR	NA	
C:	NR	NR	NA	
Change:	Gain	Reduction		At 4-6 weeks, treatment group had highly significant ($P < 0.01$) reduction in PD and gain in attachment levels in relation to controls in PD 4-6 mm and = 7 mm.
T:	0.79 (NR)	1.22 (NR)	NA	
C:	0.32 (NR)	0.75 (NR)	NA	
Test:	ANOVA	ANOVA		
P value:	< 0.01	< 0.01		
PD = 7 mm (1-51 sites) per subject				**Quality Score:** 46; 38
Baseline:				
T:	NR	NR	NA	
C:	NR	NR	NA	
Final: 104 weeks				
T:	NR	NR	NA	
C:	NR	NR	NA	Spirochetes ($\bar{x}$%):
Change:	Gain			Baseline Final
T:	1.69 (NR)	2.83 (NR)	NA	T: 59.1 (18.0 22.9 (17.0)
C:	1.03 (NR)	1.78 (NR)	NA	C: 60.0 (12.7) 34.8 (20.3)
Test:	ANOVA	ANOVA		
P value:	0.06	< 0.01		

Evidence Table 3a. Effectiveness of Systemic Metronidazole as an Adjunct to Scaling and Root Planing to Treat Chronic Periodontitis (continued)

Study Description	Study Design Characteristics	Disease Characteristics	Examiner Characteristics	Description of Scaling and Root Planing
Noyan et al., 1997[75] **Study Period:** 6 weeks **Study/Treatment Site:** NR **Location:** Turkey **Patient Population:** Adults with at least 1 approximal site per quadrant with PD = 5 mm	**Design Type:** RCT **Subject/Site Allocation:** Random **Blinding:** NR **Placebo:** No **Split-mouth:** Yes	**Severity:** NR **Types of Teeth:** NR **Widman flap:** NR	**Number:** 2 **Trained:** NR **Assigned to Subjects:** NR	**SRP performed:** Mechanical subgingival debridement at selected sites in 2 quadrants, repeated 7 days later. **Time spent:** NR

Evidence Table 3a. Effectiveness of Systemic Metronidazole as an Adjunct to Scaling and Root Planing to Treat Chronic Periodontitis (continued)

Eligible Study Groups and How Defined:	Study Group Characteristics	Compliance Monitoring	Baseline Measures	Time Interval(s)
Subject/Site allocation: 10 subjects T: 5 subjects C: 5 subjects **Dose, Mode, Schedule:** T: SRP plus 250 mg 1xday metronidazole for 7 days and second SRP after 1 week C: SRP at baseline and second SRP at week 1	**Age:** Range: 35 to 51 **Gender:** Male: 3 Female: 7 **Race/Ethnicity:** NR	NR	Before SRP	2 times (at baseline and 6 weeks)

Evidence Table 3a. Effectiveness of Systemic Metronidazole as an Adjunct to Scaling and Root Planing to Treat Chronic Periodontitis (continued)

Study Description	Outcomes Assessed	Adverse Effects	Study Group Attrition and Reasons	Type of Analysis
Noyan et al., 1997[75] (continued)	**Clinical Measurement:** PII PD CAL GI **Radiographic Techniques:** NR **Microbiological Methods:** Subgingival samples, agar colonies, anaerobic counts **Subject Self Report:** NR	NR	NR	**Type of analysis reported:** All who completed follow-up

Evidence Table 3a. Effectiveness of Systemic Metronidazole as an Adjunct to Scaling and Root Planing to Treat Chronic Periodontitis (continued)

	Outcomes Accessed			
	Attachment Level mm	Probing Depth mm	Spirochetes	
(N of Pts)	$\bar{x}$ (SD)	$\bar{x}$ (SD)	$\bar{x}$ % (SD)	Comments
				Quality Score: 31; 23
Baseline:				
T: 5	9.61 (NR)	5.53 (NR)	NA	
C: 5	9.56 (NR)	5.19 (NR)	NA	
Final: 6 weeks				
T: 5	8.61 (NR)	3.62 (NR)	NA	
C: 5	8.97 (NR)	3.88 (NR)	NA	
Change:				
T:	1.00 (NR)	1.91 (NR)	NA	
C:	0.59 (NR)	1.31 (NR)	NA	
Test:	Krustal Wallis, ANOVA	Krustal Wallis, ANOVA		
P value:	0.001	0.001		

Evidence Table 3a. Effectiveness of Systemic Metronidazole as an Adjunct to Scaling and Root Planing to Treat Chronic Periodontitis (continued)

Study Description	Study Design Characteristics	Disease Characteristics	Examiner Characteristics	Description of Scaling and Root Planing
Palmer et al., 1998[76] **Study Period:** 24 weeks **Study/Treatment Site:** Hospital Dental Clinic, United Medical and Dental Schools of Guy's and St. Thomas Hospitals **Location:** London, UK **Patient Population:** Patients referred from dental practitioners, with PD of = 5 mm and attachment loss = 2 mm and bone loss = 4 mm	**Design Type:** RCT **Subject/Site Allocation:** Random **Blinding:** Examiners blind **Placebo:** No **Split-mouth:** No	**Severity:** Moderate to advanced adult periodontitis **Types of Teeth:** NR **Widman flap:** NR	**Number:** NR **Trained:** NR **Assigned to Subjects:** Same examiner throughout study	**SRP performed:** Subgingival scaling by ultrasonic instrumentation under local anesthesia of all affected teeth **Time spent:** 2 appointments, 90 minutes per appointment, 1 week apart, 2 contralateral quadrants done at each appointment

Evidence Table 3a. Effectiveness of Systemic Metronidazole as an Adjunct to Scaling and Root Planing to Treat Chronic Periodontitis (continued)

Eligible Study Groups and How Defined:	Study Group Characteristics	Compliance Monitoring	Baseline Measures	Time Interval(s)
Subject/Site allocation: 58 subjects T: 31 subjects C: 27 subjects **Dose, Mode, Schedule:** T: SRP plus 200 mg metronidazole 3xday for 7 days C: SRP only	**Age:** Mean: T: 44.7 (6.2) C: 50.5 (6.1) Range: 35 to 65 **Gender:** Male: 47 Female: 43 **Race/Ethnicity:** NR	NR	Before SRP	4 times (at baseline and weeks 8 and 24)

Evidence Table 3a. Effectiveness of Systemic Metronidazole as an Adjunct to Scaling and Root Planing to Treat Chronic Periodontitis (continued)

Study Description	Outcomes Assessed	Adverse Effects	Study Group Attrition and Reasons	Type of Analysis
Palmer et al., 1998[76] (continued)	**Clinical Measurement:** BOP/SBI PII PD CAL **Radiographic Techniques:** NR **Microbiological Methods:** Plaque microbiota, bacterial morphotype evaluated with dark field microscopy **Subject Self Report:** NR	NR	Failed to attend 2nd appointment or re-evaluation (6) (not reported as to which treatment group these subjects were assigned to)	**Type of analysis reported:** Full participants only Only sites with baseline PD = 4-6 mm were evaluated

Evidence Table 3a. Effectiveness of Systemic Metronidazole as an Adjunct to Scaling and Root Planing to Treat Chronic Periodontitis (continued)

	Outcomes Accessed			
	Attachment Level mm	Probing Depth mm	Spirochetes	
(N of Pts)	$\bar{x}$ (SD)	$\bar{x}$ (SD)	$\bar{x}$ % (SD)	Comments
Baseline:				Probing depth presented graphically, no statistical significance found between groups for PD, CAL, or spirochetes
T:	NR	NR	47.1 (10.1)	
C:	NR	NR	47.2 (13.0)	
Final: 26 weeks (6 months)				
T:	NR	NR	25.8 (10.3)	**Quality Score:** 46; 46
C:	NR	NR	25.6 (10.9)	
Change:	Gain			
T:	0.67 (0.67)	1.62 (NR)	NR	
C:	0.51 (0.43)	1.68 (NR)	NR	
Test:	ANOVA	ANOVA	ANOVA	
P value:	NS	NS	NS	

Evidence Table 3a. Effectiveness of Systemic Metronidazole as an Adjunct to Scaling and Root Planing to Treat Chronic Periodontitis (continued)

Study Description	Study Design Characteristics	Disease Characteristics	Examiner Characteristics	Description of Scaling and Root Planing
Author and Year: Rooney et al., 2002[70] **Study Period:** 26 weeks (6 months) **Site of Study:** Department of Perodontology, Bristol Dental School and Hospital **Location:** UK **Patients Selected:** Patients <46 years old referred by practitioners who had failed to respond to non-surgical periodontal treatment with PD = 6 mm and BOP.	**Design Type:** RCT **Subject/Site Allocation:** Random **Blinding:** Examiners and patients blind **Placebo:** Yes **Split-mouth:** Yes, for microbiotic samples, 1 in each quadrant	**Severity:** Advanced chronic periodontal disease **Types of Teeth:** All but 3rd molars and severely malpositioned teeth **Widman flap:** NR	**Number:** 2 **Trained:** NR **Assigned to Patients:** Same clinician provided treatment throughout study	**SRP performed:** Quadrant root planings under local anesthesia with ultrasonic scaler and Gracey curettes. SRP done by 2 experienced periodontists. **Time spent on SRP:** 45 minutes for all teeth in quadrant; SRPs separated by maximum of 12 days, usually 7 days.

Evidence Table 3a. Effectiveness of Systemic Metronidazole as an Adjunct to Scaling and Root Planing to Treat Chronic Periodontitis (continued)

Eligible Study Groups and How Defined:	Study Group Characteristics	Compliance Monitoring	Baseline Measures	Assessment Time Interval(s)
Subject/Site allocation: 31 subjects T: 16 subjects C: 15 subjects **Dose, Mode, Schedule:** All received 0.2% chlorhexidine mouthrinse (10ml, 60s) 2xday until 1 week after non-surgical therapy T: SRP plus 200 mg metronidazole + placebo (calcium lactate tablets) 3xday for 7 days C: SRP plus placebo (lactose capsules and calcium lactate tablets) 3xday for 7 days	**Age:** Range: 20 to 45 **Gender Distribution:** NR **Race/Ethnicity:** NR	NR	Before SRP	4 times (at baseline, and months 1, 3, and 6)

Evidence Table 3a. Effectiveness of Systemic Metronidazole as an Adjunct to Scaling and Root Planing to Treat Chronic Periodontitis (continued)

Study Description	Outcomes Assessed	Adverse Effects	Study Group Attrition and Reasons	Type of Analysis
Rooney et al., 2002[70] (continued)	**Clinical Measurement:** PD CAL BOP Presence of Suppuration Plaque deposits **Radiographic Techniques:** NR **Microbiological Methods:** Following incubation, anaerobic counts from agar plates for *P.g., P.i., A..a.*, and others **Patient Self Report:** NR	None	66 recruited for full study; 4 were lost: lacked one month data (1); lacked 3 month data (1); had no 6 month data (3); no 3 and 6 month data (2); unable to determine which treatment groups the 4 were assigned to	**Type of analysis reported:** Full participants only

Evidence Table 3a. Effectiveness of Systemic Metronidazole as an Adjunct to Scaling and Root Planing to Treat Chronic Periodontitis (continued)

	Outcomes Accessed				
		Attachment Level mm	Probing Depth mm	Spirochetes	
	(N of Pts)	$\bar{x}$ (SD)	$\bar{x}$ (SD)	$\bar{x}$ % (SD)	Comments
Baseline:					Presented as % of sites with low (0-3 mm) or high (= 6 mm), not in actual mm measurements or changes.
T:	NR	NR	NR	NA	
C:	NR	NR	NR	NA	
Final: 26 weeks					
T:	16	NR	NR	NA	
C:	15	NR	NR	NA	Differences in PD and CAL treatment effects were significantly greater in the treatment group than in the control.
Change:					
T:		NR	NR	NA	
C:		NR	NR	NA	
Test		ANCOVA	ANCOVA		Microbiological data showed significant difference for treatment group versus control only at 1 month and not at months 3 and 6.
P-value		=0.05	=0.001		
					For PD = 6 mm, at 24 weeks there was a significant PD change in favor of the treatment ($P < 0.05$) but a nonsignificant CAL change.
					Quality Score: 69; 54

Evidence Table 3a. Effectiveness of Systemic Metronidazole as an Adjunct to Scaling and Root Planing to Treat Chronic Periodontitis (continued)

Study Description	Study Design Characteristics	Disease Characteristics	Examiner Characteristics	Description of Scaling and Root Planing
Soder, Frithiof, et al., 1990[72] **Study Period:** 26 weeks (6 months) **Study/Treatment Site:** NR **Location:** Stockholm, Germany **Patient Population:** Young adult patients originally randomly selected from register of residents for Stockholm in 1985. This sample group is a subset with persistent pockets = 5 mm in = 3 teeth and radiographic marginal alveolar bone loss	**Design Type:** RCT **Subject/Site Allocation:** Random **Blinding:** Examiners and patients blind **Placebo:** Yes **Split-mouth:** No	**Severity:** Moderate to advanced recalcitrant to comprehen-sive non-surgical treatment **Types of Teeth:** NR **Widman flap:** NR	**Number:** 4 (authors) **Trained:** Calibration (gold standard) **Assigned to Subjects:** NR	**SRP performed:** All received deep scaling **Time spent:** NR

Evidence Table 3a. Effectiveness of Systemic Metronidazole as an Adjunct to Scaling and Root Planing to Treat Chronic Periodontitis (continued)

Eligible Study Groups and How Defined:	Study Group Characteristics	Compliance Monitoring	Baseline Measures	Time Interval(s)
Subject/Site allocation: 98 subjects started 92 completed T: 46 sites C: 46 sites **Dose, Mode, Schedule:** T: SRP plus 400 mg metronidazole tablets 3xday for 1 week C: SRP plus placebo	**Age:** Range: 31-40 **Gender:** Male: 52 Female: 46 **Race/Ethnicity:** NR	Checked by interviews and tablet count. 92 complied, 2 lost to follow up appts, 4 reduced their intake between 2 and 6 days	Before SRP	3 times (at baseline and months 1 and 6)

Evidence Table 3a. Effectiveness of Systemic Metronidazole as an Adjunct to Scaling and Root Planing to Treat Chronic Periodontitis (continued)

Study Description	Outcomes Assessed	Adverse Effects	Study Group Attrition and Reasons	Type of Analysis
Soder, Frithiof, et al., 1990[72] (continued)	**Clinical Measurement:** BOP/SBI PD Furcation involvement Tooth morbidity Gingival retraction Presence of purulent exudates PI **Radiographic Techniques:** Bone loss/regeneration **Microbiological Methods:** Crevicular fluid microbiota (samples from Ramfjord teeth) **Subject Self Report:** Recording of remaining teeth, filled services, improvement of oral conditions, cervical sensitivity	Gastric discomfort (6); severe diarrhea (1); objected to taste of metronidazole (8) (T: 15, C: 9)	Refused to take tablets (1); left Sweden and did not attend clinic (3); worked too far from clinic (1); lacked time (1) Not clear which treatment group each was assigned to	**Type of analysis reported:** Full participants only

Evidence Table 3a. Effectiveness of Systemic Metronidazole as an Adjunct to Scaling and Root Planing to Treat Chronic Periodontitis (continued)

	Outcomes Accessed			
(N of Pts)	Attachment Level mm $\bar{x}$ (SD)	Probing Depth mm $\bar{x}$ (SD)	Spirochetes $\bar{x}$ % (SD)	Comments
Baseline:				The results show the supplementary effect of adjunctive metronidazole in non-surgical treatment of moderate and advanced periodontitis
T:	NA	2.81 (0.61)	6.69 (12.15)	
C:	NA	2.75 (0.46)	7.65 (10.46)	
Final: 26 weeks				
T: 46 sites	NA	2.35 (0.61)	4.35 (6.31)	The mean percentage of spirochetes as related to the total number of microorganisms counted did not differ significantly between groups
C: 46 sites (43 for spirochetes)	NA	2.34 (0.43)	7.86 (12.51)	
Change:				
T:	NA	0.46* (NR)	2.34* (NR)	
C:	NA	0.41* (NR)	-0.21 (NR)	
Test:		NR	t-test	
P value:		NR	NS	**Quality Score:** 85; 85

Evidence Table 3b. Effectiveness of Local Metronidazole as an Adjunct to Scaling and Root Planing to Treat Chronic Periodontitis

Study Description	Study Design Characteristics	Disease Characteristics	Examiner Characteristics	Description of Scaling and Root Planing
Author and Year: Al-Mubarak et al., 2000[80] **Study Period:** 13 weeks (90 days) **Site of Study:** NR **Location:** NR **Patients Selected:** Adult patients with at least 1 tooth in each quadrant with PD = 5 mm	**Design Type:** RCT **Subject/Site Allocation:** Random **Blinding:** Examiner blind **Placebo:** No **Split-mouth:** Yes	**Severity:** Moderate to advanced signs of adult periodontitis **Types of Teeth:** No teeth with profound furcation involvement or advanced degree of mobility **Widman flap:** NR	**Number:** 1 **Trained:** Calibrated **Assigned to Patients:** Same provider throughout study	**SRP performed:** One session of SRP for all teeth with PD > 5 mm within the involved quadrant **Time spent on SRP:** One hour

Evidence Table 3b. Effectiveness of Local Metronidazole as an Adjunct to Scaling and Root Planing to Treat Chronic Periodontitis (continued)

Eligible Study Groups and How Defined:	Study Group Characteristics	Compliance Monitoring	Baseline Measures	Assessment Time Interval(s)
Subject/Site allocation: 15 subjects started 14 completed T: 14 subjects C: 14 subjects **Dose, Mode, Schedule:** T: SRP plus 25% metronidazole gel applied on days 0 and 7 C: SRP only	**Mean Age:** Mean: 58.6 Range: 41 to 79 **Gender Distribution:** Male: 8 Female: 7 **Race/Ethnicity:** NR	NR	Before SRP	2 times (at baseline and 90 days)

Evidence Table 3b. Effectiveness of Local Metronidazole as an Adjunct to Scaling and Root Planing to Treat Chronic Periodontitis (continued)

Study Description	Outcomes Assessed	Adverse Effects	Study Group Attrition and Reasons	Type of Analysis
Al-Mubarak et al, 2000[80] (continued)	**Clinical Measurement:** PD Plaque Registration BOP **Radiographic Techniques:** NR **Microbiological Methods:** NR **Patient Self Report:** NR	NR	1 female subject withdrew from study before second examination	**Type of analysis reported:** Full participants only

Evidence Table 3b. Effectiveness of Local Metronidazole as an Adjunct to Scaling and Root Planing to Treat Chronic Periodontitis (continued)

	Outcomes Accessed			
	Attachment Level mm	Probing Depth mm	Spirochetes	
(N of Pts)	$\bar{x}$ (SD)	$\bar{x}$ (SD)	$\bar{x}$ (SD)	Comments
Baseline:				Treatment group had significantly more PD improvement than control ($P < 0.03$)
T:	NA	NR	NA	
C:	NA	NR	NA	
Final: 13 weeks (90 days)				**Quality Score:** 46; 46
T:	NA	NR	NA	
C:	NA	NR	NA	
Change:				
T:	NA	2.2 (0.6)	NA	
C:	NA	1.4 (0.8)	NA	
Test:		NR		
P value:		< 0.03		

Evidence Table 3b. Effectiveness of Local Metronidazole as an Adjunct to Scaling and Root Planing to Treat Chronic Periodontitis (continued)

Study Description	Study Design Characteristics	Disease Characteristics	Examiner Characteristics	Description of Scaling and Root Planing
Awartani et al., 1998[28] **Study Period:** 14 weeks **Study/Treatment Site:** College of Dentistry, King Saud University **Location:** Saudi Arabia **Patient Population:** Patients with at least 1 tooth in each quadrant with PD = 5 mm	**Design Type:** RCT **Subject/Site Allocation:** Random to quadrants **Blinding:** Examiners blind **Placebo:** No **Split-mouth:** Yes	**Severity:** Mild to moderate periodontitis **Types of Teeth:** NR **Widman flap:** NR	**Number:** 1 **Trained:** NA **Assigned to Subjects:** Same examiner throughout study	**SRP performed:** Subgingival scaling performed under local anesthesia, moderate to heavy supragingival calculus removed by ultrasonic scaling; subgingival SRP as needed by Gracey curettes **Time spent:** 1 session per quadrant

Evidence Table 3b. Effectiveness of Local Metronidazole as an Adjunct to Scaling and Root Planing to Treat Chronic Periodontitis (continued)

Eligible Study Groups and How Defined:	Study Group Characteristics	Compliance Monitoring	Baseline Measures	Time Interval(s)
Subject/Site allocation: 13 subjects (247 teeth) started 12 subjects completed T: 60 teeth (360 sites) C: 63 teeth (378 sites) **Dose, Mode, Schedule:** T: SRP plus 25% metronidazole gel applied once daily on days 0 and 7 C: SRP alone	**Age:** Mean: 37.3 Range: 28 to 57 **Gender:** All Male **Race/Ethnicity:** NR	NR	Before SRP	5 times (at baseline and weeks 2, 4, 6, and 14)

Evidence Table 3b. Effectiveness of Local Metronidazole as an Adjunct to Scaling and Root Planing to Treat Chronic Periodontitis (continued)

Study Description	Outcomes Assessed	Adverse Effects	Study Group Attrition and Reasons	Type of Analysis
Awartani et al., 1998[28] (continued)	**Clinical Measurement:** BOP/SBI PII PD GI **Radiographic Techniques:** NR **Microbiological Methods:** NR **Subject Self Report:** NR	None reported by subjects	1 subject failed to show up for last examination	**Type of analysis reported:** All subjects who completed all follow-ups

Evidence Table 3b. Effectiveness of Local Metronidazole as an Adjunct to Scaling and Root Planing to Treat Chronic Periodontitis (continued)

	Outcomes Accessed				
	(N of Pts)	Attachment Level mm $\bar{x}$ (SD)	Probing Depth mm $\bar{x}$ (SD)	Spirochetes $\bar{x}$ % (SD)	Comments
Baseline:					For the treatment of mild to moderate adult periodontitis subgingival scaling alone is as effective as the combination of scaling and antibiotic therapy
T:	360 sites	NA	4.61 (NR)	NA	
C:	378 sites	NA	4.65(NR)	NA	
Final:	14 weeks				
T:	NR	NA	NR	NA	
C:	NR	NA	NR	NA	**Quality Score:** 54; 54
Change:			Reduction		
T:		NA	0.21 (NR)	NA	
C:		NA	0.33 (NR)	NA	
Test:			Tukey's and Scheffe's Multiple Range		
P value:			NS		

Evidence Table 3b. Effectiveness of Local Metronidazole as an Adjunct to Scaling and Root Planing to Treat Chronic Periodontitis (continued)

Study Description	Study Design Characteristics	Disease Characteristics	Examiner Characteristics	Description of Scaling and Root Planing
Aziz-Gandour and Newman, 1986[77]	**Design Type:** RCT	**Severity:** Chronic periodontitis	**Number:** NR	**SRP performed:** Supra and subgingival scaling, root planing and sub-contact area debridement and polishing
Study Period: 12 weeks (84 days)	**Subject/Site Allocation:** Random	**Types of Teeth:** NR	**Trained:** Nr	
Study/Treatment Site: Health Department Clinic	**Blinding:** Examiners and patients blind	**Widman flap:** NR	**Assigned to Subjects:** NR	**Time spent:** NR
Location: UK	**Placebo:** Yes			
Patient Population: Patients with approximal surface pockets = 4 mm with bone reabsorption as seen on radiographs	**Split-mouth:** No			

Evidence Table 3b. Effectiveness of Local Metronidazole as an Adjunct to Scaling and Root Planing to Treat Chronic Periodontitis (continued)

Eligible Study Groups and How Defined:	Study Group Characteristics	Compliance Monitoring	Baseline Measures	Time Interval(s)
Subject/Site allocation: 16 subjects T: 10 (210 sites) C: 6 (118 sites) **Dose, Mode, Schedule:** T: SRP plus irrigation with 0.05% metronidazole formulation for 28 days C: SRP plus irrigation with 0.1% quinine sulphate formulation for 28 days	**Age:** T: Mean: 42 Range: 29 to 54 C: Mean: 48 Range: 43 to 55 **Gender:** T: Male: 5 Female: 5 C: Male: 4 Female: 2 **Race/Ethnicity:** NR	Yes with irrigation profiency checked at day 7	Before SRP	5 times (at baseline and days 7, 28, 56, and 84)

Evidence Table 3b. Effectiveness of Local Metronidazole as an Adjunct to Scaling and Root Planing to Treat Chronic Periodontitis (continued)

Study Description	Outcomes Assessed	Adverse Effects	Study Group Attrition and Reasons	Type of Analysis
Aziz-Gandour and Newman, 1986[77] (continued)	**Clinical Measurement:** SBI PII PD GI Gingival recession **Radiographic Techniques:** NR **Microbiological Methods:** NR **Subject Self Report:** NR	NR	1 subject excluded from overall study excluded because of failure to attend all visits, but it is not clear which treatment group subject was assigned to	**Type of analysis reported:** Full participants only

