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Supportive periodontal therapy (SPT) for maintaining the dentition in adults treated for periodontitis (Review)

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Supportive periodontal therapy (SPT) for maintaining the dentition in adults treated for periodontitis.
Cochrane Database of Systematic Reviews 2018, Issue 1. Art. No.: CD009376.
DOI: 10.1002/14651858.CD009376.pub2.

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TABLE OF CONTENTS

[Intervention Review]

Supportive periodontal therapy (SPT) for maintaining the dentition in adults treated for periodontitis

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Editorial group: Cochrane Oral Health Group.
Publication status and date: New, published in Issue 1, 2018.

Citation: Manresa C, Sanz-Miralles EC, Twigg J, Bravo M. Supportive periodontal therapy (SPT) for maintaining the dentition in adults treated for periodontitis. *Cochrane Database of Systematic Reviews* 2018, Issue 1. Art. No.: CD009376. DOI: 10.1002/14651858.CD009376.pub2.

ABSTRACT

Background

Periodontitis is a bacterially-induced, chronic inflammatory disease that destroys the connective tissues and bone that support teeth. Active periodontal treatment aims to reduce the inflammatory response, primarily through eradication of bacterial deposits. Following completion of treatment and arrest of inflammation, supportive periodontal therapy (SPT) is employed to reduce the probability of re-infection and progression of the disease; to maintain teeth without pain, excessive mobility or persistent infection in the long term, and to prevent related oral diseases.

According to the American Academy of Periodontology, SPT should include all components of a typical dental recall examination, and importantly should also include periodontal re-evaluation and risk assessment, supragingival and subgingival removal of bacterial plaque and calculus, and re-treatment of any sites showing recurrent or persistent disease. While the first four points might be expected to form part of the routine examination appointment for periodontally healthy patients, the inclusion of thorough periodontal evaluation, risk assessment and subsequent treatment - normally including mechanical debridement of any plaque or calculus deposits - differentiates SPT from routine care.

Success of SPT has been reported in a number of long-term, retrospective studies. This review aimed to assess the evidence available from randomised controlled trials (RCTs).

Objectives

To determine the effects of supportive periodontal therapy (SPT) in the maintenance of the dentition of adults treated for periodontitis.

Search methods

Cochrane Oral Health's Information Specialist searched the following databases: Cochrane Oral Health's Trials Register (to 8 May 2017), the Cochrane Central Register of Controlled Trials (CENTRAL) (the Cochrane Library, 2017, Issue 5), MEDLINE Ovid (1946 to 8 May 2017), and Embase Ovid (1980 to 8 May 2017). The US National Institutes of Health Trials Registry (ClinicalTrials.gov) and the World Health Organization International Clinical Trials Registry Platform were searched for ongoing trials. No restrictions were placed on the language or date of publication when searching the electronic databases.

Selection criteria

Randomised controlled trials (RCTs) evaluating SPT versus monitoring only or alternative approaches to mechanical debridement; SPT alone versus SPT with adjunctive interventions; different approaches to or providers of SPT; and different time intervals for SPT delivery.

We excluded split-mouth studies where we considered there could be a risk of contamination.

Participants must have completed active periodontal therapy at least six months prior to randomisation and be enrolled in an SPT programme. Trials must have had a minimum follow-up period of 12 months.

Data collection and analysis

Two review authors independently screened search results to identify studies for inclusion, assessed the risk of bias in included studies and extracted study data. When possible, we calculated mean differences (MDs) and 95% confidence intervals (CIs) for continuous variables. Two review authors assessed the quality of evidence for each comparison and outcome using GRADE criteria.

Main results

We included four trials involving 307 participants aged 31 to 85 years, who had been previously treated for moderate to severe chronic periodontitis. Three studies compared adjuncts to mechanical debridement in SPT versus debridement only. The adjuncts were local antibiotics in two studies (one at high risk of bias and one at low risk) and photodynamic therapy in one study (at unclear risk of bias). One study at high risk of bias compared provision of SPT by a specialist versus general practitioner. We did not identify any RCTs evaluating the effects of SPT versus monitoring only, or of providing SPT at different time intervals, or that compared the effects of mechanical debridement using different approaches or technologies.