Evidence Table 3b. Effectiveness of Local Metronidazole as an Adjunct to Scaling and Root Planing to Treat Chronic Periodontitis (continued)

Outcomes Accessed					
	(N of Pts)	Attachment Level mm $\bar{x}$ (SD)	Probing Depth mm $\bar{x}$ (SD)	Spirochetes $\bar{x}$ % (SD)	Comments
Baseline:					PD reductions reached a maximum at day 28 (last day of treatment) and were less at days 56 and 84.
T:	NR	NA	5.3 (NR)	NA	
C:	NR	NA	4.6 (NR)	NA	
Final:	12 weeks				There were sig diffs at all times between treatment and placebo, favoring metronidazole treatment for 84 days (*P* <0.01).
T:	10 (210 sites)	NA	NR	NA	
C:	6 (118 sites)	NA	NR	NA	
Change:					
T:		NA	NR	NA	
C:		NA	NR	NA	PD final outcomes in graphic form only.
Test:			Chi Square		
P value:			<0.01		**Quality Score:** 46; 46

Evidence Table 3b. Effectiveness of Local Metronidazole as an Adjunct to Scaling and Root Planing to Treat Chronic Periodontitis (continued)

Study Description	Study Design Characteristics	Disease Characteristics	Examiner Characteristics	Description of Scaling and Root Planing
Griffiths et al., 2000[79] **Study Period:** 39 weeks (9 months) **Study/Treatment Site:** Department of Periodontology, Eastman Dental Institute London Royal Air Force Institute of Dental Health and Training at Haton, Bucks **Location:** UK **Patient Population:** Patients referred by general dental practitioners for treatment; at least 2 sites in each quadrant with PD = 5 mm other than 3rd molars	**Design Type:** RCT **Subject/Site Allocation:** Random **Blinding:** Examiners blind **Placebo:** No **Split-mouth:** Yes	**Severity:** Chronic adult periodontitis **Types of Teeth:** No third molars **Widman flap:** NR	**Number:** 2 (1 at each center) **Trained:** Calibration (gold standard) **Assigned to Subjects:** Same examiner throughout study	**SRP performed:** Subgingival scaling of all quadrants. Supragingival scaling was provided if necessary to facilitate home care procedures **Time spent:** Supragingival scaling of not more than 20 minutes; subgingival debridement: 60 minutes per quadrant, 1 wk apart, = 2 times

Evidence Table 3b. Effectiveness of Local Metronidazole as an Adjunct to Scaling and Root Planing to Treat Chronic Periodontitis (continued)

Eligible Study Groups and How Defined:	Study Group Characteristics	Compliance Monitoring	Baseline Measures	Time Interval(s)
Subject/Site allocation: 88 subjects (average of 42 sites per subject) 10 sites per quadrant T: 1,770 sites C: 1,780 sites **Dose, Mode, Schedule:** T: SRP plus 25% metronidazole gel applied 1xweek for 3 weeks for each quadrant (1 week delay between quadrants) C: SRP alone	**Age:** Mean: 46 (clinic 1) 47 (clinic 2) Range: 34 to 71 **Gender:** Male: 42 Female: 46 **Race/Ethnicity:** NR	NA	Before SRP	5 times (at baseline and months 1, 3, 6, and 9)

Evidence Table 3b. Effectiveness of Local Metronidazole as an Adjunct to Scaling and Root Planing to Treat Chronic Periodontitis (continued)

Study Description	Outcomes Assessed	Adverse Effects	Study Group Attrition and Reasons	Type of Analysis
Griffiths et al., 2000[79] (continued)	**Clinical Measurement:** BOP/SBI PD CAL **Radiographic Techniques:** NR **Microbiological Methods:** NR **Subject Self Report:** NR	NR	NR	**Type of analysis reported:** Intent to treat

Evidence Table 3b. Effectiveness of Local Metronidazole as an Adjunct to Scaling and Root Planing to Treat Chronic Periodontitis (continued)

		Outcomes Accessed			
	(N of Pts)	Attachment Level mm $\bar{x}$ (SD)	Probing Depth mm $\bar{x}$ (SD)	Spirochetes $\bar{x}$ % (SD)	Comments
Baseline:					**Quality Score:** 62; 62
T:	1,770 sites	11.2 (1.6*)	5.9 (0.6*)	NA	
C:	1,780 sites	11.2 (1.6*)	6.0 (0.5*)	NA	
Final:	36 weeks				
T:	NR	NR	NR	NA	
C:	NR	NR	NR	NA	
Change:		Gain	Reduction		
T:		0.8 (NR)	1.5 (NR)	NA	
C:		0.4 (NR)	1.0 (NR)	NA	
Test:		paired t-test	paired t-test		
P value:		< 0.001	< 0.001		

* NR as to standard error or standard deviation.

Evidence Table 3b. Effectiveness of Local Metronidazole as an Adjunct to Scaling and Root Planing to Treat Chronic Periodontitis (continued)

Study Description	Study Design Characteristics	Disease Characteristics	Examiner Characteristics	Description of Scaling and Root Planing
Kinane and Radvar 1999[53] **Study Period:** 26 weeks (6 months) **Study/Treatment Site:** Hospital Dental Clinic **Location:** Glasgow, Scotland **Patient Population:** Patients with persistent pockets that did not respond to SRP, with at least 4 non-adjacent teeth, with PD = 5 mm and BOP	**Design Type:** RCT **Subject/Site Allocation:** Random **Blinding:** Examiner blind **Placebo:** No **Split-mouth:** No	**Severity:** Chronic periodontitis with previously unsuccessful mechanical therapy **Types of Teeth:** NR **Widman flap:** NR	**Number:** 1 **Trained:** NR **Assigned to Subjects:** Same examiner throughout study	**SRP performed:** SRP under local anesthesia **Time spent:** NR

Evidence Table 3b. Effectiveness of Local Metronidazole as an Adjunct to Scaling and Root Planing to Treat Chronic Periodontitis (continued)

Eligible Study Groups and How Defined:	Study Group Characteristics	Compliance Monitoring	Baseline Measures	Time Interval(s)
Subject/Site allocation: 39 subjects (4 sites per subject) T: 19 subjects C: 20 subjects **Dose, Mode, Schedule:** T: SRP plus 25% metronidazole gel 2xday, repeated after 7 days C: SRP only	**Age:** Mean: 45 ± 6.4 Range: NR **Gender: (Full study)** Male: 29 Female: 50 **Race/Ethnicity:** NR	NA	Before SRP	4 times (at baseline, 6 weeks and at months 3 and 6)

Evidence Table 3b. Effectiveness of Local Metronidazole as an Adjunct to Scaling and Root Planing to Treat Chronic Periodontitis (continued)

Study Description	Outcomes Assessed	Adverse Effects	Study Group Attrition and Reasons	Type of Analysis
Kinane and Radvar 1999[53] (continued)	**Clinical Measurement:** BOP/SBI PII PD CAL GI Supperation **Radiographic Techniques:** NR **Microbiological Methods:** NR **Subject Self Report:** NR	Yes, found none	2 from treatment, 1 from control group, reasons not given	**Type of analysis reported:** All with any follow-up **Analysis adjusted:** GLM, baseline value as continuous covariate

Evidence Table 3b. Effectiveness of Local Metronidazole as an Adjunct to Scaling and Root Planing to Treat Chronic Periodontitis (continued)

	Outcomes Accessed			
(N of Pts)	Attachment Level mm $\bar{x}$ (SD)	Probing Depth mm $\bar{x}$ (SD)	Spirochetes $\bar{x}$ % (SD)	Comments
Baseline:				This is a follow-up study
T:	NR	5.506 (0.152 se)	NA	
C:	NR	5.480 (0.175 se)	NA	**Quality Score:** 54; 62
Final: 26 weeks				
T: 17 (75 sites)	NR	NR	NA	
C: 19 (79 sites)	NR	NR	NA	
Change:	Gain	Reduction		
T:	0.541 (0.214)	0.929 (0.196)	NA	
C:	0.537 (0.143)	0.711 (0.188)	NA	
Test:	GLM	GLM		
P value:	0.768	NS		

Evidence Table 3b. Effectiveness of Local Metronidazole as an Adjunct to Scaling and Root Planing to Treat Chronic Periodontitis (continued)

Study Description	Study Design Characteristics	Disease Characteristics	Examiner Characteristics	Description of Scaling and Root Planing
Lie et al., 1998[34] **Study Period:** 26 weeks **Study/Treatment Site:** Department of Periodontology, University of Bergen **Location:** Bergen, Norway **Patient Population:** Patients referred for treatment, previously untreated, with PD = 5 mm and BOP	**Design Type:** RCT **Subject/Site Allocation:** Random **Blinding:** Examiner and patients blind **Placebo:** No **Split-mouth:** Yes	**Severity:** Moderate to severe **Types of Teeth:** Single-rooted **Widman flap:** NR	**Number:** 2 (1 operator; 1 examiner, blind) **Trained:** NR **Assigned to Subjects:** 1 operator and 1 examiner assigned to all patients	**SRP performed:** Subgingival SRP with sonic instrument and curettes, two sessions, 1 week apart **Time spent:** NR

Evidence Table 3b. Effectiveness of Local Metronidazole as an Adjunct to Scaling and Root Planing to Treat Chronic Periodontitis (continued)

Eligible Study Groups and How Defined:	Study Group Characteristics	Compliance Monitoring	Baseline Measures	Time Interval(s)
Subject/Site allocation: 18 subjects T: 18 sites C: 18 sites **Dose, Mode, Schedule:** T: SRP plus application of 25% metronidazole sustained release gel after each SRP session, 1 week apart C: Two SRP sessions, at baseline and week 1	**Age:** Range: 36 to 77 **Gender:** NR **Race/Ethnicity:** NR	NA	Before SRP	3 times (at baseline and months 3 and 6)

Evidence Table 3b. Effectiveness of Local Metronidazole as an Adjunct to Scaling and Root Planing to Treat Chronic Periodontitis (continued)

Study Description	Outcomes Assessed	Adverse Effects	Study Group Attrition and Reasons	Type of Analysis
Lie et al., 1998[34] (continued)	**Clinical Measurement:** BOP/SBI PD CAL **Radiographic Techniques:** NR **Microbiological Methods:** Use of commercial kit **Subject Self Report:** NR	NR	None	**Type of analysis reported:** All subjects who completed all follow-ups

Evidence Table 3b. Effectiveness of Local Metronidazole as an Adjunct to Scaling and Root Planing to Treat Chronic Periodontitis (continued)

	Outcomes Accessed			
	Attachment Level mm	Probing Depth mm	Spirochetes	
(N of Pts)	$\bar{x}$ (SD)	$\bar{x}$ (SD)	$\bar{x}$ % (SD)	Comments
Defect Sites:				Clinical and microbiological recordings were also performed on non-defect sites: the ANOVA revealed no differences for probing depth between treatment groups (*P* = 0.6247). The same findings apply to the attachment level measure (*P* = 0.3966). *A.a.* were rarely detected by the diagnostic handling. *P.g.* was significantly reduced in all treatment groups
Baseline:				
T: 18 (18 sites)	13.2 (1.2)	5.0 (1.1)	NA	
C: 18 (18 sites)	13.4 (1.8)	5.1 (1.2)	NA	
Final: 26 weeks				
T: 18 (18 sites)	12.3 (1.5)	3.4 (1.0)	NA	
C: 18 (18 sites)	13.2 (1.5)	4.0 (1.4)	NA	
Change:				
T:	0.9* (NR)	1.6* (NR)	NA	
C:	0.2* (NR)	1.1* (NR)	NA	
Test:	ANOVA	ANOVA		
P value:	NS	NS		
NonDefect Sites:				**Quality Score:** 54; 62
Baseline:				
T:				
C:				
Final: 26 weeks				
T:				
C:				
Change:				
T:				
C:				
Test:				
P value:				

Evidence Table 3b. Effectiveness of Local Metronidazole as an Adjunct to Scaling and Root Planing to Treat Chronic Periodontitis (continued)

Study Description	Study Design Characteristics	Disease Characteristics	Examiner Characteristics	Description of Scaling and Root Planing
Moran et al., 1990[37] **Study Period:** 13 weeks (3 months) **Study/Treatment Site:** Health Department Clinic (Department of Peridontology, University of Wales **Location:** Wales, UK **Patient Population:** Adult patients referred by outside practitioners or other departments w/in the hospital, with pocketing = 6 mm at several sites anterior to molars	**Design Type:** RCT **Subject/Site Allocation:** Random **Blinding:** Examiners and patients blind **Placebo:** No **Split-mouth:** No	**Severity:** Chronic periodontitis **Types of Teeth:** Anterior to molars **Widman flap:** NR	**Number:** 1 **Trained:** NR **Assigned to Subjects:** Same examiner throughout study	**SRP performed:** Root planing by hand with local anesthesia using Gracey-type curettes **Time spent:** 10 to 15 minutes per tooth

Evidence Table 3b. Effectiveness of Local Metronidazole as an Adjunct to Scaling and Root Planing to Treat Chronic Periodontitis (continued)

Eligible Study Groups and How Defined:	Study Group Characteristics	Compliance Monitoring	Baseline Measures	Time Interval(s)
Subject/Site allocation: 69 subjects completed full study (101 pockets) T: 15 pockets C: 18 pockets Rmg subjects assigned to non-eligible treatments **Dose, Mode, Schedule:** T: SRP plus acrylic strips impregnated with metronidazole C: SRP only	**Age:** Mean: 47.6 Range: 37 to 58 **Gender:** Male: 28 Female: 41 **Race/Ethnicity:** NR	NA	Before SRP	6 times (at baseline and weeks 1, 2, 4, 8, and 12)

Evidence Table 3b. Effectiveness of Local Metronidazole as an Adjunct to Scaling and Root Planing to Treat Chronic Periodontitis (continued)

Study Description	Outcomes Assessed	Adverse Effects	Study Group Attrition and Reasons	Type of Analysis
Moran et al., 1990[37] (continued)	**Clinical Measurement:** BOP/SBI PD CAL **Radiographic Techniques:** NR **Microbiological Methods:** Crevicular fluid microbiota (white blood cells count) **Subject Self Report:** NR	NR	Failure to make all visits (4). Not clear which groups they were assigned to	**Type of analysis reported:** Full participants only

Evidence Table 3b. Effectiveness of Local Metronidazole as an Adjunct to Scaling and Root Planing to Treat Chronic Periodontitis (continued)

	Outcomes Accessed			
	Attachment Level mm	Probing Depth mm	Spirochetes	
(N of Pts)	$\bar{x}$ (SD)	$\bar{x}$ (SD)	$\bar{x}$ % (SD)	Comments
Baseline:				Maximum reductions in microbiota counts were seen in treatment sites and sustained over 12 weeks.
T: 15 pockets	7.9 (2.0)	6.6 (0.9)	NA	
C: 18 pockets	7.8 (1.9)	6.9 (1.4)	NA	
Final: 12 weeks				**Quality Score:** 62; 62
T: 15 pockets	6.0 (2.3)	3.2 (1.4)	NA	
C: 18 pockets	6.2 (2.5)	4.4 (2.2)	NA	
Change:				
T:	1.9* (NR)	3.4* (NR)	NA	
C:	1.6* (NR)	2.5* (NR)	NA	
Test:	ANCOVA	ANCOVA		
P value:	NS	NS		

Evidence Table 3b. Effectiveness of Local Metronidazole as an Adjunct to Scaling and Root Planing to Treat Chronic Periodontitis (continued)

Study Description	Study Design Characteristics	Disease Characteristics	Examiner Characteristics	Description of Scaling and Root Planing
Noyan et al., 1997[75] **Study Period:** 6 weeks **Study/Treatment Site:** NR **Location:** Turkey **Patient Population:** Adult patients with 1 tooth/quadrant having at least 1 approximal site with PD = 5 mm	**Design Type:** RCT **Subject/Site Allocation:** Random **Blinding:** NR **Placebo:** No **Split-mouth:** Yes	**Severity:** NR **Types of Teeth:** NR **Widman flap:** NR	**Number:** 2 **Trained:** NR **Assigned to Subjects:** NR	**SRP performed:** Careful mechanical subgingival debridement at selected sites in 2 quadrants, repeated 7 days later in 3 quadrants **Time spent:** NR

Evidence Table 3b. Effectiveness of Local Metronidazole as an Adjunct to Scaling and Root Planing to Treat Chronic Periodontitis (continued)

Eligible Study Groups and How Defined:	Study Group Characteristics	Compliance Monitoring	Baseline Measures	Time Interval(s)
Subject/Site allocation: 10 subjects T: 5 subjects (5 sites) C: 5 subjects (5 sites) **Dose, Mode, Schedule:** T: SRP plus 25% metronidazole gel at day 0 and 7, SRP again at day 7 C: SRP at baseline and week 1	**Age:** Range: 35 to 51 **Gender:** Male: 3 Female: 7 **Race/Ethnicity:** NR	NA	Before SRP	2 times (at baseline and 6 weeks)

Evidence Table 3b. Effectiveness of Local Metronidazole as an Adjunct to Scaling and Root Planing to Treat Chronic Periodontitis (continued)

Study Description	Outcomes Assessed	Adverse Effects	Study Group Attrition and Reasons	Type of Analysis
Noyan et al., 1997[75] (continued)	**Clinical Measurement:** PII PD CAL GI **Radiographic Techniques:** NR **Microbiological Methods:** Subgingival samples, agar colonies, anaerobic counts (*A.a.)* **Subject Self Report:** NR	NR	NR	**Type of analysis reported:** All who completed follow-up

Evidence Table 3b. Effectiveness of Local Metronidazole as an Adjunct to Scaling and Root Planing to Treat Chronic Periodontitis (continued)

	Outcomes Accessed			
	Attachment Level mm	Probing Depth mm	Spirochetes	
(N of Pts)	$\bar{x}$ (SD)	$\bar{x}$ (SD)	$\bar{x}$ % (SD)	Comments
Baseline:				Variations in the number of sites infected with the same microorganisms and the great dissimilarities in bacterial counts at initial exam did not allow for a statistical analysis for the evaluation of the effects of different treatment modalities on cultivated subgingival microbiota. **Quality Score:** 23; 23
T: 5 (5sites)	8.79 (NR)	5.57 (NR)	NA	
C: 5 (5sites)	9.56 (NR)	5.19 (NR)	NA	
Final: 6 weeks				
T: 5 (5 sites)	7.54 (NR)	3.48 (NR)	NA	
C: 5 (5 sites)	8.97 (NR)	3.88 (NR)	NA	
Change:				
T:	1.25 (NR)	2.09 (NR)	NA	
C:	0.59 (NR)	1.31 (NR)	NA	
Test:	Kruskal-Wallis ANOVA	Kruskal-Wallis ANOVA		
P value:	<0.01	NS		

Evidence Table 3b. Effectiveness of Local Metronidazole as an Adjunct to Scaling and Root Planing to Treat Chronic Periodontitis (continued)

Study Description	Study Design Characteristics	Disease Characteristics	Examiner Characteristics	Description of Scaling and Root Planing
Palmer et al., 1998[76] **Study Period:** 24 weeks **Study/Treatment Site:** Hospital Dental Clinic; United Medical and Dental Schools of the Guys and St. Thomas Hospitals **Location:** London, UK **Patient Population:** Patients referred from dental practitioners with PD of = 5 mm with attachment loss = 2 mm and bone loss = 4 mm	**Design Type:** RCT **Subject/Site Allocation:** Random **Blinding:** Examiners blind **Placebo:** No **Split-mouth:** No	**Severity:** Advanced adult periodontitis **Types of Teeth:** NR **Widman flap:** NR	**Number:** NR **Trained:** NR **Assigned to Subjects:** Same examiner throughout study	**SRP performed:** Subgingival scaling by ultrasonic instrumentation under local anesthesia of all affected teeth **Time spent:** 2 appointments, 90 minutes each, 1 week apart, 2 contralateral quadrants done at each appointment

Evidence Table 3b. Effectiveness of Local Metronidazole as an Adjunct to Scaling and Root Planing to Treat Chronic Periodontitis (continued)

Eligible Study Groups and How Defined:	Study Group Characteristics	Compliance Monitoring	Baseline Measures	Time Interval(s)
Subject/Site allocation: 90 subjects referred for full study 53 completed T: 26 subjects C: 27 subjects **Dose, Mode, Schedule:** T: SRP plus application of 25% metronidazole gel, on all PD = 4 mm sites; subgingival reapplication after 1 week in PD sites = 4 mm C: SRP only	**Age:** Mean: T: 48.1 (7.3) C: 50.5 (6.1) Range: 35 to 65 **Gender:** Male: 43 referred Female: 47 referred **Race/Ethnicity:** NR	NR	Before SRP	3 times (at baseline, and weeks 8, and 24)

Evidence Table 3b. Effectiveness of Local Metronidazole as an Adjunct to Scaling and Root Planing to Treat Chronic Periodontitis (continued)

Study Description	Outcomes Assessed	Adverse Effects	Study Group Attrition and Reasons	Type of Analysis
Palmer et al., 1998[76] (continued)	**Clinical Measurement:** BOP/SBI PII PD CAL **Radiographic Techniques:** NR **Microbiological Methods:** Plaque microbiota; bacterial morphotype evaluated with dark field microscopy **Subject Self Report:** NR	NR	Failed to attend 2nd appointment or re-evaluation (6), not reported as to which treatment grp these subjects were assigned to	**Type of analysis reported:** Full participants only Only sites with baseline probing depths = 4 to 6 mm were evaluated

Evidence Table 3b. Effectiveness of Local Metronidazole as an Adjunct to Scaling and Root Planing to Treat Chronic Periodontitis (continued)

	Outcomes Accessed				
		Attachment Level mm	Probing Depth mm	Spirochetes	
	(N of Pts)	$\bar{x}$ (SD)	$\bar{x}$ (SD)	$\bar{x}$ % (SD)	Comments
Baseline:					Probing depth presented graphically, no statistical significance found between groups for PD, CAL and spirochetes
T:	NR	NR	NR	40.6 (14.6)	
C:	NR	NR	NR	47.2 (13.0)	
Final:	26 weeks (6 months)				
T:	26	NR	NR	23.5 (10.5)	**Quality Score:** 54; 46
C:	27	NR	NR	25.6 (10.9)	
Change:		Gain	Reduction		
T:		0.47 (0.65)	1.74 (NR)	NR	
C:		0.51 (0.43)	1.68 (NR)	NR	
Test:		ANOVA	ANOVA	ANOVA	
P value:		NS	NS	NS	

Evidence Table 3b. Effectiveness of Local Metronidazole as an Adjunct to Scaling and Root Planing to Treat Chronic Periodontitis (continued)

Study Description	Study Design Characteristics	Disease Characteristics	Examiner Characteristics	Description of Scaling and Root Planing
Riep et al., 1999[78] **Study Period:** 13 weeks (3 months) **Study/Treatment Site:** Department of Periodontology, Humbolt University **Location:** Berlin, Germany **Patient Population:** Maintenance patients scheduled for SRP with PD = 6 mm in 2 non-adjacent sites in 2 different quadrants, and BOP in separate quadrants	**Design Type:** RCT **Subject/Site Allocation:** Random **Blinding:** Examiners blind **Placebo:** No **Split-mouth:** Yes	**Severity:** Local recurrent periodontitis **Types of Teeth:** Single root, teeth with furcation involvement were excluded **Widman flap:** NR	**Number:** 1 **Trained:** NA **Assigned to Subjects:** Same examiner throughout study, different person provided treatment	**SRP performed:** SRP under local anesthesia **Time spent:** NR

Evidence Table 3b. Effectiveness of Local Metronidazole as an Adjunct to Scaling and Root Planing to Treat Chronic Periodontitis (continued)

Eligible Study Groups and How Defined:	Study Group Characteristics	Compliance Monitoring	Baseline Measures	Time Interval(s)
Subject/Site allocation: 30 subjects entered 29 completed T: 58 sites C: 58 sites **Dose, Mode, Schedule:** T: SRP plus 25% metronidazole gel applied 5x during 10 days C: SRP only	**Age:** Mean: 47 **Gender:** Male: 17 Female: 12 **Race/Ethnicity:** NR	NA	Before SRP	3 times (at baseline, day 21 and 3 months)

Evidence Table 3b. Effectiveness of Local Metronidazole as an Adjunct to Scaling and Root Planing to Treat Chronic Periodontitis (continued)

Study Description	Outcomes Assessed	Adverse Effects	Study Group Attrition and Reasons	Type of Analysis
Riep et al., 1999[78] (continued)	**Clinical Measurement:** BOP/SBI PII PD CAL **Radiographic Techniques:** NR **Microbiological Methods:** Plaque microbiota (subgingival plaque samples); commercial kit analysis for *P.g., P.i., A.a.* **Subject Self Report:** NR	NR	Antibiotic treatment during course of study (1)	**Type of analysis reported:** Full participants only

Evidence Table 3b. Effectiveness of Local Metronidazole as an Adjunct to Scaling and Root Planing to Treat Chronic Periodontitis (continued)

Outcomes Accessed				
(N of Pts)	Attachment Level mm $\bar{x}$ (SD)	Probing Depth mm $\bar{x}$ (SD)	Spirochetes $\bar{x}$ % (SD)	Comments
Baseline:				Microbial Outcomes Assessed:
T: 29 (58 sites)	NR	6.8 (NR)	NA	*P.g.* was statistically significantly reduced in both groups from baseline, but not significantly between groups
C: 29 (58 sites)	NR	6.6 (NR)	NA	
Final: 12 weeks				For *P.i.,* the values decreased significantly, but only after SRP
T: 29 (58 sites)	NR	5.1 (NR)	NA	
C: 29 (58 sites)	NR	4.9 (NR)	NA	*A.a.* was not significantly different from either treatment
Change:	Gain	Reduction		
T:	1.31 (0.8)	1.7 (NR)	NA	
C:	1.14 (0.8)	1.7 (NR)	NA	
Test:	Wilcoxen Signed-Ranks Test	Wilcoxen Signed-Ranks Test		**Quality Score:** 46; 38
P value:	NS	NS		

Evidence Table 3b. Effectiveness of Local Metronidazole as an Adjunct to Scaling and Root Planing to Treat Chronic Periodontitis (continued)

Study Description	Study Design Characteristics	Disease Characteristics	Examiner Characteristics	Description of Scaling and Root Planing
Stelzel and Florès-de-Jacoby, 2000[36]	**Design Type:** RCT	**Severity:** Adult periodontitis	**Number:** NR	**SRP performed:** Subgingival SRP
Study Period: 37 weeks (9 months)	**Subject/Site Allocation:** Random	**Types of Teeth:** NR	**Trained:** NR	**Time spent:** NR
Study/Treatment Site: Health Department Clinic	**Blinding:** Patient blind	**Widman flap:** NR	**Assigned to Subjects:** NR	
Location: Helsinki, Germany	**Placebo:** No			
Patient Population: Patients with = 2 pockets with PD = 5 mm and BOP in each quadrant	**Split-mouth:** Yes			

Evidence Table 3b. Effectiveness of Local Metronidazole as an Adjunct to Scaling and Root Planing to Treat Chronic Periodontitis (continued)

Eligible Study Groups and How Defined:	Study Group Characteristics	Compliance Monitoring	Baseline Measures	Time Interval(s)
Subject/Site allocation: 64 subjects enrolled 59 completed 21 with untreated periodontitis 10 had been pretreated 28 were recall T: 522 teeth (986 pockets) C: 506 teeth (945 pockets) Only 45 subjects were evaluated for microbiological samples **Dose, Mode, Schedule:** T: SRP plus 25% metronidazole gel applied 2xday at day 0 and 7 C: SRP only	**Age:** Average: 47 Range: 23 to 70 **Gender:** NR **Race/Ethnicity:** NR	NA	NR	4 times (at baseline and days 91, 175, and 259)

Evidence Table 3b. Effectiveness of Local Metronidazole as an Adjunct to Scaling and Root Planing to Treat Chronic Periodontitis (continued)

Study Description	Outcomes Assessed	Adverse Effects	Study Group Attrition and Reasons	Type of Analysis
Stelzel and Florès-de-Jacoby, 2000[36] (continued)	**Clinical Measurement:** BOP/SBI PD CAL **Radiographic Techniques:** NR **Microbiological Methods:** Plaque microbiota, dark field microscopy **Subject Self Report:** NR	No clinically relevant side effects noted	Irregular participation or other reasons unrelated to study (5)	**Type of analysis reported:** Full participants only

Evidence Table 3b. Effectiveness of Local Metronidazole as an Adjunct to Scaling and Root Planing to Treat Chronic Periodontitis (continued)

	Outcomes Accessed				
	(N of Pts)	Attachment Level mm $\bar{x}$ (SD)	Probing Depth mm $\bar{x}$ (SD)	Spirochetes $\bar{x}$ % (SD)	Comments
Baseline:					Spirochetes and motil rods were combined in analysis and no significant difference was found in them between treatments.
T:	NR	6.65 (1.13)	6.00 (0.62)	NR	
C:	NR	6.69 (1.22)	6.02 (0.62)	NR	
Final:	37 weeks				
T:	59 (522 teeth)	5.64 (0.96)	4.63 (0.75)	NR	**Quality Score:** 69; 62
C:	59 (506 teeth)	5.75 (1.03)	4.83 (0.92)	NR	
Change:					
T:		1.01* (NR)	1.37 (NR)	NR	
C:		0.94* (NR)	1.19 (NR)	NR	
Test:		Wilcoxen	Wilcoxen		
P value:		NS	<0.05		

Evidence Table 4. Effectiveness of Systemic Metronidazole and Amoxicillin as an Adjunct to Scaling and Root Planing to Treat Chronic Periodontitis

Study Description	Study Design Characteristics	Disease Characteristics	Examiner Characteristics	Description of Scaling and Root Planing
Berglundh et al., 1998[81] **Study Period:** 104 weeks **Study/Treatment Site:** Department of Periodontology, Göteborg University **Location:** Göteborg, Sweden **Patient Population:** Patients were referred to the clinic	**Design Type:** RCT **Subject/Site Allocation:** Random **Blinding:** NR **Placebo:** Yes **Split-mouth:** No	**Severity:** Advanced periodontitis **Types of Teeth:** NR **Widman flap:** NR	**Number:** NR **Trained:** NR **Assigned to Subjects:** NR	**SRP performed:** Non-surgical subgingival scaling and root planing under local anesthesia; SRP in 2 quadrants (mandible, maxilla) **Time spent:** Required 3 to 5 sessions to complete

Evidence Table 4. Effectiveness of Systemic Metronidazole and Amoxicillin as an Adjunct to Scaling and Root Planing to Treat Chronic Periodontitis (continued)

Eligible Study Groups and How Defined:	Study Group Characteristics	Compliance Monitoring	Baseline Measures	Time Interval(s)
Subject/Site allocation: 16 subjects T: 8 subjects C: 8 subjects **Dose, Mode, Schedule:** T: SRP plus 250 mg metronidazole 3xday and 375 mg amoxicillin 2xday for 2 weeks C: SRP with placebo 3xday for 2 weeks	**Age:** Range: 35 to 58 **Gender:** Male: 6 Female: 10 **Race/Ethnicity:** NR	NR	NR	4 times (at baseline and months 2, 12, and 24)

Evidence Table 4. Effectiveness of Systemic Metronidazole and Amoxicillin as an Adjunct to Scaling and Root Planing to Treat Chronic Periodontitis (continued)

Study Description	Outcomes Assessed	Adverse Effects	Study Group Attrition and Reasons	Type of Analysis
Berglundh et al., 1998[81] (continued)	**Clinical Measurement:** BOP/SBI PII PD CAL Tooth Loss (# of remaining teeth) **Radiographic Techniques:** Bone Loss Regeneration **Microbiological Methods:** Plaque microbiota sampling (*A.a., P.g., P.i.*) **Subject Self Report:** NR	NR	NR	**Type of analysis reported:** Full participants only

Evidence Table 4. Effectiveness of Systemic Metronidazole and Amoxicillin as an Adjunct to Scaling and Root Planing to Treat Chronic Periodontitis (continued)

	Outcomes Accessed			
	Attachment Level mm	Probing Depth mm	Spirochetes	
(N of Pts)	$\bar{x}$ (SD)	$\bar{x}$ (SD)	$\bar{x}$% (SD)	Comments
				Microbial Outcomes:
Baseline:				*P.g.:*
T: 8	NR	4.8 (0.7)	NA	Baseline Final
C: 8	NR	4.5 (0.8)	NA	T: 19.1 T: 0.0
				C: 9.8 C: 1.8
Final: 104 weeks				*A.a.:*
T: 8	2.1 (0.4)	2.7 (0.2)	NA	Baseline Final
C: 8	1.5 (0.5)	2.9 (0.6)	NA	T: 0.1 T: 0.0
				C: 0.5 C: 0.1
Change:				Using the study treatment resulting in an improvement of the periodontal conditions and elimination of *A.a.* and *P.g.*
T:	1.1 (0.3)	2.1* (NR)	NA	
C:	0.8 (0.4)	1.6* (NR)	NA	
Test:		NR	NR	
P value:		NR	NR	
				P.i.:
				Baseline Final
				T: 0.1 T: 0.0
				C: 0.5 T: 0.1
				Quality Score: 46; 54

Evidence Table 4. Effectiveness of Systemic Metronidazole and Amoxicillin as an Adjunct to Scaling and Root Planing to Treat Chronic Periodontitis (continued)

Study Description	Study Design Characteristics	Disease Characteristics	Examiner Characteristics	Description of Scaling and Root Planing
Flemmig et al., 1998[82] **Study Period:** 52 weeks **Study/Treatment Site:** Department of Peridontology, Julius Maximilian University **Location:** Wurzburg, Germany **Patient Population:** Patients 30 yrs + with subgingival detection with *A.a.* and/or *P.g.* and = 4 pockets with PD = 6 mm	**Design Type:** RCT **Subject/Site Allocation:** Random **Blinding:** Subject blind **Placebo:** No **Split-mouth:** No	**Severity:** Untreated periodontitis **Types of Teeth:** NR **Widman flap:** NR	**Number:** 1 **Trained:** Dental students **Assigned to Subjects:** Same dentist throughout study	**SRP performed:** Supra and subgingival full mouth scaling under local anesthesia performed by dental students until no supragingival plaque or calculus visible and no pathological exposed and subgingival root surfaces felt hard and smooth **Time spent:** 2 hours per quadrant

Evidence Table 4. Effectiveness of Systemic Metronidazole and Amoxicillin as an Adjunct to Scaling and Root Planing to Treat Chronic Periodontitis (continued)

Eligible Study Groups and How Defined:	Study Group Characteristics	Compliance Monitoring	Baseline Measures	Time Interval(s)
Subject/Site allocation: 48 subjects enrolled 38 completed T: 18 subjects C: 20 subjects **Dose, Mode, Schedule:** T: SRP plus 250 mg metronidazole 3xday and 375 mg amoxicillin 3xday plus 0.06% chlorhexidine subgingival irrigation 1xday, for 8 days C: SRP and oral hygiene instructions	**Age:** Mean: 51.8 ± 11.0 **Gender:** Male: 17 Female: 21 **Race/Ethnicity:** NR	At day 10, remaining tablets of prescribed medication were counted	NR	5 times (10 days, months 3, 6, 9, and 12)

Evidence Table 4. Effectiveness of Systemic Metronidazole and Amoxicillin as an Adjunct to Scaling and Root Planing to Treat Chronic Periodontitis (continued)

Study Description	Outcomes Assessed	Adverse Effects	Study Group Attrition and Reasons	Type of Analysis
Flemmig et al., 1998[82] (continued)	**Clinical Measurement:** PD CAL **Radiographic Techniques:** NR **Microbiological Methods:** Plaque microbiota (*A.a., P.g.*) Swab samples (tongue, tonsils, and buccal mucosa) Polymerase Chain Reaction **Subject Self Report:** NR	Gastro-intestinal intolerance (4) (mainly diarrhea during or after taking prescribed medication)	Lost for gastro-intestinal intolerance (2); developed serious medical conditions not related to antibiotic therapy (2); concomitant dental therapy (1); relocation (3); inability to attend regular study appoint-ments (2)	**Type of analysis reported:** Full participants only Subject is the unit of analysis

Evidence Table 4. Effectiveness of Systemic Metronidazole and Amoxicillin as an Adjunct to Scaling and Root Planing to Treat Chronic Periodontitis (continued)

	Outcomes Accessed			
	Attachment Level mm	Probing Depth mm	Spirochetes	
(N of Pts)	$\bar{x}$ (SD)	$\bar{x}$ (SD)	$\bar{x}$% (SD)	Comments
Baseline:				Data presented graphically. The highest CAL was found in sites with probing depths of = 7 mm at baseline followed by sites 4-6 mm deep at baseline. There were no sig differences btw groups. In subjects with *A.a.,* a significantly higher incidence of CAL gain of 2 mm or more was achieved in treatment group over control ($P < 0.05$). The adverse was true for *P.g.* where there was a loss ($P < 0.05$). **Quality Score:** 38; 31
T: 18	NR	NR	NA	
C: 20	NR	NR	NA	
Final: 52 weeks				
T: 18	NR	NR	NA	
C: 20	NR	NR	NA	
Change:				
T:	NR	NR	NA	
C:	NR	NR	NA	
Test:				
P value:				

Evidence Table 4. Effectiveness of Systemic Metronidazole and Amoxicillin as an Adjunct to Scaling and Root Planing to Treat Chronic Periodontitis (continued)

Study Description	Study Design Characteristics	Disease Characteristics	Examiner Characteristics	Description of Scaling and Root Planing
Author and Year: Rooney et al., 2002[70] **Study Period:** 26 weeks (6 months) **Site of Study:** Department of Perodontology, Bristol Dental School and Hospital **Location:** UK **Patients Selected:** Patients <46 years old referred by practitioners who had failed to respond to non-surgical periodontal treatment with PD = 6 mm and BOP.	**Design Type:** RCT **Subject/Site Allocation:** Random **Blinding:** Examiners and patients blind **Placebo:** Yes **Split-mouth:** Yes, for microbiotic samples, 1 in each quadrant	**Severity:** Advanced chronic periodontal disease **Types of Teeth:** All but 3rd molars and severely malpositioned teeth **Widman flap:** NR	**Number:** 2 **Trained:** NR **Assigned to Patients:** Same clinician provided treatment throughout study	**SRP performed:** Quadrant root planings under local anesthesia with ultrasonic scaler and Gracey curettes. SRP done by 2 experienced periodontists. **Time spent on SRP:** 45 minutes for all teeth in quadrant; SRPs separated by maximum of 12 days, usually 7 days.

Evidence Table 4. Effectiveness of Systemic Metronidazole and Amoxicillin as an Adjunct to Scaling and Root Planing to Treat Chronic Periodontitis (continued)

Eligible Study Groups and How Defined:	Study Group Characteristics	Compliance Monitoring	Baseline Measures	Assessment Time Interval(s)
Subject/Site allocation: 30 subjects T: 15 subjects C: 15 subjects **Dose, Mode, Schedule:** All received 0.2% chlorhexidine mouthrinse (10ml, 60s) 2xday until 1 week after non-surgical therapy T: SRP plus 250 mg amoxicillin + 200 mg metronidazole 3xday for 7 days C: SRP plus placebo (lactose capsules and calcium lactate tablets) 3xday for 7 days	**Age:** Range: 20 to 45 **Gender Distribution:** NR **Race/Ethnicity:** NR	NR	Before SRP	4 times (at baseline, and months 1, 3, and 6)

Evidence Table 4. Effectiveness of Systemic Metronidazole and Amoxicillin as an Adjunct to Scaling and Root Planing to Treat Chronic Periodontitis (continued)

Study Description	Outcomes Assessed	Adverse Effects	Study Group Attrition and Reasons	Type of Analysis
Rooney et al., 2002[70] (continued)	**Clinical Measurement:** PD CAL BOP Presence of Suppuration Plaque deposits **Radiographic Techniques:** NR **Microbiological Methods:** Following incubation, anaerobic counts from agar plates for *P.g., P.i., A..a.*, and others **Patient Self Report:** NR	None	66 recruited for full study; 4 were lost: lacked one month data (1); lacked 3 month data (1); had no 6 month data (3); no 3 and 6 month data (2); unable to determine which treatment groups the 4 were assigned to	**Type of analysis reported:** Full participants only

Evidence Table 4. Effectiveness of Systemic Metronidazole and Amoxicillin as an Adjunct to Scaling and Root Planing to Treat Chronic Periodontitis (continued)

	Outcomes Accessed			
	Attachment Level mm	Probing Depth mm	Spirochetes	
(N of Pts)	$\bar{x}$ (SD)	$\bar{x}$ (SD)	$\bar{x}$ % (SD)	Comments
Baseline:				Presented as % of sites with low (0-3 mm) or high (= 6 mm), not in actual mm measurements or changes.
T: NR	NR	NR	NA	
C: NR	NR	NR	NA	
Final: 26 weeks				
T: 15 pts	NR	NR	NA	
C: 15 pts	NR	NR	NA	Differences in PD and CAL treatment effects were significantly greater in the treatment group than in the control.
Change:				
T:	NR	NR	NA	
C:	NR	NR	NA	
Test	ANCOVA	ANCOVA		Microbiological data showed significant difference for treatment group versus control only at 1 month and not at months 3 and 6.
P-value	=0.05	=0.001		
				Quality Score: 69; 54

Evidence Table 4. Effectiveness of Systemic Metronidazole and Amoxicillin as an Adjunct to Scaling and Root Planing to Treat Chronic Periodontitis (continued)

Study Description	Study Design Characteristics	Disease Characteristics	Examiner Characteristics	Description of Scaling and Root Planing
Author and Year: Winkel et al., 2001[83] **Study Period:** 12 weeks (3 months) **Site of Study:** Clinics for Periodontology **Location:** Amsterdam and Utrecht, Netherlands **Patients Selected:** Patients referred to clinic for PD treatment = 1 sites in = 3 quadrants with PD > 6 mm and CAL = 3 mm plus BOP and radiographic evidence of bone loss	**Design Type:** RCT **Subject/Site Allocation:** Random **Blinding:** Examiners and patients blind **Placebo:** Yes **Split-mouth:** No	**Severity:** Generalized severe adult periodontitis **Types of Teeth:** NR **Widman flap:** NR	**Number:** 1 at each clinic **Trained:** NR **Assigned to Subjects:** One examiner for all clinical and biological samples at each clinic and throughout study	**SRP performed:** Full mouth scaling and root planing, under local anesthetic, if requested. Approximately 6 weeks later, subjects were recalled and SRP was readministered to pockets with PD > 3 mm and BOP **Time spent on SRP:** 3 to 6 sessions of 1 hour each over 6 week period

Evidence Table 4. Effectiveness of Systemic Metronidazole and Amoxicillin as an Adjunct to Scaling and Root Planing to Treat Chronic Periodontitis (continued)

Eligible Study Groups and How Defined:	Study Group Characteristics	Compliance Monitoring	Baseline Measures	Assessment Time Interval(s)
Subject/Site allocation: 49 subjects completed T: 23 subjects C: 26 subjects **Dose, Mode, Schedule:** T: SRP plus 375 mg amoxicillin and 250 mg metronidazole tablets, 3xday for 7 days C: SRP plus identical placebos, 3xday for 7 days	**Age:** Mean: 42 T: 45 C: 40 Range: 28 to 63 **Gender Distribution:** Male: T: 11 C: 10 Female: T: 12 C: 16 **Race/Ethnicity:** NR	Subjects were asked to return unused meds after 7 days. No tablets were returned, though 1 subject complained about missing 1 tablet.	Before SRP	3 times (at baseline, 6 weeks and 3 months after medicine completion)

Evidence Table 4. Effectiveness of Systemic Metronidazole and Amoxicillin as an Adjunct to Scaling and Root Planing to Treat Chronic Periodontitis (continued)

Study Description	Outcomes Assessed	Adverse Effects	Study Group Attrition and Reasons	Type of Analysis
Winkel et al., 2001[83] (continued)	**Clinical Measurement:** PII PD BI CAL **Radiographic Techniques:** NR **Microbiological Methods:** Plaque sampling (*P.m., P.g., B.f., B.i.*) Mowbell's et al., 1991, 1994 **Subject Self Report:** NR	Face rash (T:1, C:1); gastro-intestinal intolerance (T: 9); rash on neck (T: 1); nausea after alcohol (T: 1)	Severe headache, severe diarrhea, refused tablets because of size, unwilling to avoid alcohol (T: 4); pregnant (C: 1)	**Type of analysis reported:** Full participants only

Evidence Table 4. Effectiveness of Systemic Metronidazole and Amoxicillin as an Adjunct to Scaling and Root Planing to Treat Chronic Periodontitis (continued)

	Outcomes Accessed			
	Attachment Level mm	Probing Depth mm	Spirochetes	
(N of Pts)	$\bar{x}$ (SD)	$\bar{x}$ (SD)	$\bar{x}$% (SD)	Comments
Baseline:				Sites with *P.g.* had significantly greater PD reduction with treatment (1.52mm) placebo (1.1mm) and there was difference in the group that had no *P.g.*
T: 23	7.7 (1.8)	7.81 (0.9)	NA	
C: 26	7.4 (1.1)	8.1 (1.2)	NA	
Final: 12 weeks				The greatest PD reduction was found at sites with initial PD = 7 mm (T: 3.2 mm, C: 2.5 mm). These sites had most pronounced CAL gains (T: 2.0 mm, C: 1.5 mm)
T: 23	5.8 (1.5)	4.6 (0.9)	NA	
C: 26	5.1 (1.4)	5.6 (1.3)	NA	
Change:	Gain	Reduction		
T:	2.3* (NR)	3.2* (NR)	NA	
C:	1.9* (NR)	2.5* (NR)	NA	
Test:	Mann Whitney	Mann Whitney		
P value:	NS	<0.05		**Quality Score:** 85; 77

Evidence Table 5. Effectiveness of Local Chlorhexidine Combinations as an Adjunct to Scaling and Root Planing to Treat Chronic Periodontitis

Study Description	Study Design Characteristics	Disease Characteristics	Examiner Characteristics	Description of Scaling and Root Planing
Aziz-Gandour and Newman, 1986[77]	**Design Type:** RCT	**Severity:** Chronic peridontitis	**Number:** NR	**SRP performed:** Supra and subgingival scaling, root planing and sub-contact area debridement and polishing
Study Period: 12 weeks (84 days)	**Subject/Site Allocation:** Random	**Types of Teeth:** NR	**Trained:** NR	
Study/Treatment Site: Health Department Clinic	**Blinding:** Examiners and patients blind	**Widman flap:** NR	**Assigned to Subjects:** NR	**Time spent:** NR
Location: UK	**Placebo:** Yes			
Patient Population: Patients with approximal surface pockets and = 4 mm bone reabsorption as seen on radiographs	**Split-mouth:** No			

Evidence Table 5. Effectiveness of Local Chlorhexidine Combinations as an Adjunct to Scaling and Root Planing to Treat Chronic Periodontitis (continued)

Eligible Study Groups and How Defined:	Study Group Characteristics	Compliance Monitoring	Baseline Measures	Time Interval(s)
Subject/Site allocation: 12 subjects T: 6 subjects (147 surfaces) C: 6 subjects (118 surfaces) **Dose, Mode, Schedule:** T: SRP plus 0.2% chlorhexidine irrigation 1xday for 28 days C: SRP plus 0.1% quinine sulphate irrigation	**Age:** Mean: T: 43 C: 48 Range: T: 32 to 53 C: 43 to 55 **Gender:** Male: T: 1 C: 2 Female: T: 5 C: 4 **Race/Ethnicity:** NR	Yes, with irrigation	Before SRP	5 times (at baseline and days 7, 28, 56, and 84)

Evidence Table 5. Effectiveness of Local Chlorhexidine Combinations as an Adjunct to Scaling and Root Planing to Treat Chronic Periodontitis (continued)

Study Description	Outcomes Assessed	Adverse Effects	Study Group Attrition and Reasons	Type of Analysis
Aziz-Gandour and Newman, 1986[77] (continued)	**Clinical Measurement:** SBI PII PD GI Gingival recession **Radiographic Techniques:** NR **Microbiological Methods:** NR **Subject Self Report:** NR	NR	1 subject excluded from full study because of failure to attend all visits, but it is not clear which treatment group subject was assigned to	**Type of analysis reported:** Full participants only

Evidence Table 5. Effectiveness of Local Chlorhexidine Combinations as an Adjunct to Scaling and Root Planing to Treat Chronic Periodontitis (continued)

	Outcomes Accessed			
	Attachment Level mm	Probing Depth mm	Spirochetes	
(N of Pts)	$\bar{x}$ (SD)	$\bar{x}$ (SD)	$\bar{x}$ % (SD)	Comments
Baseline:				For chlorhexidine and control groups, there were significant differences in pocket depth only at day 56 visit.
T: 6 (147 sites)	NA	4.8 (NR)	NA	
C: 6 (118 sites)	NA	4.6 (NR)	NA	
Final: 12 weeks (84 days)				
T: NR	NA	NR	NA	Clinically, the differences between groups was relatively small.
C: NR	NA	NR	NA	
Change:				
T:	NA	NR	NA	**Quality Score:** 54; 46
C:	NA	NR	NA	
Test:		ChiSquare, Paired t-test		
P value:		NS		

Evidence Table 5. Effectiveness of Local Chlorhexidine as an Adjunct to Scaling and Root Planing to Treat Chronic Periodontitis (continued)

Study Description	Study Design Characteristics	Disease Characteristics	Examiner Characteristics	Description of Scaling and Root Planing
Azmak et al., 2002[93] **Study Period:** 26 weeks (6 months) **Study/Treatment Site:** Ege University **Location:** Izmir, Turkey **Patient Population:** Patients with 2 interproximal sites selected from anterior teeth with PD 6 to 8 mm and BOP, = 4 sites with = 4 mm attachment loss, and at least 2 teeth between selected sites	**Design Type:** RCT **Subject/Site Allocation:** Random **Blinding:** Examiners blind **Placebo:** No **Split-mouth:** Yes	**Severity:** Moderate to severe chronic periodontitis **Types of Teeth:** NR **Widman flap:** NR	**Number:** NR **Trained:** NR **Assigned to Subjects:** Same examiner throughout study	**SRP performed:** Under local anesthesia **Time spent:** 5 minutes per tooth