No included trials measured our primary outcome 'tooth loss'; however, studies evaluated signs of inflammation and potential periodontal disease progression, including bleeding on probing (BoP), clinical attachment level (CAL) and probing pocket depth (PPD).

There was no evidence of a difference between SPT delivered by a specialist versus a general practitioner for BoP or PPD at 12 months (very low-quality evidence). This study did not measure CAL or adverse events.

Due to heterogeneous outcome reporting, it was not possible to combine data from the two studies comparing mechanical debridement with or without the use of adjunctive local antibiotics. Both studies found no evidence of a difference between groups at 12 months (low to very low-quality evidence). There were no adverse events in either study.

The use of adjunctive photodynamic therapy did not demonstrate evidence of benefit compared to mechanical debridement only (very low-quality evidence). Adverse events were not measured.

The quality of the evidence is low to very low for these comparisons. Future research is likely to change the findings, therefore the results should be interpreted with caution.

Authors' conclusions

Overall, there is insufficient evidence to determine the superiority of different protocols or adjunctive strategies to improve tooth maintenance during SPT. No trials evaluated SPT versus monitoring only. The evidence available for the comparisons evaluated is of low to very low quality, and hampered by dissimilarities in outcome reporting. More trials using uniform definitions and outcomes are required to address the objectives of this review.

PLAIN LANGUAGE SUMMARY

Supportive periodontal therapy (SPT) to preserve teeth in people previously treated for periodontitis

Background

Periodontitis (gum disease) is a chronic condition caused by bacteria, which stimulate inflammation and destruction of the bone and gum tissue supporting teeth. People treated for periodontitis can reduce the probability of re-infection and disease progression through regular supportive periodontal therapy (SPT). SPT starts once periodontitis has been treated satisfactorily, meaning that inflammation has been controlled and destruction of tissues supporting the tooth (bone and gums) has been arrested. SPT aims to maintain teeth in function, without pain, excessive mobility or persistent infection over the long term. SPT treatment typically includes ensuring excellent

oral hygiene, frequent monitoring for progression or recurrence of disease, and removal of microbial deposits by dental professionals. Although success of SPT has been suggested through a number of long-term, retrospective studies, it is important to consider evidence available from randomised controlled trials (RCTs).

Review question

This review explored the effects of different SPT approaches in adults previously treated for periodontitis.

Study characteristics

We searched the medical and dental literature up to 8 May 2017. We found four relevant studies known as randomised controlled trials (RCTs), with 307 participants aged 31 to 85 years. All participants had previously been treated for moderate to severe chronic periodontitis and enrolled in a SPT programme for at least three months. Studies evaluated participants for at least 12 months after starting their SPT programme.

The studies compared: additional use of an antibiotic (doxycycline in one study, minocycline in another) to professional cleaning (debridement); additional use of photodynamic therapy to debridement only, and SPT provided by a specialist versus a general dentist. We did not identify any RCTs comparing the effects of providing SPT versus monitoring only, the effects of SPT provided at different time intervals or the effects of mechanical debridement using different approaches or technologies.

None of the studies reported tooth loss. However, studies evaluated signs of inflammation and potential periodontal disease progression, including bleeding on probing, clinical attachment level and probing pocket depth.

Key results

The very limited amount of evidence did not provide evidence of one approach being better than another to improve tooth maintenance during SPT. Low- to very low-quality evidence suggests that adjunctive treatments may not provide any additional benefit for SPT compared with mechanical debridement alone. Evidence of very low quality suggests that SPT performed by general dentists under specialised prescription may be as effective as specialised treatment. Overall, there is not enough evidence available to recommend a certain approach or additional treatment in SPT to maintain teeth, promote gum health and prevent relapse.

Quality of the evidence

There were only four small studies, and only one of them was at low risk of bias. We judged the evidence to be of low or very low quality, therefore we cannot be confident in any conclusions drawn from the studies' results.