Evidence Table 5. Effectiveness of Local Chlorhexidine as an Adjunct to Scaling and Root Planing to Treat Chronic Periodontitis (continued)

Eligible Study Groups and How Defined:	Study Group Characteristics	Compliance Monitoring	Baseline Measures	Time Interval(s)
Subject/Site allocation: 22 subjects enrolled 20 completed 2 sites per mouth T: 20 sites C: 20 sites **Dose, Mode, Schedule:** T: SRP plus 2.5 mg chlorhexidine chip in isolated pockets C: SRP only	**Age:** Range: 36 to 62 **Gender:** Both **Race/Ethnicity:** NR	NA	Before SRP	4 times (at baseline and months 1, 3, and 6) GCF MMP measured at baseline, days 2 and 10, and months 1, 3, and 6

Evidence Table 5. Effectiveness of Local Chlorhexidine as an Adjunct to Scaling and Root Planing to Treat Chronic Periodontitis (continued)

Study Description	Outcomes Assessed	Adverse Effects	Study Group Attrition and Reasons	Type of Analysis
Azmak et al., 2002[93] (continued)	**Clinical Measurement:** BOP/SBI PII PD CAL GCI GCF-MMP – 8 levels **Radiographic Techniques:** NR **Microbiological Methods:** NR **Subject Self Report:** NR	NR	Use of antibiotics (2)	**Type of analysis reported:** Full participants only

Evidence Table 5. Effectiveness of Local Chlorhexidine as an Adjunct to Scaling and Root Planing to Treat Chronic Periodontitis (continued)

	Outcomes Accessed			
	Attachment Level mm	Probing Depth mm	Spirochetes	
(N of Pts)	$\bar{x}$ (SD)	$\bar{x}$ (SD)	$\bar{x}$ % (SD)	Comments
Baseline:				Outcome data presented graphically.
T: 20 sites	8.83 (1.34)	7.00 (0.69)	NA	
C: 20 sites	8.72 (0.84)	6.83 (0.86)	NA	Improvements were not statistically significant at 1, 3, and 6 months for PD and CAL.
Final: 26 weeks				
T: 20 sites	NR	NR	NA	
C: 20 sites	NR	NR	NA	**Quality Score:** 38; 31
Change:				
T: 20 sites	NR	NR	NA	
C: 20 sites	NR	NR	NA	
Test:	Repeated Measures ANCOVA	Repeated Measures ANCOVA		
P value:	0.574	0.138		

Evidence Table 5. Effectiveness of Local Chlorhexidine as an Adjunct to Scaling and Root Planing to Treat Chronic Periodontitis (continued)

Study Description	Study Design Characteristics	Disease Characteristics	Examiner Characteristics	Description of Scaling and Root Planing
Braatz et al., 1985[30] **Study Period:** 24 weeks **Study/Treatment Site:** NR **Location:** USA **Patient Population:** Patients with at least 2 sites with PD = 7 mm on single-rooted teeth with BOP	**Design Type:** RCT **Subject/Site Allocation:** Random **Blinding:** NR **Placebo:** No **Split-mouth:** Yes	**Severity:** Generalized chronic periodontitis **Types of Teeth:** Single-rooted **Widman flap:** NR	**Number:** 1 **Trained:** NA **Assigned to Subjects:** Same examiner throughout study	**SRP performed:** Single episode of supra and subgingival instrumentation under local anesthesia **Time spent:** NR

Evidence Table 5. Effectiveness of Local Chlorhexidine as an Adjunct to Scaling and Root Planing to Treat Chronic Periodontitis (continued)

Eligible Study Groups and How Defined:	Study Group Characteristics	Compliance Monitoring	Baseline Measures	Time Interval(s)
Subject/Site allocation: 14 subjects (2 to 25 sites per subject) T: 54 sites C: 52 sites **Dose, Mode, Schedule:** T: SRP plus irrigation with 0.2% chlorhexidine 1xday for 24 weeks on 1 side of maxillary and/or mandibular jaw C: SRP only	**Age:** Range: 40 to 70 **Gender:** Male: 8 Female: 6 **Race/Ethnicity:** NR	Yes, subjects were checked every 2 weeks for their ability to irrigate the experi-mental sites	Before SRP	3 times (at baseline and weeks 12 and 24)

Evidence Table 5. Effectiveness of Local Chlorhexidine as an Adjunct to Scaling and Root Planing to Treat Chronic Periodontitis (continued)

Study Description	Outcomes Assessed	Adverse Effects	Study Group Attrition and Reasons	Type of Analysis
Braatz et al., 1985[30] (continued)	**Clinical Measurement:** BOP/SBI PD CAL **Radiographic Techniques:** NR **Microbiological Methods:** Spirochete analysis, dark field microscopy **Subject Self Report:** NR	NR	NR	**Type of analysis reported:** Full participants only

Evidence Table 5. Effectiveness of Local Chlorhexidine as an Adjunct to Scaling and Root Planing to Treat Chronic Periodontitis (continued)

	Outcomes Accessed				
	(N of Pts)	Attachment Level mm $\bar{x}$ (SD)	Probing Depth mm $\bar{x}$ (SD)	Spirochetes $\bar{x}$ % (SD)	Comments
Baseline:					Chlorhexidine group and control group did not differ significantly in any of the studied parameters so treatment did not augment SRP
T:	54 sites	NR	7.6 (0.9)	6.8% (9.0)	
C:	52 sites	NR	7.5 (0.7)	9.2% (11.0)	
Final:	24 weeks				
T:	54 sites	NR	4.3 (1.4)	0.8% (3.0)	**Quality Score:** 46; 38
C:	52 sites	NR	4.5 (1.5)	1.2% (4.1)	
Change:		Gain			
T:	54 sites	1.4 (1.4)	3.3* (NR)	NR	
C:	52 sites	1.2 (1.1)	3.0* (NR)	NR	
Test:		ANOVA	ANOVA	ANOVA	
P value:		NS	NS	NS	

Evidence Table 5. Effectiveness of Local Chlorhexidine as an Adjunct to Scaling and Root Planing to Treat Chronic Periodontitis (continued)

Study Description	Study Design Characteristics	Disease Characteristics	Examiner Characteristics	Description of Scaling and Root Planing
Author and Year: Grisi et al., 2002[94]	**Design Type:** RCT	**Severity:** Chronic periodontitis	**Number:** 1	**SRP performed:** Full mouth supragingival scaling under anesthesia with Gracey curets
Study Period: 39 weeks (9 months)	**Subject/Site Allocation:** Random	**Types of Teeth:** NR	**Trained:** NA	
Site of Study: NR	**Blinding:** Examiner blind	**Widman flap:** NR	**Assigned to Subjects:** NR	**Time spent on SRP:** NR
Location: Brazil	**Placebo:** No			
Patients Selected: Patients with PD = 5 mm in at least 4 sites and BOP	**Split-mouth:** No			

Evidence Table 5. Effectiveness of Local Chlorhexidine as an Adjunct to Scaling and Root Planing to Treat Chronic Periodontitis (continued)

Eligible Study Groups and How Defined:	Study Group Characteristics	Compliance Monitoring	Baseline Measures	Assessment Time Interval(s)
Subject/Site allocation: 20 subjects invited 19 subjects enrolled and completed T: 10 (41 sites) C: 9 (43 sites) **Dose, Mode, Schedule:** T: SRP plus chlorhexidine chip at baseline and at 3 and 6 months in all pockets = 5 mm; chip position assessed at days 3 and 7 after placement C: SRP alone Note: Full mouth supragingival prophylaxis 1xmonth for both treatment and control groups.	**Age:** Mean: 41.8 ± 5.6 Range: 35 to 56 **Gender Distribution:** Male: 11 (T: 5, C: 3) Female: 9 (T: 5, C: 6) **Race/Ethnicity:** NR	NR	Before SRP	4 times (at baseline and months 3, 6, and 9)

Evidence Table 5. Effectiveness of Local Chlorhexidine as an Adjunct to Scaling and Root Planing to Treat Chronic Periodontitis (continued)

Study Description	Outcomes Assessed	Adverse Effects	Study Group Attrition and Reasons	Type of Analysis
Grisi et al., 2002[94] (continued)	**Clinical Measurement:** PII GR PD BOP Suppuration CAL PBS **Radiographic Techniques:** NR **Microbiological Methods:** BANA Test; Microbes: *B.f., T.d., P.g.* **Subject Self Report:** NR	NR	Antibiotic use during test period (1)	**Type of analysis reported:** Full participants only

Evidence Table 5. Effectiveness of Local Chlorhexidine as an Adjunct to Scaling and Root Planing to Treat Chronic Periodontitis (continued)

	Outcomes Accessed			
	Attachment Level mm	Probing Depth mm	Spirochetes	
(N of Pts)	$\bar{x}$ (SD)	$\bar{x}$ (SD)	$\bar{x}$ (SD)	Comments
Baseline:				SRP produced a significant reduction in microorganisms. The addition of the chlorhexidine chip did not augment the results. **Quality Score:** 46; 38
T: 10 (41 sites)	NR	5.2 (0.6)	NA	
C: 9 (39 sites)	NR	5.2 (0.6)	NA	
Final: 39 weeks (9 months)				
T: 10 (41 sites)	NR	3.0 (0.8)	NA	
C: 9 (39 sites)	NR	2.9 (0.6)	NA	
Change:	Gain	Reduction		
T: 10 (41 sites)	0.6 (0.7)	2.2 (0.7)	NA	
C: 9 (39 sites)	1.0 (0.4)	2.4 (0.7)	NA	
Test:	Mann-Whitney	Mann-Whitney		
P value:	0.07	NS		

Evidence Table 5. Effectiveness of Local Chlorhexidine as an Adjunct to Scaling and Root Planing to Treat Chronic Periodontitis (continued)

Study Description	Study Design Characteristics	Disease Characteristics	Examiner Characteristics	Description of Scaling and Root Planing
Heasman et al., 2001[92] **Study Period:** 26 weeks (6 months) **Study/Treatment Site:** Department of Periodontology of Newcastle Dental School and Hospital **Location:** UK **Patient Population:** Adults with = 10 natural uncrowned teeth; = 1 pocket per quadrant with PD = 5 mm and persistent BOP	**Design Type:** RCT **Subject/Site Allocation:** Random **Blinding:** Examiners blind **Placebo:** No **Split-mouth:** Yes (left side, right side)	**Severity:** Moderate to advanced chronic periodontitis **Types of Teeth:** Molars **Widman flap:** NR	**Number:** 2 **Trained:** Calibration (Gold standard) **Assigned to Subjects:** Same examiner throughout study. Clinician placed all periochips, always in the absence of examiner	**SRP performed:** At baseline, supragingival ultrasonic scaling and prophylaxis of all teeth. All target sites were root planed under local anesthesia **Time spent:** Maximum of 5 minutes per tooth for supragingival scaling

Evidence Table 5. Effectiveness of Local Chlorhexidine as an Adjunct to Scaling and Root Planing to Treat Chronic Periodontitis (continued)

Eligible Study Groups and How Defined:	Study Group Characteristics	Compliance Monitoring	Baseline Measures	Time Interval(s)
Subject/Site allocation: 26 subjects recruited 24 completed T: 87 sites C: 165 sites **Dose, Mode, Schedule:** T: SRP plus 2.5 mg controlled release chlorhexidine chip inserted in pockets C: SRP only	**Age:** Mean: 42.6 Range: 34 to 59 **Gender:** Male: 8 Female:18 **Race/Ethnicity:** White: 100%	NA	Before SRP	4 times (at baseline and months 1, 3, and 6)

Evidence Table 5. Effectiveness of Local Chlorhexidine as an Adjunct to Scaling and Root Planing to Treat Chronic Periodontitis (continued)

Study Description	Outcomes Assessed	Adverse Effects	Study Group Attrition and Reasons	Type of Analysis
Heasman et al., 2001[92] (continued)	**Clinical Measurement:** BOP/SBI PII PD CAL **Radiographic Techniques:** NR **Microbiological Methods:** NR **Subject Self Report:** NR	Only 1 subject reported any oral symptoms at any time during trial	Withdrew after 3 mos for non-treatment related reasons (2)	**Type of analysis reported:** Intent to treat

Evidence Table 5. Effectiveness of Local Chlorhexidine as an Adjunct to Scaling and Root Planing to Treat Chronic Periodontitis (continued)

		Outcomes Accessed			
	(N of Pts)	Attachment Level mm $\bar{x}$ (SD)	Probing Depth mm $\bar{x}$ (SD)	Spirochetes $\bar{x}$ % (SD)	Comments
Baseline:					The results suggest that the chlorhexidine chip is beneficial for subjects on maintenance therapy although the benefit is not apparent until 6 months after placement
T:	87 sites	14.23 (0.19 se)	6.64 (0.12 se)	NA	
C:	165 sites	14.14 (0.16 se)	6.47 (0.11 se)	NA	
Final:	26 weeks				
T:	NR	NR	NR	NA	
C:	NR	NR	NR	NA	**Quality Score:** 54; 54
Change:		Gain	Reduction		
T:	NR	0.43 (0.15 se)	0.78 (0.12 se)	NA	
C:	NR	0.15 (0.09 se)	0.45 (0.13 se)	NA	
Test:		t-test	t-test		
P value:		0.048	0.05		

Evidence Table 5. Effectiveness of Local Chlorhexidine as an Adjunct to Scaling and Root Planing to Treat Chronic Periodontitis (continued)

Study Description	Study Design Characteristics	Disease Characteristics	Examiner Characteristics	Description of Scaling and Root Planing
Jeffcoat et al., 1998[91] **Study Period:** 39 weeks (9 months) **Study/Treatment Site:** 10 centers at 10 different universities **Location:** USA **Patient Population:** Patients with = 10 natural teeth and = 4 teeth with PD of 5 to 8 mm and BOP	**Design Type:** RCT **Subject/Site Allocation:** Random **Blinding:** Examiners and patients blind **Placebo:** Yes **Split-mouth:** Yes	**Severity:** Adult periodontitis **Types of Teeth:** NR **Widman flap:** NR	**Number:** At least one at each center **Trained:** Calibration (gold standard) **Assigned to Subjects:** Same examiner throughout study	**SRP performed:** All subjects received scaling and root planing **Time spent:** 1 hour for all teeth for removal of supragingival calculus and 1 hour for SRP

Evidence Table 5. Effectiveness of Local Chlorhexidine as an Adjunct to Scaling and Root Planing to Treat Chronic Periodontitis (continued)

Eligible Study Groups and How Defined:	Study Group Characteristics	Compliance Monitoring	Baseline Measures	Time Interval(s)
Subject/Site allocation: 447 subjects entered 419 subjects completed T: 211 sites C: 208 sites **Dose, Mode, Schedule:** T: SRP plus 2.5 mg controlled release chlorhexidine chips at baseline, 3 and 6 months if PD = 5 mm C: SRP with placebo chip	**Age:** Mean: 46.4 Range: 27 to 79 **Gender:** Male: 207 Female: 240 **Race/Ethnicity:** NH White: 336 (75.2%) NH Black: 85 (19%) Hispanic: 8 (1.8%) Asian/Pacific Islander: 12 (2.7%) Other: 6 (1.3%)	NA	Before SRP	6 times (at baseline, day 7, week 6, and months 3, 6, and 9)

Evidence Table 5. Effectiveness of Local Chlorhexidine as an Adjunct to Scaling and Root Planing to Treat Chronic Periodontitis (continued)

Study Description	Outcomes Assessed	Adverse Effects	Study Group Attrition and Reasons	Type of Analysis
Jeffcoat et al., 1998[91] (continued)	**Clinical Measurement:** BOP/SBI PII PD CAL GI Staining examination **Radiographic Techniques:** NR **Microbiological Methods:** NR **Subject Self Report:** NR	Higher in treatment group: minor and transient toothache (including pain, tenderness, aching, throbbing, soreness, discomfort, or sensitivity)	Concurrent medical/ dental treatment; illness; lack of follow-up	**Type of analysis reported:** Intent to treat, analysis adjusted

Evidence Table 5. Effectiveness of Local Chlorhexidine as an Adjunct to Scaling and Root Planing to Treat Chronic Periodontitis (continued)

		Outcomes Accessed			
	(N of Pts)	Attachment Level mm $\bar{x}$ (SD)	Probing Depth mm $\bar{x}$ (SD)	Spirochetes $\bar{x}$ % (SD)	Comments
					Quality Score: 85; 93
Baseline:					
T:	225	5.27 (1.34 se)	5.73 (0.59 se)	NA	
C:	222	5.14 (1.48 se)	5.64 (0.55 se)	NA	
Final: 39 weeks (9 months)					
T:		NR	NR	NA	
C:		NR	NR	NA	
Change:		Gain	Reduction		
T:	211	0.75 (0.06 se)	0.95 (0.05 se)	NA	
C:	208	0.55 (0.06 se)	0.69 (0.05 se)	NA	
Test:		NR	NR		
P value:		0.012	0.00056		

Evidence Table 5. Effectiveness of Local Chlorhexidine as an Adjunct to Scaling and Root Planing to Treat Chronic Periodontitis (continued)

Study Description	Study Design Characteristics	Disease Characteristics	Examiner Characteristics	Description of Scaling and Root Planing
Author and Year: MacAlpine 1985[31] **Study Period:** 24 weeks **Site of Study:** NR **Location:** NR (Swedish and US authors) **Patients Selected:** Patients with PD = 6 mm demonstrated by attachment loss, BOP, and subgingival calculus	**Design Type:** Clinical trial **Subject/Site Allocation:** Assignment method not reported **Blinding:** NR **Placebo:** Yes **Split-mouth:** Yes	**Severity:** Generalized chronic periodontitis **Types of Teeth:** Single root **Widman flap:** No	**Number:** 1 **Trained:** NA **Assigned to Subjects:** Same investigator throughout study	**SRP performed:** Supra and subgingival instrumentation under local anesthesia until operator was confident that the tooth surfaces had been equately debrided **Time spent on SRP:** NR

Evidence Table 5. Effectiveness of Local Chlorhexidine as an Adjunct to Scaling and Root Planing to Treat Chronic Periodontitis (continued)

Eligible Study Groups and How Defined:	Study Group Characteristics	Compliance Monitoring	Baseline Measures	Assessment Time Interval(s)
Subject/Site allocation: 11 subjects 4 or 8 sites per subject T: 16 sites C: 16 sites **Dose, Mode, Schedule:** T: SRP plus subgingival irrigation with 2% chlorhexidine solution every 2 weeks for 24 weeks C: SRP and saline irrigation, every 2 weeks for 24 weeks	**Age:** Range: 25-67 **Gender Distribution:** Males: 2 Females: 9 **Race/Ethnicity:** NR	NA	Before SRP	4 times (at baseline, and weeks 8, 16, and 24) Spirochetes were assessed at baseline and weeks 7, 15, and 23

Evidence Table 5. Effectiveness of Local Chlorhexidine as an Adjunct to Scaling and Root Planing to Treat Chronic Periodontitis (continued)

Study Description	Outcomes Assessed	Adverse Effects	Study Group Attrition and Reasons	Type of Analysis
MacAlpine 1985[31] (continued)	**Clinical Measurement:** BOP Plaque scores PD CAL **Radiographic Techniques:** NR **Microbiological Methods:** Subgingival plaque samples (% spirochetes); dark field microscopy **Subject Self Report:** NR	NR	NR	**Type of analysis reported:** All who completed treatment

Evidence Table 5. Effectiveness of Local Chlorhexidine as an Adjunct to Scaling and Root Planing to Treat Chronic Periodontitis (continued)

	Outcomes Accessed			
(N of Pts)	Attachment Level mm $\bar{x}$ (SD)	Probing Depth mm $\bar{x}$ (SD)	Spirochetes $\bar{x}$ % (SD)	Comments
				Quality Score: 38; 38
Baseline:				
T: 16 sites	NR	7.7 (0.9)	32 (20)	
C: 16 sites	NR	7.4 (0.6)	39 (21)	
Final: 24 weeks				
T: 16 sites	NR	4.2 (1.0)	2 (3)	
C: 16 sites	NR	4.9 (1.8)	4 (7)	
Change:	Gain	Reduction		
T:	1.7 (1.3)	1.7 (1.3)	NR	
C:	0.8 (1.4)	0.8 (1.4)	NR	
Test:	ANOVA	ANOVA		
P value:	NS	NS		

Evidence Table 5. Effectiveness of Local Chlorhexidine as an Adjunct to Scaling and Root Planing to Treat Chronic Periodontitis (continued)

Study Description	Study Design Characteristics	Disease Characteristics	Examiner Characteristics	Description of Scaling and Root Planing
Oosterwaal et al., 1991[89] **Study Period:** 36 weeks **Study/Treatment Site:** Department of Periodontology, University of Nijmegen **Location:** Netherlands **Patient Population:** Patients referred with 4 interdental pockets of 7 to 9 mm affecting single rooted teeth, BOP, alveolar bone and attachment loss	**Design Type:** RCT **Subject/Site Allocation:** Random **Blinding:** Examiners and patients blind **Placebo:** Yes **Split-mouth:** Yes	**Severity:** Advanced periodontitis **Types of Teeth:** Single-rooted **Widman flap:** NR	**Number:** 2 **Trained:** NR **Assigned to Subjects:** NR	**SRP performed:** Selected pockets got both hand and ultrasonic mechanical (Gracey curettes) debridement. Other pockets got SRP 4 weeks later **Time spent:** NR

Evidence Table 5. Effectiveness of Local Chlorhexidine as an Adjunct to Scaling and Root Planing to Treat Chronic Periodontitis (continued)

Eligible Study Groups and How Defined:	Study Group Characteristics	Compliance Monitoring	Baseline Measures	Time Interval(s)
Subject/Site allocation: 10 subjects T: 10 sites C: 10 sites **Dose, Mode, Schedule:** T: SRP plus 2% chlorhexidine gel, applied 3 times within 10 minutes after SRP C: SRP with placebo gel applied 3 times with syringe within 10 minutes after SRP	**Age:** Mean: 48 Range: 33 to 62 **Gender:** Male: 4 Female: 6 **Race/Ethnicity:** NR	NA	Before SRP	4 times (at baseline and weeks 4, 12, and 36)

Evidence Table 5. Effectiveness of Local Chlorhexidine as an Adjunct to Scaling and Root Planing to Treat Chronic Periodontitis (continued)

Study Description	Outcomes Assessed	Adverse Effects	Study Group Attrition and Reasons	Type of Analysis
Oosterwaal et al., 1991[89] (continued)	**Clinical Measurement:** BOP/SBI PII PD **Radiographic Techniques:** NR **Microbiological Methods:** Subgingival microflora by microscopic and culture studies of plaque samples (% spirochetes, motile rods, non-motile rods) **Subject Self Report:** NR	NR	NR	**Type of analysis reported:** Full participants only

Evidence Table 5. Effectiveness of Local Chlorhexidine as an Adjunct to Scaling and Root Planing to Treat Chronic Periodontitis (continued)

	Outcomes Accessed			
	Attachment Level mm	Probing Depth mm	Spirochetes	
(N of Pts)	$\bar{x}$ (SD)	$\bar{x}$ (SD)	$\bar{x}$ % (SD)	Comments
Baseline:				Data on clinical outcomes presented graphically.
T: 10 (10 sites)	NA	7.6 (0.7)	NR	
C: 10 (10 sites)	NA	NR	NR	
				Effect of SRP and chlorhexidine gel did not differ from SRP and placebo gel.
Final: 36 weeks				
T: 10 (10 sites)	NA	4.7 (1.0)	NR	
C: 10 (10 sites)	NA	NR	NR	
				No differences among groups in PD or % spirochetes after 36 weeks.
Change:				
T:	NA	NR	NR	
C:	NA	NR	NR	
Test:		ANOVA	ANOVA	**Quality Score:** 63; 54
P value:		NS	NS	

Evidence Table 5. Effectiveness of Local Chlorhexidine as an Adjunct to Scaling and Root Planing to Treat Chronic Periodontitis (continued)

Study Description	Study Design Characteristics	Disease Characteristics	Examiner Characteristics	Description of Scaling and Root Planing
Author and Year: Quirynen et al., 2000[95] **Study Period:** 35 weeks (8 months) **Site of Study:** Department of Peridontology of the University Hospital of Catholic University Leuven **Location:** Belgium **Patients Selected:** Patients referred by general dental practitioner with at least 2 multi-rooted teeth and 3 single-rooted teeth in the 1st quadrant and at least 6 sites with PD = 7mm	**Design Type:** NR **Subject/Site Allocation:** Unknown **Blinding:** NR **Placebo:** No **Split-mouth:** No	**Severity:** Advanced chronic adult periodontitis **Types of Teeth:** Single and multi-rooted third molars excluded **Widman flap:** NR	**Number:** 1 **Trained:** NA **Assigned to Subjects:** Same examiner throughout study	**SRP performed:** Under local anesthesia, using periodontal curettes, on all pockets within 24 hours. **Time spent on SRP:** Completed during 2 sessions within 24 hours, starting with the lower jaw.

Evidence Table 5. Effectiveness of Local Chlorhexidine as an Adjunct to Scaling and Root Planing to Treat Chronic Periodontitis (continued)

Eligible Study Groups and How Defined:	Study Group Characteristics	Compliance Monitoring	Baseline Measures	Assessment Time Interval(s)
Subject/Site allocation: 24 subjects in relevant treatment groups T: 12 subjects C: 12 subjects **Dose, Mode, Schedule:** T: SRP plus 2x during first 24 hours: brush tongue with 1% chlorhexidine gel for 60 sec; rinse mouth 2x with 0.2% chlorhexidine solution for 1 min; spray tonsils 4x/tonsil with 0.2% chlorhexidine spray; subgingival irrigation of pockets 3x within 10 min with 1% chlorhexidine gel. All repeated a third time at day 8. At home for next 2 months: chlorhexidine rinse 2xday and tonsil spray C: SRP alone	**Age:** Range: 37 to 69 **Gender Distribution:** Male: 20 Female: 16 **Race/Ethnicity:** White: 100%	Via question-naire	Before SRP	5 times (at baseline, at end of months 1, 2, 4, and 8)

Evidence Table 5. Effectiveness of Local Chlorhexidine as an Adjunct to Scaling and Root Planing to Treat Chronic Periodontitis (continued)

Study Description	Outcomes Assessed	Adverse Effects	Study Group Attrition and Reasons	Type of Analysis
Quirynen et al., 2000[95] (continued)	**Clinical Measurement:** GI PI PD Gingival recession or over growth CAL BOP **Radiographic Techniques:** NR **Microbiological Methods:** Differential phase-contrast microscopy (coccoid cells, motile rods, spirochetes and others) **Subject Self Report:** Questionnaire	Yes, subjects rated subjective outcomes (pain, swelling)	NR	**Type of analysis reported:** Full participants only

Evidence Table 5. Effectiveness of Local Chlorhexidine as an Adjunct to Scaling and Root Planing to Treat Chronic Periodontitis (continued)

	Outcomes Accessed				
	(N of Pts)	Attachment Level mm $\bar{x}$ (SD)	Probing Depth mm $\bar{x}$ (SD)	Spirochetes $\bar{x}$ % (SD)	Comments
Single-rooted					At each follow-up visit a statistically significant ($P < 0.001$) improvement at end of baseline was recorded for PD in both groups. The difference between the Treatment and Control groups were never statistically significant.
Baseline:					
T:	12	NR	6.2 (2.0)	NR	
C:	12	NR	6.2 (1.8)	NR	
Final:	35 weeks (8 months)				
T:	12	NR	4.0 (1.0)	NR	
C:	12	NR	3.9 (1.5)	NR	
Change:		Gain	Reduction		All pockets showed a statistically significant gain in CAL over the entire experimental period. Differences between groups were small and insignificant For initial PD = 7 mm, the control group had a 0.3 greater gain in CAL for both single and multi-root teeth
T:		NR	2.2 (1.8)	NR	
C:		NR	2.3 (1.3)	NR	
Test:			Mann Whitney U		
P value:			NS		
Multi-rooted					Statistically significant differences in reduction of spirochetes at 8 months (data presented graphically) **Quality Score:** 54; 54
Baseline:					
T:	12	NR	6.4 (1.9)	NR	
C:	12	NR	6.6 (1.6)	NR	
Final:	35 weeks (8 months)				
T:	12	NR	4.5 (1.4)	NR	
C:	12	NR	4.2 (1.3)	NR	
Change:		Gain	Reduction		
T:		NR	1.9 (1.5)	NR	
C:		NR	2.4 (1.3)	NR	
Test:			Mann Whitney U		
P value:			NS		

Evidence Table 5. Effectiveness of Local Chlorhexidine as an Adjunct to Scaling and Root Planing to Treat Chronic Periodontitis (continued)

Study Description	Study Design Characteristics	Disease Characteristics	Examiner Characteristics	Description of Scaling and Root Planing
Reynolds et al., 1992[88] **Study Period:** 4 weeks (28 days) **Study/Treatment Site:** Dental School, University of Maryland **Location:** USA **Patient Population:** New patients	**Design Type:** RCT **Subject/Site Allocation:** Random **Blinding:** Examiners and patients blind **Placebo:** Yes **Split-mouth:** No	**Severity:** Early to moderate adult periodontitis **Types of Teeth:** NR **Widman flap:** NR	**Number:** NR **Trained:** NR **Assigned to Subjects:** NR	**SRP performed:** Entire dentition ultrasonically scaled and irrigated until all supra and subgingival calculus was removed **Time spent:** 30 to 40 minutes for ultrasonic scaling per subject

Evidence Table 5. Effectiveness of Local Chlorhexidine as an Adjunct to Scaling and Root Planing to Treat Chronic Periodontitis (continued)

Eligible Study Groups and How Defined:	Study Group Characteristics	Compliance Monitoring	Baseline Measures	Time Interval(s)
Subject/Site allocation: 60 subjects T: 30 subjects C: 30 subjects **Dose, Mode, Schedule:** T: SRP plus 200 ml subgingival irrigation with 0.12% chlorhexidine (single episode) C: SRP with placebo, subgingival irrigation with sterile water (single episode)	**Age:** Range: 28 to 58 **Gender:** Male: 28 Female: 32 **Race/Ethnicity:** NR	NA	Before SRP	3 times (at baseline and weeks 2 and 4)

Evidence Table 5. Effectiveness of Local Chlorhexidine as an Adjunct to Scaling and Root Planing to Treat Chronic Periodontitis (continued)

Study Description	Outcomes Assessed	Adverse Effects	Study Group Attrition and Reasons	Type of Analysis
Reynolds et al., 1992[88] (continued)	**Clinical Measurement:** PII PD GI **Radiographic Techniques:** NR **Microbiological Methods:** Plaque microbiota on a subset of 15 subjects (spirochetes and mobile organisms) Cell morphology Dark field microscopy **Subject Self Report:** NR	NR	NR	**Type of analysis reported:** NR

Evidence Table 5. Effectiveness of Local Chlorhexidine as an Adjunct to Scaling and Root Planing to Treat Chronic Periodontitis (continued)

	Outcomes Accessed			
	Attachment Level mm	Probing Depth mm	Spirochetes	
(N of Pts)	$\bar{x}$ (SD)	$\bar{x}$ (SD)	$\bar{x}$ (%SD)	Comments
Baseline:				Data in graphic form only.
T: NR	NA	NR	NR	
C: NR	NA	NR	NR	PD changes were nonsignificantly greater in chlorhexidine 7-9 mm and 4-6 mm PD groups only.
Final: 4 weeks				
T: NR	NA	NR	NR	
C: NR	NA	NR	NR	No significant changes in the % spirochetes.
Change:				
T: NR	NA	NR	NR	**Quality Score:** 69; 69
C: NR	NA	NR	NR	
Test:				
P value:				

Evidence Table 5. Effectiveness of Local Chlorhexidine as an Adjunct to Scaling and Root Planing to Treat Chronic Periodontitis (continued)

Study Description	Study Design Characteristics	Disease Characteristics	Examiner Characteristics	Description of Scaling and Root Planing
Shiloah and Patters 1994[54] **Study Period:** 4 weeks **Study/Treatment Site:** Graduate Program University Clinic **Location:** USA **Patient Population:** Volunteer adults with PD = 5 mm in non-adjacent sites with = 5 mm PD, attachment loss and presence of target organism	**Design Type:** RCT **Subject/Site Allocation:** Random sites within subjects **Blinding:** Examiner blind **Placebo:** Yes **Split-mouth:** Yes	**Severity:** Moderate to severe periodontitis **Types of Teeth:** Single and multi-rooted **Widman flap:** NR	**Number:** 1 **Trained:** Standardization Calibration (Gold standard) **Assigned to Subjects:** Same examiner throughout study	**SRP performed:** Thorough SRP of entire dentition performed with ultrasonic scaler and Gracey curets, under local anesthesia **Time spent:** 4 to 7 hours per subject over several visits

Evidence Table 5. Effectiveness of Local Chlorhexidine as an Adjunct to Scaling and Root Planing to Treat Chronic Periodontitis (continued)

Eligible Study Groups and How Defined:	Study Group Characteristics	Compliance Monitoring	Baseline Measures	Time Interval(s)
Subject/Site allocation: 7 subjects, 1 or 2 teeth per subject T: 12 sites C: 12 sites **Dose, Mode, Schedule:** T: SRP plus irrigation with 0.12% chlorhexidine solution, 2cc/site, 1 aplication C: SRP plus irrigation of pockets with 0.85%, saline, 2cc/site	**Age:** Mean: 47.8 Range: 33 to 65 **Gender:** Male: 2 Female: 5 **Race/Ethnicity:** NR	NA	Before SRP	3 times (at baseline, week 1, and month 1)

Evidence Table 5. Effectiveness of Local Chlorhexidine as an Adjunct to Scaling and Root Planing to Treat Chronic Periodontitis (continued)

Study Description	Outcomes Assessed	Adverse Effects	Study Group Attrition and Reasons	Type of Analysis
Shiloah and Patters 1994[54] (continued)	**Clinical Measurement:** PII PD CAL GI Gingival fluid flow **Radiographic Techniques:** NR **Microbiological Methods:** DNA/RNA probe for subgingival flora (*A.a., P.g., P.i.*) **Subject Self Report:** NR	NR	NR	**Type of analysis reported:** Full participants only

Evidence Table 5. Effectiveness of Local Chlorhexidine as an Adjunct to Scaling and Root Planing to Treat Chronic Periodontitis (continued)

	Outcomes Accessed			
	Attachment Level mm	Probing Depth mm	Spirochetes	
(N of Pts)	$\bar{x}$ (SD)	$\bar{x}$ (SD)	$\bar{x}$ % (SD)	Comments
Baseline:				Data shown graphically.
T: 12 sites	NR	NR	NA	
C: 12 sites	NR	NR	NA	Although PD decreased significantly (P = 0.0001) no significant difference among the treatment groups was noted (P = 0.67).
Final: 4 weeks				
T: 12 sites	NR	NR	NA	
C: 12 sites	NR	NR	NA	
Change:				Attachment loss was reduced by an average 1 mm following therapy. Although CAL decreased significantly (P = 0.0001) no significant difference among treatment groups was noted (P = 0.06).
T: 12 sites	NR	NR	NA	
C: 12 sites	NR	NR	NA	
Test:	ANOVA	ANOVA		
P value:	NS	NS		
				Treatment resulted in reduction of 3 target species of 67% at month 1
				Quality Score: 54; 54

Evidence Table 5. Effectiveness of Local Chlorhexidine as an Adjunct to Scaling and Root Planing to Treat Chronic Periodontitis (continued)

Study Description	Study Design Characteristics	Disease Characteristics	Examiner Characteristics	Description of Scaling and Root Planing
Soskolne et al., 1997[90] **Study Period:** 26 weeks (6 months) **Study/Treatment Site:** Royal Air Force Base at Halton, UK; Newcastle, UK; Jerusalem, Israel **Location:** UK and Israel **Patient Population:** Patients with = 1 PD 5 to 8 mm and BOP in each of 2 maxillary quadrants	**Design Type:** RCT **Subject/Site Allocation:** Random to 2 quadrants of the upper jaw **Blinding:** Examiners and patients blind **Placebo:** No **Split-mouth:** Yes	**Severity:** Moderate adult periodontitis **Types of Teeth:** NR **Widman flap:** NR	**Number:** 3 (1 at each center) **Trained:** Calibration (gold standard) **Assigned to Subjects:** Same examiner throughout study	**SRP performed:** Full mouth mechanical supra- and subgingival scaling **Time spent:** =1 hour

Evidence Table 5. Effectiveness of Local Chlorhexidine as an Adjunct to Scaling and Root Planing to Treat Chronic Periodontitis (continued)

Eligible Study Groups and How Defined:	Study Group Characteristics	Compliance Monitoring	Baseline Measures	Time Interval(s)
Subject/Site allocation: 118 eligible subjects at baseline 94 completed T: 94 subjects (401 pockets) C: 94 subjects (412 pockets) **Dose, Mode, Schedule:** T: SRP plus 2.5 mg chlorhexidine chip inserted into each pocket of 5 to 8 mm in designated quadrant at baseline and 3 months if pocket was still 5 to 8mm C: SRP only	**Age:** Mean: 47.5 Range: 30 to 65 **Gender:** Male: 60 Female: 58 **Race/Ethnicity:** NR	NA	Before SRP	4 times (at baseline, 1, 3, and 6 months)

Evidence Table 5. Effectiveness of Local Chlorhexidine as an Adjunct to Scaling and Root Planing to Treat Chronic Periodontitis (continued)

Study Description	Outcomes Assessed	Adverse Effects	Study Group Attrition and Reasons	Type of Analysis
Soskolne et al., 1997[90] (continued)	**Clinical Measurement:** BOP/SBI PII PD CAL GI Staining index **Radiographic Techniques:** NR **Microbiological Methods:** NR **Subject Self Report:** NR	NR	Antibiotic or anti-inflammatory drug use; loss to follow-up, or withdrawal of consent (24)	**Type of analysis reported:** All with any follow-up

Evidence Table 5. Effectiveness of Local Chlorhexidine as an Adjunct to Scaling and Root Planing to Treat Chronic Periodontitis (continued)

	Outcomes Accessed			
	Attachment Level mm	Probing Depth mm	Spirochetes	
(N of Pts)	$\bar{x}$ (SD)	$\bar{x}$ (SD)	$\bar{x}$ % (SD)	Comments
Baseline:				Results show that the treatment of periodontal pockets with chlorhexidine as an adjunct to SRP provides a significantly greater improvement
T:	NR	5.99 (0.05 se)	NA	
C:	NR	6.01 (0.05 se)	NA	
Final: 26 weeks (6 months)				
T: 94 (401 pockets)	NR	NR	NA	For initial PD = 7 mm: Create CAL gain for treatment group of 0.65 mm, $P < 0.001$.
C: 94 (412 pockets)	NR	NR	NA	
Change:	Gain	Reduction		
T: 94 (401 pockets)	0.47 (0.062 se)	1.16 (0.058 se)	NA	Create PD reduction in treatment group of 0.22, $P = 0.0001$
C: 94 (412 pockets)	0.31 (0.06 se)	0.70 (0.056 se)	NA	
Test:	MANOVA	MANOVA		
P value:	< 0.05	= 0.0001		
				Quality Score: 62; 54

Evidence Table 5. Effectiveness of Local Chlorhexidine as an Adjunct to Scaling and Root Planing to Treat Chronic Periodontitis (continued)

Study Description	Study Design Characteristics	Disease Characteristics	Examiner Characteristics	Description of Scaling and Root Planing
Southard et al., 1989[86] **Study Period:** 15 weeks **Study/Treatment Site:** Department of Periodontics, School of Dentistry, University of Missouri **Location:** Kansas City, MO **Patient Population:** Volunteer patients with at least 1 site with PD = 6 mm and BOP in each quadrant	**Design Type:** RCT **Subject/Site Allocation:** Randomized 4 quadrant design **Blinding:** Examiners and patients blind **Placebo:** No **Split-mouth:** Yes	**Severity:** Moderate periodontitis **Types of Teeth:** Posterior **Widman flap:** NR	**Number:** 2 **Trained:** NR **Assigned to Subjects:** Same clinician performed all treatments, while a 2nd examiner measured all clinical parameters	**SRP performed:** 2 assigned quadrants received SRP. Anesthesized by standard nerve blocks or local infiltration techniques. Areas were debrided by hand with a Gracey curette until the root was deemed smooth by tactile sensation with a periodontal probe **Time spent:** NR

Evidence Table 5. Effectiveness of Local Chlorhexidine as an Adjunct to Scaling and Root Planing to Treat Chronic Periodontitis (continued)

Eligible Study Groups and How Defined:	Study Group Characteristics	Compliance Monitoring	Baseline Measures	Time Interval(s)
Subject/Site allocation: 8 subjects T: 16 sites C: 16 sites **Dose, Mode, Schedule:** T: SRP plus irrigation with 2% chlorhexidine at baseline and weeks 1, 2, and 3 on all teeth in quadrant C: SRP only	**Age:** Range: 35 to 65 **Gender:** Male: 4 Female: 4 **Race/Ethnicity:** NR	NA	Before SRP	5 times (at baseline and weeks 5, 7, 11, and 15)

Evidence Table 5. Effectiveness of Local Chlorhexidine as an Adjunct to Scaling and Root Planing to Treat Chronic Periodontitis (continued)

Study Description	Outcomes Assessed	Adverse Effects	Study Group Attrition and Reasons	Type of Analysis
Southard et al., 1989[86] (continued)	**Clinical Measurement:** PII PD CAL GI Bleeding tendency **Radiographic Techniques:** NR **Microbiological Methods:** *B.g.* plaque sample, fluorescent antibody reagent, fluorescent microscope **Subject Self Report:** NR	NR	NR	**Type of analysis reported:** Full participants only

Evidence Table 5. Effectiveness of Local Chlorhexidine as an Adjunct to Scaling and Root Planing to Treat Chronic Periodontitis (continued)

	Outcomes Accessed			
	Attachment Level mm	Probing Depth mm	Spirochetes	
(N of Pts)	$\bar{x}$ (SD)	$\bar{x}$ (SD)	$\bar{x}$ % (SD)	Comments
Baseline:				No significant treatment effects
T: 8	14.4 (NR)	6.6 (NR)	NA	
C: 8	13.6 (NR)	6.3 (NR)	NA	*B.g.* was significantly reduced only in treatment group vs control ($P < 0.01$) but did not extend to the 15th week
Final: 15 weeks				
T: 8	12.7 (NR)	4.2 (NR)	NA	
C: 8	12.0 (NR)	3.8 (NR)	NA	
Change:	Gain	Reduction		**Quality Score:** 54; 38
T:	1.7 (NR)	2.4* (NR)	NA	
C:	1.6 (NR)	2.5* (NR)	NA	
Test:	Newman Keuls	Newman Keuls		
P value:	NS	NS		

Evidence Table 5. Effectiveness of Local Chlorhexidine as an Adjunct to Scaling and Root Planing to Treat Chronic Periodontitis (continued)

Study Description	Study Design Characteristics	Disease Characteristics	Examiner Characteristics	Description of Scaling and Root Planing
Taggart et al., 1990[87] **Study Period:** 10 weeks **Study/Treatment Site:** Health Department Clinic (Department of Periodontology and Preventive Dentistry, United Medical and Dental schools of Guy's and St. Thomas' Hospitals **Location:** London, England **Patient Population:** Patients with with chronic PD involving both sides of the jaw to a similar extent; at least 1 pair of pockets 4 to 6-7 mm (or above) in contra-lateral quadrants and radiographic evidence of bone loss	**Design Type:** NR **Subject/Site Allocation:** Random assigned to upper quadrants **Blinding:** NR **Placebo:** Yes **Split-mouth:** Yes	**Severity:** Moderate to advanced chronic periodontitis **Types of Teeth:** Upper quadrants, no third molars or central incisors **Widman flap:** NR	**Number:** NR **Trained:** NR **Assigned to Subjects:** NR	**SRP performed:** Instrumentation on test and control quadrants with an ultrasonic handpiece scaler, under local anesthesia, until the subgingival root surfaces were considered sufficiently smooth **Time spent:** NR

Evidence Table 5. Effectiveness of Local Chlorhexidine as an Adjunct to Scaling and Root Planing to Treat Chronic Periodontitis (continued)

Eligible Study Groups and How Defined:	Study Group Characteristics	Compliance Monitoring	Baseline Measures	Time Interval(s)
Subject/Site allocation: 10 subjects 2 sites per subject T: 10 sites C: 10 sites **Dose, Mode, Schedule:** T: SRP plus irrigation with 0.02% chlorhexidine once during scaling C: SRP with placebo (irrigation with water once during scaling)	**Age:** Range: 28 to 51 **Gender:** Male: 3 Female: 7 **Race/Ethnicity:** NR	NA	Before SRP	4 times (at baseline and weeks 2, 6, and 10)

Evidence Table 5. Effectiveness of Local Chlorhexidine as an Adjunct to Scaling and Root Planing to Treat Chronic Periodontitis (continued)

Study Description	Outcomes Assessed	Adverse Effects	Study Group Attrition and Reasons	Type of Analysis
Taggart et al., 1990[87] (continued)	**Clinical Measurement:** SBI PII PD CAL **Radiographic Techniques:** NR **Microbiological Methods:** Plaque microbiota (cocci, spirochetes, motile rods and other rod forms), dark field microscopy **Subject Self Report:** NR	NR	NR	**Type of analysis reported:** Full participants only

Evidence Table 5. Effectiveness of Local Chlorhexidine as an Adjunct to Scaling and Root Planing to Treat Chronic Periodontitis (continued)

	Outcomes Accessed				
	(N of Pts)	Attachment Level mm $\bar{x}$ (SD)	Probing Depth mm $\bar{x}$ (SD)	Spirochetes $\bar{x}$ % (SD)	Comments
Baseline:					Chlorhexidine has a slight adjunctive effect in the reduction of pocket depth but not significant
T:	10 (10 sites)	NR	3.5 (0.6)	24.9 (12.4)	
C:	10 (10 sites)	NR	3.4 (0.5)	23.3 (14)	
Final:	10 weeks				**Quality Score:** 46; 46
T:	NR	NR	2.6 (0.3)	9.6 (14.7)	
C:	NR	NR	2.6 (0.7)	13.1 (15.3)	
Change:		Gain	Reduction		
T:	NR	0.5 (1.1 se)	0.9 (NR)	15.3* (NR)	
C:	NR	0.4 (1.0 se)	0.8 (NR)	16.2* (NR)	
Test:		NR	ANOVA	ANOVA	
P value:		NS	NS	NS	

Evidence Table 5. Effectiveness of Local Chlorhexidine as an Adjunct to Scaling and Root Planing to Treat Chronic Periodontitis (continued)

Study Description	Study Design Characteristics	Disease Characteristics	Examiner Characteristics	Description of Scaling and Root Planing
Unsal et al., 1994[59] **Study Period:** 12 weeks **Study/Treatment Site:** Department of Peridontology, Faculty of Dentistry **Location:** University of Ankara, Turkey **Patient Population:** Adult patients with at least 3 teeth in each quadrant having 2 sites with a PD of = 4 mm and radiographic evidence of bone loss	**Design Type:** RCT **Subject/Site Allocation:** Random **Blinding:** NR **Placebo:** No **Split-mouth:** No	**Severity:** Moderate to advanced adult periodontitis **Types of Teeth:** NR **Widman flap:** NR	**Number:** NR **Trained:** NR **Assigned to Subjects:** NR	**SRP performed:** Mechanical debridement by hand with Gracey curettes and ultrasonic scaling and root planing in pockets > 4 mm **Time spent:** NR

Evidence Table 5. Effectiveness of Local Chlorhexidine as an Adjunct to Scaling and Root Planing to Treat Chronic Periodontitis (continued)

Eligible Study Groups and How Defined:	Study Group Characteristics	Compliance Monitoring	Baseline Measures	Time Interval(s)
Subject/Site allocation: 22 subjects invited 15 enrolled T: 7 subjects (97 sites) C: 8 subjects (110 sites) **Dose, Mode, Schedule:** T: SRP plus 1% chlorhexidine gel applied once C: SRP only	**Age:** Mean: 42 Range: 30 to 57 **Gender:** Male: 10 Female: 12 **Race/Ethnicity:** NR	Yes	NR	2 times (at baseline and week 12)

Evidence Table 5. Effectiveness of Local Chlorhexidine as an Adjunct to Scaling and Root Planing to Treat Chronic Periodontitis (continued)

Study Description	Outcomes Assessed	Adverse Effects	Study Group Attrition and Reasons	Type of Analysis
Unsal et al., 1994[59] (continued)	**Clinical Measurement:** Bleeding index PII PD CAL GI Position of gingival margin **Radiographic Techniques:** NR **Microbiological Methods:** NR **Subject Self Report:** NR	NR	NR	**Type of analysis reported:** Intent to treat

Evidence Table 5. Effectiveness of Local Chlorhexidine as an Adjunct to Scaling and Root Planing to Treat Chronic Periodontitis (continued)

	Outcomes Accessed				
	(N of Pts)	Attachment Level mm $\bar{x}$ (SD)	Probing Depth mm $\bar{x}$ (SD)	Spirochetes $\bar{x}$ % (SD)	Comments
Baseline:					No statistically significant differences were found in the reduction of the probing depths or gains in attachment level between the treatment groups **Quality Score:** 46; 46
T:	7 (99 sites)	4.03 (1.50)	4.90 (1.11)	NA	
C:	8 (110 sites)	3.66 (1.22)	5.14 (1.45)	NA	
Final:	12 weeks				
T:	7	3.33 (1.76)	3.32 (1.01)	NA	
C:	8	2.62 (1.24)	3.32 (0.73)	NA	
Change:					
T:		1.04 (0.16)	1.58 (0.96)	NA	
C:		0.70 (1.09)	1.83 (0.54)	NA	
Test:		ANOVA	ANOVA		
P value:		NS	NS		

Evidence Table 5. Effectiveness of Local Chlorhexidine as an Adjunct to Scaling and Root Planing to Treat Chronic Periodontitis (continued)

Study Description	Study Design Characteristics	Disease Characteristics	Examiner Characteristics	Description of Scaling and Root Planing
Watts and Newman, 1986[84] **Study Period:** 12 weeks (84 days) **Study/Treatment Site:** Eastman Dental Hospital **Location:** UK **Patient Population:** Adult patients referred for periodontal treatment with PD = 5 mm and radiographic evidence of bone loss	**Design Type:** RCT **Subject/Site Allocation:** Random **Blinding:** Examiners and patients blind **Placebo:** Yes **Split-mouth:** No	**Severity:** Chronic periodontitis **Types of Teeth:** NR **Widman flap:** NR	**Number:** NR **Trained:** NR **Assigned to Subjects:** NR	**SRP performed:** Supra and subgingival scaling and root planing of the test sites, reduction of any overhanging restorations that were present and full mouth polishing using a rubber cup **Time spent:** NR

Evidence Table 5. Effectiveness of Local Chlorhexidine as an Adjunct to Scaling and Root Planing to Treat Chronic Periodontitis (continued)

Eligible Study Groups and How Defined:	Study Group Characteristics	Compliance Monitoring	Baseline Measures	Time Interval(s)
Subject/Site allocation: 11 subjects 262 sites T: 5 pockets (128 sites) C: 6 pockets (134 sites) **Dose, Mode, Schedule:** T: SRP plus irrigation with 0.02% chlorhexidine 1xday for 28 days C: SRP with 0.01% quinine sulphate (placebo) irrigation 1xday for 28 days	**Age:** Mean: 39 Range: T: 26 to 49 C: 34 to 48 **Gender:** Male: T: 3 C: 1 Female: T: 2 C: 5 **Race/Ethnicity:** NR	NA	Before SRP	4 times (at baseline and days 28, 56, and 84)

Evidence Table 5. Effectiveness of Local Chlorhexidine as an Adjunct to Scaling and Root Planing to Treat Chronic Periodontitis (continued)

Study Description	Outcomes Assessed	Adverse Effects	Study Group Attrition and Reasons	Type of Analysis
Watts and Newman, 1986[84] (continued)	**Clinical Measurement:** SBI PII PD **Radiographic Techniques:** NR **Microbiological Methods:** NR **Subject Self Report:** Found the procedure pleasant	No injuries or staining noted	NR	**Type of analysis reported:** Full participants only. Sites less than 5 mm PD were eliminated prior to the next visit.

Evidence Table 5. Effectiveness of Local Chlorhexidine as an Adjunct to Scaling and Root Planing to Treat Chronic Periodontitis (continued)

	Outcomes Accessed			
	Attachment Level mm	Probing Depth mm	Spirochetes	
(N of Pts)	$\bar{x}$ (SD)	$\bar{x}$ (SD)	$\bar{x}$ % (SD)	Comments
Baseline:				No significant added benefit with 0.02% chlorhexidine was apparent. Data presented graphically.
T: 5 (128 sites)	NA	6.1 (NR)	NA	
C: 6 (134 sites)	NA	5.9 (NR)	NA	
Final: 12 weeks				Chi Square of PD reduction = 4.9
T: NR	NA	NR	NA	
C: NR	NA	NR	NA	**Quality Score:** 46; 46
Change:				
T:	NA	NR	NA	
C:	NA	NR	NA	
Test:		Chi Square		
P value:		NS		

Evidence Table 5. Effectiveness of Local Chlorhexidine as an Adjunct to Scaling and Root Planing to Treat Chronic Periodontitis (continued)

Study Description	Study Design Characteristics	Disease Characteristics	Examiner Characteristics	Description of Scaling and Root Planing
Wennström et al., 1987[85] **Study Period:** 52 weeks **Study/Treatment Site:** Graduate Program, Department of Periodontology, University Clinic **Location:** Sweden **Patient Population:** Patients with PD = 6 mm and BOP selected from the waiting list	**Design Type:** RCT **Subject/Site Allocation:** Random assignment of quadrants **Blinding:** Examiners blind **Placebo:** Yes **Split-mouth:** Yes	**Severity:** Moderate to severe periodontal disease **Types of Teeth:** NR **Widman flap:** NR	**Number:** 1 **Trained:** NA **Assigned to Subjects:** Same examiner throughout study	**SRP performed:** Subgingival mechanical debridement of entire dentition at week 32 of study **Time spent:** 6 visits during 6 weeks

Evidence Table 5. Effectiveness of Local Chlorhexidine as an Adjunct to Scaling and Root Planing to Treat Chronic Periodontitis (continued)

Eligible Study Groups and How Defined:	Study Group Characteristics	Compliance Monitoring	Baseline Measures	Time Interval(s)
Subject/Site allocation: 10 subjects T: 28 sites C: 24 sites **Dose, Mode, Schedule:** All subjects received professional tooth cleaning every 4 weeks T: SRP plus irrigation with 0.2% chlorhexidine 3xweek C: SRP plus irrigation with saline 3xweek	**Age:** Mean: 43.1 Range: 22 to 61 **Gender:** NR **Race/Ethnicity:** NR	NA	Before SRP	3 times (at baseline and weeks 40 and 52) 52 week study, SRP and treatment at week 32

Evidence Table 5. Effectiveness of Local Chlorhexidine as an Adjunct to Scaling and Root Planing to Treat Chronic Periodontitis (continued)

Study Description	Outcomes Assessed	Adverse Effects	Study Group Attrition and Reasons	Type of Analysis
Wennström et al., 1987[85] (continued)	**Clinical Measurement:** BOP/SBI PII PD CAL GI **Radiographic Techniques:** Bone Loss/Regeneration **Microbiological Methods:** Crevicular fluid microbiota **Subject Self Report:** NR	NR	NR	**Type of analysis reported:** Full participants only

Evidence Table 5. Effectiveness of Local Chlorhexidine as an Adjunct to Scaling and Root Planing to Treat Chronic Periodontitis (continued)

	Outcomes Accessed			
(N of Pts)	Attachment Level mm $\bar{x}$ (SD)	Probing Depth mm $\bar{x}$ (SD)	Spirochetes $\bar{x}$ % (SD)	Comments
Baseline:				Results are presented in terms of percentage of sites
T:	NR	6.7 (NR)	NA	
C:	NR	6.9 (NR)	NA	**Quality Score:** 46; 46
Final: 52 weeks				
T:	NR	4.8 (NR)	NA	
C:	NR	5.1 (NR)	NA	
Change:	Gain	Reduction		
T: 28 sites	0.6 (0.4)	1.9* (NR)	NA	
C: 24 sites	0.7 (0.5)	1.8* (NR)	NA	
Test:	Paired t-test	NR		
P value:	NS	NR		

Evidence Table 6a. Effectiveness of Other Systemic Antibiotics as an Adjunct to Scaling and Root Planing to Treat Chronic Periodontitis

Study Description	Study Design Characteristics	Disease Characteristics	Examiner Characteristics	Description of Scaling and Root Planing
Bain et al., 1994[97] **Study Period:** 24 weeks (6 months) **Study/Treatment Site:** 7 dental faculties at Canadian Universities **Location:** Canada **Patient Population:** Patients = 15 teeth and = 2 sites in interproximal areas with PD = 7 mm and a contacting adjacent tooth; radiographic evidence of bone loss	**Design Type:** RCT **Subject/Site Allocation:** Random **Blinding:** Examiner and patients blind **Placebo:** Yes **Split-mouth:** No	**Severity:** Advanced chronic peridontitis **Types of Teeth:** NR **Widman flap:** NR	**Number:** 7 (1 per center) **Trained:** NR **Assigned to Subjects:** NR	**SRP performed:** Thorough scaling and root planing **Time spent:** 3 to 5 hours during the 2 weeks of drug therapy

Evidence Table 6a. Effectiveness of Other Systemic Antibiotics as an Adjunct to Scaling and Root Planing to Treat Chronic Periodontitis (continued)

Eligible Study Groups and How Defined:	Study Group Characteristics	Compliance Monitoring	Baseline Measures	Time Interval(s)
Subject/Site allocation: 193 started 189 completed T: 93 subjects C: 96 subjects **Dose, Mode, Schedule:** T: SRP plus 1,500,000 IU of spiramycin ("500" capsules), 2xday, for 14 days C: SRP plus placebo 2xday for 14 days	**Age:** Mean: T: 47.3 ± 1.0 C: 48.5 ± 1.2 **Gender:** NR **Race/Ethnicity:** NR	Bottle check at 2 week visit for a count of unusued medication	Before SRP	5 times (at baseline and weeks 2, 8, 12, 24)

Evidence Table 6a. Effectiveness of Other Systemic Antibiotics as an Adjunct to Scaling and Root Planing to Treat Chronic Periodontitis (continued)

Study Description	Outcomes Assessed	Adverse Effects	Study Group Attrition and Reasons	Type of Analysis
Bain et al., 1994[97] (continued)	**Clinical Measurement:** BOP/SBI PII PD CAL GCF **Radiographic Techniques:** NR **Microbiological Methods:** Crevicular fluid microbiota **Subject Self Report:** NR	Two subjects (1 from each group) terminated due to periodontal symptoms and 2 (both spiramycin subjects) due to emergent signs (gastro-intestinal upset, abdominal pain, diarrhea)	Adverse events (4)	**Type of analysis reported:** Full participants only

Evidence Table 6a. Effectiveness of Other Systemic Antibiotics as an Adjunct to Scaling and Root Planing to Treat Chronic Periodontitis (continued)

	Outcomes Accessed			
	Attachment Level mm	Probing Depth mm	Spirochetes	
(N of Pts)	$\bar{x}$ (SD)	$\bar{x}$ (SD)	$\bar{x}$ % (SD)	Comments
Baseline:				Attachment level measurements were consistently slightly lower in the drug group, this was only statistically significant at the 12 week interval (P = 0.0146) **Quality Score:** 85; 85
T: 93	10.72 (0.15 se)	7.6 (0.08 se)	NA	
C: 96	10.69 (0.16 se)	7.53 (0.08 se)	NA	
Final: 24 weeks				
T: 93	8.85 (0.16 se)	4.73 (0.11 se)	NA	
C: 96	9.11 (0.19 se)	5.13 (0.14 se)	NA	
Change:				
T:	1.87* (NR)	2.87* (NR)	NA	
C:	1.58* (NR)	2.40* (NR)	NA	
Test:	ANOVA	ANOVA		
P value:	NS	< 0.0075		

Evidence Table 6a. Effectiveness of Other Systemic Antibiotics as an Adjunct to Scaling and Root Planing to Treat Chronic Periodontitis (continued)

Study Description	Study Design Characteristics	Disease Characteristics	Examiner Characteristics	Description of Scaling and Root Planing
Haffajee et al., 1995[46] **Study Period:** 43 weeks (10 months) **Study/Treatment Site:** Hospital Dental Clinic **Location:** USA **Patients Selected:** Originally 98 patients aged 14-71 with evidence of prior attachment loss, at least 20 teeth and at least 4 pockets >4 mm and 4 sites of LOA >3mm, no localized JP, no rapidly progressing PD. From this pool, subjects exhibiting LOA >2.5 mm at = 1 sites anytime during 6 months observation period were admitted to study	**Design Type:** RCT **Subject/Site Allocation:** Random **Blinding:** Examiners and patients blind **Placebo:** Yes **Split-mouth:** No	**Severity:** NR **Types of Teeth:** All excluding third molars **Widman flap:** Yes, at active sites and where PD > 4mm	**Number:** 1 **Trained:** NA **Assigned to Subjects:** Same examiner throughout study	**SRP performed:** Scaling and root planing by quadrant, approximate 10 day intervals, repeated during course of study every 3 months for 1 yr **Time spent on SRP:** NR

Evidence Table 6a. Effectiveness of Other Systemic Antibiotics as an Adjunct to Scaling and Root Planing to Treat Chronic Periodontitis (continued)

Eligible Study Groups and How Defined:	Study Group Characteristics	Compliance Monitoring	Baseline Measures	Time Interval(s)
Subject/Site allocation: 21 subjects, 6 sites per tooth T: 10 subjects C: 11 subjects **Dose, Mode, Schedule:** All rinsed with 0.12% chlorhexidine for 30 days T: SRP plus 250 mg amoxicillin and 125 mg clavulanic acid 3xday for 30 days C: SRP plus placebo (250 mg sucrose) 3xday for 30 days	**Age:** Mean All: 48 ± 12 Mean T: 44 ± 15 Mean C: 48 ± 11 **Gender:** All: 57% Male T: 62% Male C: 55% Male **Race/Ethnicity:** NR	NR	Before SRP	6 times (at baseline and 2, 4, 6, 8, and 10 months)

Evidence Table 6a. Effectiveness of Other Systemic Antibiotics as an Adjunct to Scaling and Root Planing to Treat Chronic Periodontitis (continued)

Study Description	Outcomes Assessed	Adverse Effects	Study Group Attrition and Reasons	Type of Analysis
Haffajee et al., 1995[46] (continued)	**Clinical Measurement:** BOP/SBI PD CAL GI **Radiographic Techniques:** NR **Microbiological Methods:** DNA probes and colony lifts for 14 taxa in 29 of 40 subjects **Subject Self Report:** NR	NR	NR	**Type of analysis reported:** Mann-Whitney and Kruskal-Wallis, change by site, averaged for individual, then averaged for group Subject is unit of analysis

Evidence Table 6a. Effectiveness of Other Systemic Antibiotics as an Adjunct to Scaling and Root Planing to Treat Chronic Periodontitis (continued)

		Outcomes Accessed			
		Attachment Level mm	Probing Depth mm	Spirochetes	
	(N of Pts)	$\bar{x}$ (SD)	$\bar{x}$ (SD)	$\bar{x}$ % (SD)	Comments
Baseline:					Only baseline values presented in table. Change score mostly presented in bar graphs. Text presents change scores for PD, but not the associated SDs.
T:	13	4.2 (1.3)	4.1 (0.8)	NA	
C:	11	3.5 (1.2)	3.6 (0.5)	NA	
Final:	43 weeks (10 months)				
T:	13	NR	NR	NA	
C:	11	NR	NR	NA	**Quality Score:** 62; 46
Change:		Gain	Reduction		
T:		0.68 (NR)	0.75 (NR)	NA	
C:		NR	0.46 (NR)	NA	
Test:		Mann Whitney Test	Mann Whitney Test		
P value:		< 0.01	NS		

Evidence Table 6a. Effectiveness of Other Systemic Antibiotics as an Adjunct to Scaling and Root Planing to Treat Chronic Periodontitis (continued)

Study Description	Study Design Characteristics	Disease Characteristics	Examiner Characteristics	Description of Scaling and Root Planing
Ng and Bissada, 1998[98] **Study Period:** 24 weeks **Study/Treatment Site:** NR **Location:** USA **Patient Population:** Patients with generalized periodontitis and having at least 2 teeth with = 5 mm probing depth	**Design Type:** RCT **Subject/Site Allocation:** Random **Blinding:** Examiners blind **Placebo:** Yes **Split-mouth:** Yes	**Severity:** Generalized moderate adult periodontitis **Types of Teeth:** NR **Widman flap:** NR	**Number:** 1 **Trained:** NR **Assigned to Subjects:** Same examiner throughout study	**SRP performed:** Ultrasonic and hand SRP in 1 session, under local anesthesia, only half mouth received SRP **Time spent:** NR

Evidence Table 6a. Effectiveness of Other Systemic Antibiotics as an Adjunct to Scaling and Root Planing to Treat Chronic Periodontitis (continued)

Eligible Study Groups and How Defined:	Study Group Characteristics	Compliance Monitoring	Baseline Measures	Time Interval(s)
Subject/Site allocation: 16 subjects T: 8 subjects C: 8 subjects **Dose, Mode, Schedule:** T: SRP plus 200 mg doxycycline first day then 100 mg 1xday for 6 weeks C: SRP with placebo (capsules orally 1 daily)	**Age: (For full study)** Range: 32 to 72 **Gender: (For full study)** Male: 18 Female: 14 **Race/Ethnicity:** NR	Compliance with drug intake was reinforced verbally at each appointment	Before SRP	5 times (at baseline and weeks 3, 6, 12, and 24)

Evidence Table 6a. Effectiveness of Other Systemic Antibiotics as an Adjunct to Scaling and Root Planing to Treat Chronic Periodontitis (continued)

Study Description	Outcomes Assessed	Adverse Effects	Study Group Attrition and Reasons	Type of Analysis
Ng and Bissada, 1998[98] (continued)	**Clinical Measurement:** PII PD CAL GI **Radiographic Techniques:** Periapical radiographs using paralleling x-ray technique **Microbiological Methods:** NR **Subject Self Report:** NR	Adverse effects collected but none reported	None left study	**Type of analysis reported:** Full participants only

Evidence Table 6a. Effectiveness of Other Systemic Antibiotics as an Adjunct to Scaling and Root Planing to Treat Chronic Periodontitis (continued)

	Outcomes Accessed			
	Attachment Level mm	Probing Depth mm	Spirochetes	
(N of Pts)	$\bar{x}$ (SD)	$\bar{x}$ (SD)	$\bar{x}$ % (SD)	Comments
Baseline:				Doxycycline resulted in a statistically significant, yet modest, clinical improvement over placebo
T: 8	7.8 (1.2)	4.3 (0.9)	NA	
C: 8	9.0 (1.9)	4.3 (0.9)	NA	
Final: 24 weeks				**Quality Score:** 62; 77
T: 8	7.4 (0.5)	4.6 (0.4)	NA	
C: 8	9.9 (0.8)	4.0 (0.6)	NA	
Change:				
T:	0.4* (NR)	-0.3* (NR)	NA	
C:	-0.9* (NR)	0.3* (NR)	NA	
Test:	ANOVA	ANOVA		
P value:	= 0.05	NS		

Evidence Table 6a. Effectiveness of Other Systemic Antibiotics as an Adjunct to Scaling and Root Planing to Treat Chronic Periodontitis (continued)

Study Description	Study Design Characteristics	Disease Characteristics	Examiner Characteristics	Description of Scaling and Root Planing
Al-Joburi et al., 1989[45] **Study Period:** 24 weeks **Study/Treatment Site:** Several Universities **Location:** Canada **Patient Population:** Patients at least 35 years old with at least = 2 sites with probing depth = 7 mm and at least 15 teeth	**Design Type:** RCT **Subject/Site Allocation:** Random **Blinding:** Examiners and patients blind **Placebo:** Yes **Split-mouth:** No	**Severity:** Advanced adult chronic **Types of Teeth:** NR **Widman flap:** NR	**Number:** 2 (1 at each site) **Trained:** NR **Assigned to Subjects:** Same examiner throughout study	**SRP performed:** Thorough scaling and root planing (intensive) completed in 2 visits, one week apart **Time spent:** 6 hours

Evidence Table 6a. Effectiveness of Other Systemic Antibiotics as an Adjunct to Scaling and Root Planing to Treat Chronic Periodontitis (continued)

Eligible Study Groups and How Defined:	Study Group Characteristics	Compliance Monitoring	Baseline Measures	Time Interval(s)
Subject/Site allocation: 96 started full study 52 completed relevant treatments 2 interproximal sites per subject T: 28 subjects C: 24 subjects **Dose, Mode, Schedule:** T: SRP plus 500 mg spiramycin 2xday for 14 days C: SRP plus placebo, 1 capsule 2xday for 14 days	**Age:** Mean: 46 ± 0.9 **Gender:** NR **Race/Ethnicity:** NR	Yes	Before SRP	5 times (at baseline and weeks 2, 8, 12, and 24)

Evidence Table 6a. Effectiveness of Other Systemic Antibiotics as an Adjunct to Scaling and Root Planing to Treat Chronic Periodontitis (continued)

Study Description	Outcomes Assessed	Adverse Effects	Study Group Attrition and Reasons	Type of Analysis
Al-Joburi et al., 1989[45] (continued)	**Clinical Measurement:** BOP/SBI PII PD CAL **Radiographic Techniques:** NR **Microbiological Methods:** Crevicular fluid microbiota Plaque microbiota **Subject Self Report:** NR	Yes, 1 subject excluded because of nausea	17 subjects excluded: intercurrent but unrelated illness during the study which required taking antibiotics other than study medication (1); loss to follow-up (3); failed to take medication as prescribed (6); developed severe diarrhea (1)	**Type of analysis reported:** Full participants only

Evidence Table 6a. Effectiveness of Other Systemic Antibiotics as an Adjunct to Scaling and Root Planing to Treat Chronic Periodontitis (continued)

	Outcomes Accessed			
(N of Pts)	Attachment Level mm $\bar{x}$ (SD)	Probing Depth mm $\bar{x}$ (SD)	Spirochetes $\bar{x}$% (SD)	Comments
PD 1 to 3 mm:				Despite intensive SRP, the additional use of an antibiotic resulted in a significantly greater reduction in spirochete level at the 2, 8 and 24 week visits There were no significant intergroup differences in CAL or PD at 24 weeks **Quality Score:** 69; 69
Baseline:				
T: 28	7.29 (0.57)	3.00 (0.00)	28 (NR)	
C: 24	7.50 (0.84)	3.00 (0.35)	30 (NR)	
Final: 24 weeks				
T:	6.67 (0.67)	2.58 (0.34)	3 (NR)	
C:	7.80 (0.82)	3:00 (0.16)	11 (NR)	
Change:				
T:	0.62* (NR)	0.42* (NR)	NR	
C:	-0.30* (NR)	0.00* (NR)	NR	
Test:	NR	NR	NR	
P value:	NS	NS	Sig	
PD 4 to 6 mm:				
Baseline:				
T:	9.11 (0.27)	5.26 (0.11)		
C:	9.11 (0.22)	5.25 (0.08)		
Final:				
T:	8.31 (0.30)	3.94 (0.20)		
C:	8.09 (0.21)	3.53 (0.12)		
Change:				
T:	0.80* (NR)	1.32* (NR)		
C:	1.02* (NR)	1.72* (NR)		
Test:	NR	NR		
P value:	NS	NS		
PD > 7 mm:				
Baseline:				
T:	10.60 (0.27)	7.49 (0.13)		
C:	10.75 (0.29)	7.60 (0.17)		
Final:				
T:	9.14 (0.26)	4.92 (0.21)		
C:	9.21 (0.34)	4.75 (0.24)		
Change:				
T:	0.46* (NR)	2.57* (NR)		
C:	1.54* (NR)	2.85* (NR)		
Test:	NR	NR		
P value:	NS	NS		

Evidence Table 6a. Effectiveness of Other Systemic Antibiotics as an Adjunct to Scaling and Root Planing to Treat Chronic Periodontitis (continued)

Study Description	Study Design Characteristics	Disease Characteristics	Examiner Characteristics	Description of Scaling and Root Planing
Chin Quee et al., 1987[96] **Study Period:** 26 weeks (6 months) **Study/Treatment Site:** NR **Location:** NR **Patient Population:** Patients over 35 years old with = 2 sites with PD = 7mm and at least 15 teeth	**Design Type:** RCT **Subject/Site Allocation:** Random **Blinding:** Examiners and patients blind **Placebo:** Yes **Split-mouth:** No	**Severity:** Advanced periodontitis **Types of Teeth:** NR **Widman flap:** NR	**Number:** 2 **Trained:** Standardi-zation (practice on subjects before study began) **Assigned to Subjects:** Same examiner throughout study	**SRP performed:** Thorough SRP, 2 sessions of 3 hours each, one week apart **Time spent:** 6 hours

Evidence Table 6a. Effectiveness of Other Systemic Antibiotics as an Adjunct to Scaling and Root Planing to Treat Chronic Periodontitis (continued)

Eligible Study Groups and How Defined:	Study Group Characteristics	Compliance Monitoring	Baseline Measures	Time Interval(s)
Subject/Site allocation: 56 subjects recruited (2 sites/person) 50 completed T: 26 subjects C: 24 subjects **Dose, Mode, Schedule:** T: SRP plus 3 tablets (750,000 IUs spiramycin and 125 mg metronidazole) 2xday for 14 days C: SRP and placebo, 3 tablets 2xday for 14 days	**Age:** Mean: 4 T: 42 ± 1.41 C: 46 ± 1.33 **Gender:** No sig difference between groups **Race/Ethnicity:** No sig difference between groups	NR	Before SRP	8 times (at baseline, 14 days, and months 1, 2, 3, 4, 5, and 6)

Evidence Table 6a. Effectiveness of Other Systemic Antibiotics as an Adjunct to Scaling and Root Planing to Treat Chronic Periodontitis (continued)

Study Description	Outcomes Assessed	Adverse Effects	Study Group Attrition and Reasons	Type of Analysis
Chin Quee et al., 1987[96] (continued)	**Clinical Measurement:** PII GI PD CAL **Radiographic Techniques:** NR **Microbiological Methods:** Subgingival bacteria (cocoid cells, motile cells, spirochetes and other cells), dark field microscopy **Subject Self Report:** NR	Yes, only significant difference was 4 in treatment group had diarrhea in second week, did not mention others (by means of question-naire)	Lost to follow-up (6)	**Type of analysis reported:** Full participants only

Evidence Table 6a. Effectiveness of Other Systemic Antibiotics as an Adjunct to Scaling and Root Planing to Treat Chronic Periodontitis (continued)

	Outcomes Accessed			
	Attachment Level mm	Probing Depth mm	Spirochetes	
(N of Pts)	$\bar{x}$ (SD)	$\bar{x}$ (SD)	$\bar{x}$ % (SD)	Comments
Baseline:				The adjunctive use of this treatment resulted in a significant increase in attachment level as well as a significant decrease in the proportion of spirochetes, and both of these changes were sustained until the end of the study. Data presented graphically No significant intergroup differences at any time interval for PD **Quality Score:** 54; 54
T: 26	NR	NR	40 (NR)	
C: 24	NR	NR	45 (NR)	
Final: 26 weeks				
T: 26	NR	NR	3.0 (NR)	
C: 24	NR	NR	15.0 (NR)	
Change:				
T:	NR	NR	NR	
C:	NR	NR	NR	
Test:	ANOVA	ANOVA	ANOVA	
P value:	<0.05	NS	<0.05	

Evidence Table 6a. Effectiveness of Other Systemic Antibiotics as an Adjunct to Scaling and Root Planing to Treat Chronic Periodontitis (continued)

Study Description	Study Design Characteristics	Disease Characteristics	Examiner Characteristics	Description of Scaling and Root Planing
Rooney et al., 2002[70] **Study Period:** 26 weeks (6 months) **Site of Study:** Department of Perodontology, Bristol Dental School and Hospital **Location:** UK **Patients Selected:** Patients <46 years old referred by practitioners who had failed to respond to non-surgical periodontal treatment with PD = 6 mm and BOP.	**Design Type:** RCT **Subject/Site Allocation:** Random **Blinding:** Examiners and patients blind **Placebo:** Yes **Split-mouth:** Yes, for microbiotic samples, 1 in each quadrant	**Severity:** Advanced chronic periodontal disease **Types of Teeth:** All but 3rd molars and severely malpositioned teeth **Widman flap:** NR	**Number:** 2 **Trained:** NR **Assigned to Patients:** Same clinician provided treatment throughout study	**SRP performed:** Quadrant root planings under local anesthesia with ultrasonic scaler and Gracey curettes. SRP done by 2 experienced periodontists. **Time spent on SRP:** 45 minutes for all teeth in quadrant; SRPs separated by maximum of 12 days, usually 7 days.

Evidence Table 6a. Effectiveness of Other Systemic Antibiotics as an Adjunct to Scaling and Root Planing to Treat Chronic Periodontitis (continued)

Eligible Study Groups and How Defined:	Study Group Characteristics	Compliance Monitoring	Baseline Measures	Assessment Time Interval(s)
Subject/Site allocation: 31 subjects T: 16 subjects C: 15 subjects **Dose, Mode, Schedule:** All received 0.2% chlorhexidine mouthrinse (10ml, 60s) 2xday until 1 week after non-surgical therapy T: SRP plus 250 mg amoxicillin + placebo (calcium lactate tablets) 3xday for 7 days C: SRP plus placebo (lactose capsules and calcium lactate tablets) 3xday for 7 days	**Age:** Range: 20 to 45 **Gender Distribution:** NR **Race/Ethnicity:** NR	NR	Before SRP	4 times (at baseline, and months 1, 3, and 6)

Evidence Table 6a. Effectiveness of Other Systemic Antibiotics as an Adjunct to Scaling and Root Planing to Treat Chronic Periodontitis (continued)

Study Description	Outcomes Assessed	Adverse Effects	Study Group Attrition and Reasons	Type of Analysis
Rooney et al., 2002[70] (continued)	**Clinical Measurement:** PD CAL BOP Presence of Suppuration Plaque deposits **Radiographic Techniques:** NR **Microbiological Methods:** Following incubation, anaerobic counts from agar plates for *P.g., P.i., A..a.*, and others **Patient Self Report:** NR	None	66 recruited for full study; 4 were lost: lacked one month data (1); lacked 3 month data (1); had no 6 month data (3); no 3 and 6 month data (2); unable to determine which treatment groups the 4 were assigned to	**Type of analysis reported:** Full participants only

Evidence Table 6a. Effectiveness of Other Systemic Antibiotics as an Adjunct to Scaling and Root Planing to Treat Chronic Periodontitis (continued)

	Outcomes Accessed			
		Attachment Level mm	Probing Depth mm	Spirochetes	
	(N of Pts)	$\bar{x}$ (SD)	$\bar{x}$ (SD)	$\bar{x}$ % (SD)	Comments
Baseline:					Presented as % of sites with low (0-3 mm) or high (= 6 mm), not in actual mm measurements or changes.
T:	NR	NR	NR	NA	
C:	NR	NR	NR	NA	
Final: 26 weeks					
T:	16	NR	NR	NA	
C:	15	NR	NR	NA	Differences in PD and CAL treatment effects were significantly greater in the treatment group than in the control.
Change:					
T:		NR	NR	NA	
C:		NR	NR	NA	
Test		ANCOVA	ANCOVA		Microbiological data showed significant difference for treatment group versus control only at 1 month and not at months 3 and 6.
P-value		=0.05	=0.001		
					Quality Score: 69; 54

Evidence Table 6a. Effectiveness of Other Systemic Antibiotics as an Adjunct to Scaling and Root Planing to Treat Chronic Periodontitis (continued)

Study Description	Study Design Characteristics	Disease Characteristics	Examiner Characteristics	Description of Scaling and Root Planing
Smith et al., 2002[99] **Study Period:** 22 weeks **Study/Treatment Site:** The Royal London Hospital **Location:** London, UK **Patient Population:** Adult patients referred to clinic with = 2 sextants with CPITN scores of 4 and at least 20 remaining teeth	**Design Type:** RCT **Subject/Site Allocation:** Random **Blinding:** Examiners and patients blind **Placebo:** Yes **Split-mouth:** No	**Severity:** Periodontitis in adults **Types of Teeth:** Rumfjord teeth: 16, 21, 24, 36, 41, and 44 **Widman flap:** NR	**Number:** 1 **Trained:** NA **Assigned to Subjects:** Same examiner throughout study	**SRP performed:** By hand by one hygienist, minor scaling and polishing at weeks 6, 10, and 22 **Time spent:** NR

Evidence Table 6a. Effectiveness of Other Systemic Antibiotics as an Adjunct to Scaling and Root Planing to Treat Chronic Periodontitis (continued)

Eligible Study Groups and How Defined:	Study Group Characteristics	Compliance Monitoring	Baseline Measures	Time Interval(s)
Subject/Site allocation: 44 subjects completed study T: 23 subjects C: 21 subjects **Dose, Mode, Schedule:** T: SRP plus 500 mg azithromycin 1xday for 3 days at week 2 C: SRP with placebo	**Age:** Mean: 42.68 **Gender:** Male: 21 Female: 23 **Race/Ethnicity:** NR	NR	Before SRP	7 times (at baseline and weeks 1, 2, 3, 6, 10, and 22)

Evidence Table 6a. Effectiveness of Other Systemic Antibiotics as an Adjunct to Scaling and Root Planing to Treat Chronic Periodontitis (continued)

Study Description	Outcomes Assessed	Adverse Effects	Study Group Attrition and Reasons	Type of Analysis
Smith et al., 2002[99] (continued)	**Clinical Measurement:** BOP/SBI PII PD Calculus to bleeding Ind **Radiographic Techniques:** NR **Microbiological Methods:** Crevicular fluid microbiota **Subject Self Report:** NR	None reported	tooth extraction (1), and failure to take medication (1)	**Type of analysis reported:** Full participants only

Evidence Table 6a. Effectiveness of Other Systemic Antibiotics as an Adjunct to Scaling and Root Planing to Treat Chronic Periodontitis (continued)

	Outcomes Accessed			
(N of Pts)	Attachment Level mm $\bar{x}$ (SD)	Probing Depth mm $\bar{x}$ (SD)	Spirochetes $\bar{x}$% (SD)	Comments
PD = 6 mm				Deep pockets (6mm) showed statistical significant difference ($P < 0.05$) starting at week 6 Across all sites: Analysis of covariance test shows that the difference between 2 study groups is insignificant at baseline and it is significant ($P < 0.02$) at week 22
Baseline:				
T: 23	NA	6.76 (NR)	NA	
C: 21	NA	6.76 (NR)	NA	
Final: 22 weeks				
T:	NA	3.67 (NR)	NA	
C:	NA	4.54 (NR)	NA	
Change:				
T:	NA	3.09* (NR)	NA	
C:	NA	2.22* (NR)	NA	
Test:		ANCOVA		
P value:		< 0.05		
PD 4 - 5 mm				Moderate pockets (4-5mm) demonstrated significant difference between groups starting at week 6
Baseline:				
T: 23	NA	4.58 (NR)	NA	
C: 21	NA	4.58 (NR)	NA	
Final: 22 weeks				
T:	NA	2.79 (NR)	NA	
C:	NA	3.31 (NR)	NA	
Change:				
T:	NA	1.79* (NR)	NA	
C:	NA	1.27* (NR)	NA	
Test:		ANCOVA		
P value:		< 0.01		
PD 1 - 3 mm				Shallow pockets (1-3mm) was statistically different between 2 study groups at week 6 only **Quality Score:** 69; 54
Baseline:				
T: 23	NA	2.35 (NR)	NA	
C: 21	NA	2.35 (NR)	NA	
Final: 22 weeks				
T:	NA	1.94 (NR)	NA	
C:	NA	2.08 (NR)	NA	
Change:				
T:	NA	0.41* (NR)	NA	
C:	NA	0.27* (NR)	NA	
Test:		ANCOVA		
P value:		NS		

Evidence Table 6b. Effectiveness of Other Local Antibiotics as an Adjunct to Scaling and Root Planing to Treat Chronic Periodontitis

Study Description	Study Design Characteristics	Disease Characteristics	Examiner Characteristics	Description of Scaling and Root Planing
Eickholz et al., 2002[101] **Study Period:** 26 weeks (6 months) **Study/Treatment Site:** 3 Graduate Program University Clinics and Centers **Location:** Heidelberg and Frankfurt, Germany and Njmegen, Netherlands **Patient Population:** Patients over 23 years old, scheduled for periodontal treatment, with at least 3 single rooted teeth with PD of 5 mm and BOP of PD = 6 mm	**Design Type:** RCT **Subject/Site Allocation:** Random **Blinding:** Examiners and patients blind **Placebo:** Yes **Split-mouth:** Yes	**Severity:** Untreated or recurrent moderate to severe periodontitis **Types of Teeth:** Both, non-adjacent teeth **Widman flap:** NR	**Number:** 6 **Trained:** NR **Assigned to Subjects:** One examiner for baseline; a different examiner for all of remaining assessment	**SRP performed:** On all test teeth and the respective neighboring teeth by hand under local anesthesia **Time spent:** 10 minutes per tooth

Evidence Table 6b. Effectiveness of Other Local Antibiotics as an Adjunct to Scaling and Root Planing to Treat Chronic Periodontitis (continued)

Eligible Study Groups and How Defined:	Study Group Characteristics	Compliance Monitoring	Baseline Measures	Time Interval(s)
Subject/Site allocation: 111 started 108 completed T: 108 sites C: 108 sites **Dose, Mode, Schedule:** T: SRP plus 15% doxycycline gel, subgingival application C: SRP and placebo polymer gel	**Age:** Mean: 49 ± 9 Range: 23 to 71 **Gender:** Male: 42 Female: 69 **Race/Ethnicity:** NR	NA	Before SRP, but PD measured after scaling	3 times (at baseline and months 3 and 6)

Evidence Table 6b. Effectiveness of Other Local Antibiotics as an Adjunct to Scaling and Root Planing to Treat Chronic Periodontitis (continued)

Study Description	Outcomes Assessed	Adverse Effects	Study Group Attrition and Reasons	Type of Analysis
Eickholz et al., 2002[101] (continued)	**Clinical Measurement:** BOP/SBI PII PD CAL (vertical relative attachment level) GI **Radiographic Techniques:** NR **Microbiological Methods:** Plaque microbiota tested (*A.a., P.g., B.f.,* and *T.d.*) but results were reported separately **Subject Self Report:** NR	Yes, "minor compli-cations"	One singular inflammation 2 months after application of treatment gel	**Type of analysis reported:** Intent to treat

Evidence Table 6b. Effectiveness of Other Local Antibiotics as an Adjunct to Scaling and Root Planing to Treat Chronic Periodontitis (continued)

Outcomes Accessed					
	(N of Pts)	Attachment Level mm $\bar{x}$ (SD)	Probing Depth mm $\bar{x}$ (SD)	Spirochetes $\bar{x}$ % (SD)	Comments
Baseline:					Adjunctive topical subgingival application of a biodegradable doxycycline gel provided more favorable CAL gain and PD reduction than SRP alone and placebo
T:	NR	9.15 (1.99 se)	7.33 (1.55 se)	NA	
C:	NR	9.13 (2.17 se)	7.33 (1.57 se)	NA	
Final: 26 weeks					
T:		NR	NR	NA	
C:		NR	NR	NA	
Change:		Gain	Reduction		Pairwise comparisons of PD at 6 months resulted in a 0.44 (1.67 se) greater reduction (*P* = 0.0066) in doxycycline group versus placebo. For CAL it was 0.37 (1.84 se) at 6 months in favor of doxycycline (*P* = 0.038)
T:		2.0 (1.7 se)	-3.1 (1.2 se)	NA	
C:		1.6 (2.2 se)	-2.7 (1.6 se)	NA	
Test:		ANOVA	ANOVA		
P value:		0.057	0.002		
					Quality Score: 92; 92

Evidence Table 6b. Effectiveness of Other Local Antibiotics as an Adjunct to Scaling and Root Planing to Treat Chronic Periodontitis (continued)

Study Description	Study Design Characteristics	Disease Characteristics	Examiner Characteristics	Description of Scaling and Root Planing
Kimura et al., 1991[100] **Study Period:** 6 weeks **Study/Treatment Site:** Department of Periodontology, Osaka University Faculty of Dentistry **Location:** Osaka, Japan **Patient Population:** Patients with at least one site with deep PD = 5 mm on the premolars and bone loss on radiography	**Design Type:** NR **Subject/Site Allocation:** Random **Blinding:** NR **Placebo:** Yes **Split-mouth:** NR	**Severity:** Severe chronic periodontitis **Types of Teeth:** Premolars on the first molar in each jaw quadrant **Widman flap:** NR	**Number:** NR **Trained:** NR **Assigned to Subjects:** NR	**SRP performed:** Supragingival scaling followed by subgingival mechanical debridement consisting of root planing and scaling without local anesthesia **Time spent:** NR

Evidence Table 6b. Effectiveness of Other Local Antibiotics as an Adjunct to Scaling and Root Planing to Treat Chronic Periodontitis (continued)

Eligible Study Groups and How Defined:	Study Group Characteristics	Compliance Monitoring	Baseline Measures	Time Interval(s)
Subject/Site allocation: 31 subjects started 27 completed T: 27 sites C: 27 sites **Dose, Mode, Schedule:** T: SRP plus controlled release ofloxacin inserts applied in 5+ mm pockets around test tooth and adjacent teeth weekly from days 0-35 C: SRP plus placebo strips	**Age:** Mean: 43.9 Range: 29 to 53 **Gender:** Male: 14 Female: 13 **Race/Ethnicity:** NR	NA	Before	4 times (at baseline and visits 0, 1, and 4) Microbiota sampling at days 0, 14, 21, and 42

Evidence Table 6b. Effectiveness of Other Local Antibiotics as an Adjunct to Scaling and Root Planing to Treat Chronic Periodontitis (continued)

Study Description	Outcomes Assessed	Adverse Effects	Study Group Attrition and Reasons	Type of Analysis
Kimura et al., 1991[100] (continued)	**Clinical Measurement:** NR **Radiographic Techniques:** NR **Microbiological Methods:** Plaque microbiota and anaerobic culture studies of spirochetes, motile rods, coccoid cells, using dark field microscopy **Subject Self Report:** NR	Yes, none reported	Protocol violation consisting of the usage of other agents (3); deviated from the experimental schedule (1)	**Type of analysis reported:** Full participants only

Evidence Table 6b. Effectiveness of Other Local Antibiotics as an Adjunct to Scaling and Root Planing to Treat Chronic Periodontitis (continued)

	Outcomes Accessed			
	Attachment Level mm	Probing Depth mm	Spirochetes	
(N of Pts)	$\bar{x}$ (SD)	$\bar{x}$ (SD)	$\bar{x}$ % (SD)	Comments
Baseline:				No statistical significant differences in microbiological results between groups. SRP was effective in and of itself. **Quality Score:** 38; 38
T: NR	NA	NA	9.5 (10.4)	
C: NR	NA	NA	20.2 (11.7)	
Final: 4 weeks				
T:	NA	NA	3.7 (6.1)	
C:	NA	NA	5.5 (7.3)	
Change:				
T:	NA	NA	NR	
C:	NA	NA	NR	
Test:				
P value:				

Evidence Table 7. Effectiveness of Other Antimicrobials as an Adjunct to Scaling and Root Planing to Treat Chronic Periodontitis

Study Description	Study Design Characteristics	Disease Characteristics	Examiner Characteristics	Description of Scaling and Root Planing
Furuichi et al., 1997[102] **Study Period:** 8 weeks **Study/Treatment Site:** Specialist Clinic for Periodontitis, Göteborg University **Location:** Sweden **Patient Population:** Patients referred to clinic with = 2 sites, at single rooted teeth in each of 2 contralateral quadrants with PD = 5 mm and BOP	**Design Type:** RCT **Subject/Site Allocation:** Random **Blinding:** Examiner and patients blind **Placebo:** Yes **Split-mouth:** Yes	**Severity:** Moderate periodontitis **Types of Teeth:** Single-rooted **Widman flap:** NR	**Number:** 1 **Trained:** NA **Assigned to Subjects:** Same examiner throughout study	**SRP performed:** Mechanical meticulous scaling and root planing performed until root surface was hard and smooth Assigned quadrant was anaesthesized **Time spent:** NR

Evidence Table 7. Effectiveness of Other Antimicrobials as an Adjunct to Scaling and Root Planing to Treat Chronic Periodontitis (continued)

Eligible Study Groups and How Defined:	Study Group Characteristics	Compliance Monitoring	Baseline Measures	Time Interval(s)
Subject/Site allocation: 16 subjects T: 32 sites C: 32 sites **Dose, Mode, Schedule:** T: SRP plus supragingival and subgingival 0.6% tricolsan gel and 0.3% tricolsan dentifrice 2xday for 2 weeks, repeated again after 1 week washout period C: SRP plus placebo gel and a dentifrice both without triclosan	**Age:** Mean: 49.2 **Gender:** Male: 10 Female: 6 **Race/Ethnicity:** NR	NA	NR	4 times (at baseline and days 2, 7, and 14)

Evidence Table 7. Effectiveness of Other Antimicrobials as an Adjunct to Scaling and Root Planing to Treat Chronic Periodontitis (continued)

Study Description	Outcomes Assessed	Adverse Effects	Study Group Attrition and Reasons	Type of Analysis
Furuichi et al., 1997[102] (continued)	**Clinical Measurement:** BOP/SBI PII PD GI **Radiographic Techniques:** NR **Microbiological Methods:** Plaque microbiota (coccoid cells, non-motile rods, spirochetes and motile rods, filaments, and fusiforms) and dark field microscopy **Subject Self Report:** NR	NR	NR	**Type of analysis reported:** Full participants only

Evidence Table 7. Effectiveness of Other Antimicrobials as an Adjunct to Scaling and Root Planing to Treat Chronic Periodontitis (continued)

	Outcomes Accessed			
	Attachment Level mm	Probing Depth mm	Spirochetes	
(N of Pts)	$\bar{x}$ (SD)	$\bar{x}$ (SD)	$\bar{x}$ % (SD)	Comments
Baseline:				No significant differences were observed between the 2 groups regarding composition of the subgingival microbiota
T: 32 sites	NA	5.6 (0.89)	46.3 (18.9)	
C: 32 sites	NA	5.8 (0.86)	36.9 (14.0)	
Final: 8 weeks				
T:	NA	3.8 (0.81)	12.5 (7.5)	**Quality Score:** 77; 69
C:	NA	3.9 (0.72)	13.7 (7.7)	
Change:		Reduction	Reduction	
T:	NA	1.8 (0.68)	38.4 (17.4)	
C:	NA	1.9 (0.69)	21.6 (17.7)	
Test:		ANOVA	ANOVA	
P value:		0.589	0.371	

Evidence Table 7. Effectiveness of Other Antimicrobials as an Adjunct to Scaling and Root Planing to Treat Chronic Periodontitis (continued)

Study Description	Study Design Characteristics	Disease Characteristics	Examiner Characteristics	Description of Scaling and Root Planing
Listgarten et al., 1989[103] **Study Period:** 8 weeks **Study/Treatment Site:** Clinics of the School of Dental Medicine **Location:** USA **Patient Population:** Adult patients attending clinics with a pair of similar contralateral 5-10 mm pockets, not continuous with furcation involvement	**Design Type:** RCT **Subject/Site Allocation:** Random **Blinding:** Examiner and provider blind **Placebo:** Yes **Split-mouth:** Yes	**Severity:** Moderate to deep pockets **Types of Teeth:** No furcation involvement **Widman flap:** NR	**Number:** NR **Trained:** NR **Assigned to Subjects:** NR	**SRP performed:** Thorough subgingival scaling by hand of test sites **Time spent:** NR

Evidence Table 7. Effectiveness of Other Antimicrobials as an Adjunct to Scaling and Root Planing to Treat Chronic Periodontitis (continued)

Eligible Study Groups and How Defined:	Study Group Characteristics	Compliance Monitoring	Baseline Measures	Time Interval(s)
Subject/Site allocation: 56 subjects recruited 40 completed T: 20 subjects C: 20 subjects **Dose, Mode, Schedule:** T: SRP plus irrigation with 7% tetra potassium peroxydiphosphate solution applied subgingivally to each test site for a 5 second period twice a day for 8 weeks C: SRP with placebo	**Age:** Mean: 49 Range: 19 to 78 **Gender:** Male: 20 Female: 20 **Race/Ethnicity:** NR	Yes	Before SRP	4 times (at 4 weeks prior to baseline, baseline, and weeks 4 and 8)

Evidence Table 7. Effectiveness of Other Antimicrobials as an Adjunct to Scaling and Root Planing to Treat Chronic Periodontitis (continued)

Study Description	Outcomes Assessed	Adverse Effects	Study Group Attrition and Reasons	Type of Analysis
Listgarten et al., 1989[103] (continued)	**Clinical Measurement:** PII PD CAL GI **Radiographic Techniques:** NR **Microbiological Methods:** Subgingival microbial samples (coccoid cells, motile rods, spirochetes, others), dark field microscopy **Subject Self Report:** Compliance with protocol was checked by inspection of volume of residual rinse in irrigation at the 2nd and 3rd visit, and by questioning the subjects	Yes, mucosal irritation	Never start (2); mucosal irritation associated with use of test rinse (2); medication taken during course of study (2); and failed to complete all examinations or failed to comply with protocol (10)	**Type of analysis reported:** Full participants only

Evidence Table 7. Effectiveness of Other Antimicrobials as an Adjunct to Scaling and Root Planing to Treat Chronic Periodontitis (continued)

	Outcomes Accessed			
	Attachment Level mm	Probing Depth mm	Spirochetes	
(N of Pts)	$\bar{x}$ (SD)	$\bar{x}$ (SD)	$\bar{x}$ % (SD)	Comments
Baseline:				No between group differences reported.
T: 20	6.65 (0.34 se)	6.35 (0.25 se)	35.45 (4.13 se)	
C: 20	6.45 (0.36 se)	6.20 (0.34 se)	37.25 (4.30 se)	**Quality Score:** 69; 54
Final: 8 weeks				
T: 20	5.15 (0.44 se)	4.30 (0.33 se)	11.40 (3.48 se)	
C: 20	5.20 (0.47 se)	4.80 (0.42 se)	16.80 (5.14 se)	
Change:				
T:	1.50* (NR)	2.05* (NR)	NR	
C:	1.25* (NR)	1.40* (NR)	NR	
Test:	NR	NR		
P value:	NS	NS		

Evidence Table 7. Effectiveness of Other Antimicrobials as an Adjunct to Scaling and Root Planing to Treat Chronic Periodontitis

Study Description	Study Design Characteristics	Disease Characteristics	Examiner Characteristics	Description of Scaling and Root Planing
Oosterwaal et al., 1991[89] **Study Period:** 36 weeks **Study/Treatment Site:** Program University Clinic, Department of Periodontology of Nijmegen **Location:** Netherlands **Patient Population:** Patients with = 4 interdental pockets of 7 mm to 9 mm affecting single rooted teeth referred to clinic	**Design Type:** RCT **Subject/Site Allocation:** Random **Blinding:** Examiners and patients blind **Placebo:** Yes **Split-mouth:** Yes	**Severity:** Advanced periodontitis **Types of Teeth:** Single-rooted **Widman flap:** NR	**Number:** 2 **Trained:** NR **Assigned to Subjects:** NR	**SRP performed:** Mechanical debridement with Gracey curettes or ultrasonic instruments **Time spent:** NR

Evidence Table 7. Effectiveness of Other Antimicrobials as an Adjunct to Scaling and Root Planing to Treat Chronic Periodontitis (continued)

Eligible Study Groups and How Defined:	Study Group Characteristics	Compliance Monitoring	Baseline Measures	Time Interval(s)
Subject/Site allocation: 10 subjects T1: 10 sites T2: 10 sites C: 10 sites **Dose, Mode, Schedule:** T1: 1.25% amine fluoride gel (applied 3 times with syringe within 10 minutes after SRP) T2: 4% stannous fluoride gel 3x within 10 minutes C: SRP with placebo gel (applied 3 times with syringe within 10 minutes after SRP)	**Age:** Mean: 48 Range: 33 to 62 **Gender:** Male: 4 Female: 6 **Race/Ethnicity:** NR	NA	Before SRP	4 times (at baseline and weeks 4, 12, and 36)

Evidence Table 7. Effectiveness of Other Antimicrobials as an Adjunct to Scaling and Root Planing to Treat Chronic Periodontitis (continued)

Study Description	Outcomes Assessed	Adverse Effects	Study Group Attrition and Reasons	Type of Analysis
Oosterwaal et al., 1991[89] (continued)	**Clinical Measurement:** BOP/SBI PII PD **Radiographic Techniques:** NR **Microbiological Methods:** Subgingival plaque microbiota (anaerobic gram-positive bacteria), agar plates, dark field microscopy **Subject Self Report:** NR	NR	NR	**Type of analysis reported:** Full participants only

Evidence Table 7. Effectiveness of Other Antimicrobials as an Adjunct to Scaling and Root Planing to Treat Chronic Periodontitis (continued)

	Outcomes Accessed			
		Attachment Level mm	Probing Depth mm	Spirochetes	
	(N of Pts)	$\bar{x}$ (SD)	$\bar{x}$ (SD)	$\bar{x}$ % (SD)	Comments
T1: Amine Fluoride:					Statistical analysis of the bacteriological and clinical examinations failed to demonstrate any significant differences between the groups SRP in pockets not in trial within 4 weeks of baseline. **Quality Score:** 62; 54
Baseline:					
T:	10	NA	NR	NA	
C:	10	NA	NR	NA	
Final: 36 weeks					
T:	10	NA	NR	NA	
C:	10	NA	NR	NA	
Change:			Reduction		
T:		NA	NR	NA	
C:		NA	NR	NA	
Test:			ANOVA		
P value:			NS		
T2: Stannous Fluoride:					
Baseline:					
T:	10	NA	NR	NA	
C:	10	NA	NR	NA	
Final: 36 weeks					
T:	10	NA	NR	NA	
C:	10	NA	NR	NA	
Change:			Reduction		
T:		NA	NR	NA	
C:		NA	NR	NA	
Test:			ANOVA		
P value:			NS		

Evidence Table 7. Effectiveness of Other Antimicrobials as an Adjunct to Scaling and Root Planing to Treat Chronic Periodontitis (continued)

Study Description	Study Design Characteristics	Disease Characteristics	Examiner Characteristics	Description of Scaling and Root Planing
Rosling et al., 2001[104] **Study Period:** 676 weeks (13 years) **Study/Treatment Site:** Department of Periodontology **Location:** Helsingborg, Sweden **Patient Population:** Patients referred for treatment with = 8 non-molar teeth, and periodontal lesions with PD = 6 mm at = 2 teeth in each quadrant	**Design Type:** Non-RCT **Subject/Site Allocation:** Unknown **Blinding:** NR **Placebo:** Yes **Split-mouth:** No	**Severity:** Advanced destructive periodontitis **Types of Teeth:** Single-rooted teeth – "non-molar teeth" **Wideman flap:** NR	**Number:** 3 **Trained:** Calibration (Gold standard) **Assigned to Subjects:** NR	**SRP performed:** Non-surgical supra- and subgingival ultrasonic instrumentation under local anesthesia **Time spent:** 1 hour for 4 to 6 sessions, then interval between sessions never exceeded 1 week

Evidence Table 7. Effectiveness of Other Antimicrobials as an Adjunct to Scaling and Root Planing to Treat Chronic Periodontitis (continued)

Eligible Study Groups and How Defined:	Study Group Characteristics	Compliance Monitoring	Baseline Measures	Time Interval(s)
Subject/Site allocation: 223 subjects enrolled 150 completed T: 75 enrolled, 58 completed C: 148 enrolled, 92 completed **Dose, Mode, Schedule:** T: SRP plus irrigation with ultrasound device using povidone-iodine solution C: SRP plus ultrasound device using tap water	**Age:** NR **Gender:** NR **Race/Ethnicity:** NR	NA	Before SRP	14 times (complete re-examination at 12 months, years 3, 5, and 12; and yearly CAL)

Evidence Table 7. Effectiveness of Other Antimicrobials as an Adjunct to Scaling and Root Planing to Treat Chronic Periodontitis (continued)

Study Description	Outcomes Assessed	Adverse Effects	Study Group Attrition and Reasons	Type of Analysis
Rosling et al., 2001[104] (continued)	**Clinical Measurement:** BOP PD CAL Number of teeth **Radiographic Techniques:** Bone Loss/Regeneration **Microbiological Methods:** NR **Subject Self Report:** NR	NR	Withdrew for reasons unrelated to study (9); major systemic disease, moved and not appreciate treatment provided (24)	**Type of analysis reported:** Full participants only

Evidence Table 7. Effectiveness of Other Antimicrobials as an Adjunct to Scaling and Root Planing to Treat Chronic Periodontitis (continued)

	Outcomes Accessed			
	Attachment Level mm	Probing Depth mm	Spirochetes	
(N of Pts)	$\bar{x}$ (SD)	$\bar{x}$ (SD)	$\bar{x}$ % (SD)	Comments
Baseline:				The mean PD decreased between baseline and 3 months but tended to increase in both groups during 12 months to 13 years
T: 58	NR	3.9 (0.9)	NA	
C: 92	NR	3.7 (0.9)	NA	
Final: 676 weeks				
T:	NR	2.9 (0.5)	NA	**Quality Score:** 31; 23
C:	NR	3.3 (0.6)	NA	
Change:	Gain			
T:	0.28 (NR)	1.0 *(NR)	NA	
C:	0.87 (NR)	0.4* (NR)	NA	
Test:	NR	NR		
P value:	NR	NR		

Evidence Table 7. Effectiveness of Other Antimicrobials as an Adjunct to Scaling and Root Planing to Treat Chronic Periodontitis

Study Description	Study Design Characteristics	Disease Characteristics	Examiner Characteristics	Description of Scaling and Root Planing
Wennström et al., 1987[85] **Study Period:** 52 weeks **Study/Treatment Site:** Department of Periodontology School of Dentistry, University of Goteberg **Location:** Sweden **Patient Population:** Patients with 2-3 interproximal sites in each quadrant with PD = 6 mm and BOP selected from waiting list	**Design Type:** RCT **Subject/Site Allocation:** Random **Blinding:** Examiner blind **Placebo:** Yes **Split-mouth:** Yes	**Severity:** Moderate to severe periodontal disease **Types of Teeth:** NR **Widman flap:** NR	**Number:** 1 **Trained:** Specially trained dental hygienists **Assigned to Subjects:** Same examiner throughout study	**SRP performed:** Subgingival debridement of entire dentition **Time spent:** 6 visits over about 6 weeks

Evidence Table 7. Effectiveness of Other Antimicrobials as an Adjunct to Scaling and Root Planing to Treat Chronic Periodontitis (continued)

Eligible Study Groups and How Defined:	Study Group Characteristics	Compliance Monitoring	Baseline Measures	Time Interval(s)
Subject/Site allocation: 10 subjects T: 10 (28 sites) C: 10 (24 sites) **Dose, Mode, Schedule:** All patients received professional tooth cleaning once every 4 weeks. T: SRP plus irrigation with 3% hydrogen peroxide for 2 minutes 3xweek for 2 weeks intervals prior to baseline, then professional irrigation with hydrogen peroxide for 6 weeks C: SRP plus irrigation with saline 3xweek at same schedule as treatment group	**Age:** Mean: 43.1 Range: 22 to 61 **Gender:** NR **Race/Ethnicity:** NR	NR	Before SRP	3 times (at baseline and weeks 10 and 52) 52 week study, SRP and treatment at week 32

Evidence Table 7. Effectiveness of Other Antimicrobials as an Adjunct to Scaling and Root Planing to Treat Chronic Periodontitis (continued)

Study Description	Outcomes Assessed	Adverse Effects	Study Group Attrition and Reasons	Type of Analysis
Wennström et al., 1987[85] (continued)	**Clinical Measurement:** BOP/SBI PII PD CAL GI **Radiographic Techniques:** Bone Loss/Regeneration **Microbiological Methods:** Crevicular fluid microbiota **Subject Self Report:** NR	NR	NR	**Type of analysis reported:** Full participants only

Evidence Table 7. Effectiveness of Other Antimicrobials as an Adjunct to Scaling and Root Planing to Treat Chronic Periodontitis (continued)

	Outcomes Accessed			
	Attachment Level mm	Probing Depth mm	Spirochetes	
(N of Pts)	$\bar{x}$ (SD)	$\bar{x}$ (SD)	$\bar{x}$ % (SD)	Comments
Baseline:				In the comparison between the different treatment groups, the hydrogen peroxide group showed a smaller residual probing depth than the non-irrigated of the saline irrigated groups
T: 10	NR	7.1 (NR)	NA	
C: 10	NR	6.9 (NR)	NA	
Final: 52 weeks				
T: 10	NR	4.5 (NR)	NA	
C: 10	NR	5.1(NR)	NA	
Change:	Gain	Reduction		Microbiological and radiological results presented in a different paper
T:	0.8 (0.8)	2.6* (NR)	NA	
C:	0.7 (0.5)	1.8* (NR)	NA	
Test:	t-test	t-test		**Quality Score:** 46; 46
P value:	NS	< 0.05		

APPENDIX A

DENTAL DATA ABSTRACTION FORM

Abstraction Form

QUESTION: HOW DOES THE EFFECTIVENESS OF SCALING AND ROOT PLANING ACCOMPANIED BY ADJUNCTIVE THERAPY FOR CHRONIC PERIODONTITIS COMPARE TO SCALING AND ROOT PLANING THERAPY BY ITSELF AT VARYING LENGTHS OF TIME POST-TREATMENT?

A. Administrative Information

1. Abstractor:_____ 2.Abstract Date:_____

3. Abbreviated study citation

_____

first author *journal abbr*

_____

year *volume* *pages*

4. Abbreviated article title:

_____

5. Included?

- ❑ No

If no, excluded because: (*check one)*

- ❑ SRP different in control/comparison group than in treatment group
- ❑ No SRP-only control/comparison group/sites
- ❑ Treatment groups/sites did not also receive SRP
- ❑ Literature review or meta-analysis
- ❑ Practice guideline or editorial
- ❑ Special population/disease studied, described as: with HIV/AIDS or diabetes; localized disease; juvenile or early onset disease; in smokers; around implants;
- ❑ Other (Specify): _____

- ❑ Yes (go to ***B. Study Design Information***)

B. Study Design Information

1. Type of design (Check One):

   - ❑ *Randomized controlled trial(RCT)*
   - ❑ *Non-Randomized controlled trial*
   - ❑ *RCT with crossover*
   - ❑ *Other (Specify)*_____

   _____

2. Is it a split-mouth design?
   - ❑ *Yes*
   - ❑ *No*
3. Does study investigate (check one):
   - ❑ *Single-rooted teeth*
   - ❑ *Teeth bifurcated (molars)*
   - ❑ *Both*
   - ❑ *Not reported*
4. Does study characterize periodontal disease as (check all that apply):
   - ❑ *Mild*
   - ❑ *Moderate*
   - ❑ *Severe*
   - ❑ *Not reported*
5. Placebo used in control/comparison (SRP only) group/sites?
   - ❑ *Yes*
   - ❑ *No*
6. Number of eligible active treatment groups: _____
7. Study period (S*pecify begin and end calendar month/year in which conducted*)

   From _____ To _____

8. Study location(s) (Specify city/nation) _____

9. Study/treatment site(s):
   - ❑ *Hospital dental clinic*
   - ❑ *Graduate program university clinic*
   - ❑ *Undergraduate dental clinic*
   - ❑ *Health department clinic*
   - ❑ *Private dental practice*
   - ❑ *Not mentioned*
   - ❑ *Other* (Specify)_____

10. Duration of treatment:_____ *days/ weeks/months*

11. Specify eligible adjunctive therapy(ies):

    - ❑ *Amoxicillin*
    - ❑ *Augmentin*
    - ❑ *Chlorhexidine*
    - ❑ *Doxycycline*
    - ❑ *Metronidazole*
    - ❑ *Minocycline*
    - ❑ *Spiramycin*
    - ❑ *Povodine iodine*
    - ❑ *Tetracycline*
    - ❑ *Azithromycin*
    - ❑ *Clindamycin*
    - ❑ *Other* (Specify)_____

12. Dose, mode of delivery, and schedule of treatment group(s) (XX mgs, as a rinse (for local), Y times /day, week, month) and SRP only group (or with placebo if used):

    Group 1 (or only treatment group): _____

    Group 2: _____

    *Group 3:*_____

    *SRP only / or SRP with Placebo:*_____

13. Duration of evaluation period*:_____ days or _____ weeks or _____ months*

14. Drug use compliance monitoring:
    - ❑ *Yes*
    - ❑ *No*
    - ❑ *Not reported*
    - ❑ *Not applicable (e.g., professionally administered/applied)*

15. Describe the SRP as they performed it: _____

    _____

16. How much time on average was spent doing SRP? _____

17. Was it performed with
    - ❑ *An ultrasonic/Cavitron*
    - ❑ *By hand*
    - ❑ *Both*
    - ❑ *Not reported*

18. Describe supportive therapy provided to study participants and indicate frequency/intervals.
    - ❑ *Oral instruction How often:* _____
    - ❑ *Plaque removal How often:* _____
    - ❑ *Repeated SRP How often:* _____
    - ❑ *Other* _____
    - ❑ *Not reported*

19. Was baseline assessment performed before or after SRP?
    - ❑ *Before*
    - ❑ *After*
    - ❑ *Not Reported*

20. Number of evaluation time points (*e.g. 4 times* not including baseline) _____ and regular intervals of _____ (*e.g., every two weeks*). If intervals vary, specify evaluation points:

    _____

21. Blinding to active drug:
    - ❑ *Examiners blind*
    - ❑ *Patient blind*
    - ❑ *Patients and examiners blind (double blind)*
    - ❑ *No blinding*
    - ❑ *Not reported*

22. Outcomes (parameters measured) and citations:

CLINICAL MEASUREMENT

- ❑ *Bleeding on Probing (BOP/SBI)* *Citation:* _____
- ❑ *Plaque Index (PlI)* *Citation:* _____
- ❑ *Probing Pocket Depth (PPD)* *Citation:* _____
- ❑ *Clinical Attachment Level (CAL)* *Citation:* _____
- ❑ *Gingival Index (GI)* *Citation:* _____
- ❑ *Gingival Recession* *Citation:* _____
- ❑ *Tooth Loss* *Citation:* _____
- ❑ *Tooth Mobility* *Citation:* _____
- ❑ *Other* (Specify) *Citation:* _____

RADIOGRAPHIC TECHNIQUES

- ❑ *Bone Loss/Regeneration* *Citation:* _____
- ❑ *Other* (Specify) *Citation:* _____

MICROBIOLOGICAL METHODS

- ❑ *Chromatography* *Citation:* _____
- ❑ *DNA/RNA probe* *Citation:* _____
- ❑ *Crevicular fluid microbiota* *Citation:* _____
- ❑ *Plaque microbiota* *Citation:* _____
- ❑ *Other (*Specify*)* *Citation:* _____

PATIENT SELF REPORT

- ❑ *Patient Satisfaction* *Citation:* _____
- ❑ *Other* (Specify) *Citation:* _____

C. Sample Information

1. Description of population sampled (recurrent disease, never treated, clinic patients, private care)___

_____

_____

2. Initial sample size -- *persons (teeth)*:

   _____= Total subjects (sites)

   _____= Group 1 or only active drug group subjects (sites)

   _____= Group 2 (second active drug) subjects (sites)

   _____= Group 3 (third active drug) subjects (sites)

   _____= SRP only/SRP with placebo subjects (sites)

3. Subject/Site allocation to treatment/control conditions (Check one):

   - ❑ *Random*
   - ❑ *Systematic*
   - ❑ *Cluster*
   - ❑ *Convenience*
   - ❑ *Unknown*
   - ❑ *Other (Specify)*_____

4. Specific inclusion and exclusion criteria. (Specify tooth or person level considerations.)

- ❑ *Pregnant/breast feeding excluded*
- ❑ *Concurrent drug therapy excluded*
- ❑ *Diabetes history excluded*
- ❑ *Diagnosed systemic infection excluded*
- ❑ *Serious medical illness excluded*
- ❑ *Need for prophylactic antibiotic before dental treatment excluded*
- ❑ *Use of study drug within ____ months excluded*
- ❑ *Hypersensitivity/allergic to study drug excluded*
- ❑ *At least _____ teeth in _____ quadrant/mouth (circle one) with ____mm pocket included*
- ❑ *Age at least _____ included*
- ❑ *Other: _____*

  _____

  _____

D. Group Characteristics

Total (All Study Groups Combined)

1. Age: *mean:_____ median: _____ range: _____*
2. Gender: *number (%) male:_____ number (%) female:_____*
3. Race/Ethnicity: *number (%) NH White: _____*

   number (%) NH Black: _____

   number (%) Hispanic (independent of race): _____

   number (%) NH Asian/PacificIslander: _____

   number (%) other (specify):_____

Group 1

1. Age: *mean:*_____ *median:* _____ *range:* _____

2. Gender: *number (%) male:*_____ *number (%) female:*_____

3. Race/Ethnicity: *number (%) NH White:* _____

   number (%) NH Black: _____

   number (%) Hispanic (independent of race): _____

   number (%) NH Asian/Pacific Islander: _____

   *number (%) Other(Specify):*_____

Group 2

1. Age: *mean:*_____ *median:* _____ *range:* _____

2. Gender: *number (%) male:*_____ *number (%) female:*_____

3. Race/Ethnicity: *number (%) NH White:* _____

   number (%) NH Black: _____

   number (%) Hispanic (independent of race): _____

   number (%) NH Asian/PacificIslander: _____

   *number (%) Other(Specify):*_____

Group 3

1. Age: *mean:*_____ *median:* _____ *range:* _____

2. Gender: *number (%) male:*_____ *number (%) female:*_____

3. Race/Ethnicity: *number (%) NH White:* _____

   number (%) NH Black: _____

   number (%) Hispanic (independent of race): _____

   number (%) NH Asian/PacificIslander: _____

   *number (%) Other(Specify):*_____

SRP only/SRP plus placebo Group

1. Age: *mean:_____ median: _____ range: _____*
2. Gender: *number (%) male:_____ number (%) female:_____*
3. Race/Ethnicity: *number (%) NH White: _____*

   number (%) NH Black: _____

   number (%) Hispanic (independent of race): _____

   number (%) NH Asian/PacificIslander: _____

   number (%) Other(Specify):_____

E. Provider/Examiner information

1. Number of examiners:_____
2. Examiners received:
   - ❑ *Instruction in use of measures (written, pictures)*
   - ❑ *Standardization (Practice on patients)*
   - ❑ *Calibration (Gold standard examiner)*
   - ❑ *None/ Not reported*
   - ❑ *Not applicable (No clinical examination/measures: only one examiner)*
3. How are examiners assigned to patients at assessments?
   - ❑ *Random at each assessment*
   - ❑ *Repeat at each assessment*
   - ❑ *Not reported*
   - ❑ *Only one examiner*

F. Analysis Information

1. Analysis adjusted for clustered observations
   - ❑ *Yes*
   - ❑ *No*
   - ❑ *Not reported*
2. Type of analysis reported:
   - ❑ *Intent to treat*
   - ❑ *All with any follow-up*
   - ❑ *Full participants only*
3. Reasons/criteria for exclusion from analysis:

_____

_____

G. Outcome Information

1. Did study look for adverse effects?
   - ❑ *Yes, found none*
   - ❑ *Yes, but none reported*
   - ❑ *Yes, found adverse effects (number and type) by study group.*

   Specify: _____

   _____

   _____

   - ❑ *Never mentioned looking*
2. Frequency with which modified Wideman flap procedure was performed in study?
   - ❑ *Always/Often* (25% of time or more)
   - ❑ *Occasionally* (5-24 % of time)
   - ❑ *Rarely or Never* (0-4 % of time)
   - ❑ *Frequency Not Reported*

Comparison of Assessme nt 1 (Baseline) to Assessment 2

	Assessment 1 (Baseline)				Assessment 2				Group Comparisons Specify Coefficient, P-value/NS/Direction (+/-)						
Group	SRP Only	Treat 1	Treat 2	Treat 3	SRP Only	Treat 1	Treat 2	Treat 3	Statistical Test or Measure	T1 to SRP	T2 to SRP	T3 to SRP	T1 to T2	T2 to T3	T1 to T3
Number in Group															
Outcome Measures (Describe)															
1															
2															
3															
4															
5															
6															

Comparison of Assessment 2 / Baseline to Assessment 3

	Assessment 3				Group Comparisons Specify Coefficient, P-value/NS, Direction (+/-)					
Group	SRP Only	Treat 1	Treat 2	Treat 3	Treat 1 to SRP	Treat 2 to SRP	Treat 3 to SRP	Treat 1 to Treat 2	Treat 2 to Treat 3	Treat 1 to Treat 3
Number in Group										
Outcome Measures (Describe)										
1										
2										
3										
4										
5										
6										

Comparison of Assessment 3 / Baseline to Assessment 4

	Assessment 4				Group Comparisons Specify Coefficient, P-value/NS, Direction (+/-)					
Group	SRP Only	Treat 1	Treat 2	Treat 3	Treat 1 to SRP	Treat 2 to SRP	Treat 3 to SRP	Treat 1 to Treat 2	Treat 2 to Treat 3	Treat 1 to Treat 3
Number in Group										
Outcome Measures (Describe)										
1										
2										
3										
4										
5										
6										

Comparison of Assessment 4 / Baseline to Assessment 5

	Assessment 5				Group Comparisons Specify Coefficient, P-value/NS, Direction (+/-)					
Group	SRP Only	Treat 1	Treat 2	Treat 3	Treat 1 to SRP	Treat 2 to SRP	Treat 3 to SRP	Treat 1 to Treat 2	Treat 2 to Treat 3	Treat 1 to Treat 3
Number in Group										
Outcome Measures (Describe)										
1										
2										
3										
4										
5										
6										

Comparison of Assessment 5 / Baseline to Assessment 6

	Assessment 6				Group Comparisons Specify Coefficient, P-value/NS, Direction (+/-)					
Group	SRP Only	Treat 1	Treat 2	Treat 3	Treat 1 to SRP	Treat 2 to SRP	Treat 3 to SRP	Treat 1 to Treat 2	Treat 2 to Treat 3	Treat 1 to Treat 3
Number in Group										
Outcome Measures (Describe)										
1										
2										
3										
4										
5										
6										

APPENDIX B

QUALITY REVIEW CHECKLIST

QUALITY REVIEW CHECKLIST **Article:**			
Internal Validity			
1.	Random Assignment of Treatment	Y	N/NR
2	Blinding of Examiners	Y	N/NR
3	Blinding of Subjects	Y	N/NR
4	Use of Placebo	Y	N
5	Total Sample Size = 40	Y	N
6	Equal Sized Sample in Treatment and Control Groups	Y	N/NR
External Validity			
7	Judge external validity to be Good based on data reported (on disease, qualifications for participation in study, study setting, and subjects characteristics)	Y	N/NR
8	Attrition from enrolled group = 10%	Y	N
9	Multi-center Trial	Y	N/NR
Analysis			
10	Use all enrolled subjects in the analysis (or only those who completed)	Y	N
11	Reported if any Adverse Effects/Harms	Y	N
12	Are appropriate statistical techniques employed (adjust for multiple comparisons [Duncan, Scheffe, etc.], take into account lack of independence between observations [GLM, Sudaan, etc])	Y	N/NR
13	Reported means and variances (for baseline and end for T and C groups, or as change from baseline to end) as well as number of sites/teeth/people for each group or reported difference between change for the T and C groups	Y	N/NR
OVERALL RATING:			