Authors' conclusions

We found insufficient evidence about the best approaches to SPT, and no RCTs evaluated SPT versus monitoring only. The evidence we found was low to very low quality, and studies used different methods to report their results, making comparison difficult. More studies are needed that report their findings in a uniform manner.

SUMMARY OF FINDINGS FOR THE MAIN COMPARISON [Explanation]

Supportive periodontal therapy (SPT) performed by specialists compared with SPT performed by non-specialist clinicians

Population: adults treated for periodontitis and receiving SPT
Settings: dental clinic
Intervention: SPT performed by general dental practitioners under specialist prescription
Comparison: SPT performed in a specialist practice

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	Number of participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	Non-specialist	Specialist				
Tooth loss	Not measured					
Bleeding on probing (%) at 12-month follow-up	Mean BoP 36.7%	Mean BoP was 7.40% higher (8.12 lower to 22.92 higher)		35 participants (1 study)	⊕◯◯◯ **very low**[a]	
Clinical attachment loss	Not measured					
Adverse events	Not measured					
Probing pocket depth (mm) (final scores) at 12-month follow-up	Mean PPD 3.0 mm	Mean PPD was 0.20 higher (0.40 lower to 0.80 higher)		35 participants (1 study)	⊕◯◯◯ **very low**[a]	

*The basis for the **assumed risk** (e.g. the median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).
CI: confidence interval; **MD**: mean difference

GRADE Working Group grades of evidence
High quality: we are very confident that the true effect lies close to that of the estimate of the effect
Moderate quality: we are moderately confident in the effect estimate; the true effect is likely to be close to the estimate of effect, but there is a possibility that it is substantially different
Low quality: we are moderately confident in the effect estimate; the true effect is likely to be close to the estimate of effect, but there is a possibility that it is substantially different
Very low quality: we have very little confidence in the effect estimate; the true effect is likely to be substantially different from the estimate of effect

[a] Single study at high risk of bias, small sample size and imprecision in the effect estimate - downgraded three levels

BACKGROUND

Description of the condition

Periodontitis can be defined as "inflammation of the periodontal tissues resulting in clinical attachment loss, alveolar bone loss, and periodontal pocketing" (AAP 2001). The immune-mediated, inflammatory response leading to attachment loss is primarily related to the accumulation of pathogenic bacteria in subgingival plaque, leading to a dysbiotic community that targets specific aspects of host immunity to further disable immune surveillance, while promoting an overall inflammatory response (Lamont 2015). This uncontrolled inflammation leads to an apical migration of the gingival junctional epithelium resulting in the formation of a periodontal 'pocket', wherein the anatomical space between the gingival margin and the point of attachment of the gingiva to the affected tooth is increased. Not all patients are susceptible to periodontal disease; a dysfunctional immune response is at least partly implicated in differences in severity and progression of periodontitis in patients with similar microbial bioburden (Cekici 2014; Kornman 2008; Seymour 1991; Seymour 2001).

Periodontal disease can be classified as chronic or aggressive, and localised or generalised. The classifications are primarily determined by the presentation of the disease and its progression over time, but they imply different aetiologies. Chronic periodontitis, the most prevalent form of disease, typically progresses slowly (although short intermittent periods of rapid progression may occur). The microbial aetiology of chronic periodontitis may vary, but importantly disease severity and the rate of progression is proportional to plaque accumulation (or other local risk factors such as the presence of overhanging restoration margins) (Lindhe 1999). In contrast, aggressive periodontitis is characterised by familial aggregation, rapid destruction of periodontal tissues, often in younger people (under 30 years of age), in spite of relatively low levels of dental plaque or other known risk factors. This form of periodontal disease is associated with increased populations of characteristic bacterial pathogens *Aggregatibacter actinomycetamcomitans* and *Porphyromonas gingivalis* in dental plaque (Lang 1999). Specific familial polymorphisms associated with a dysregulated immune response are also known to be present in many cases (Lamont 2015). Both chronic and aggressive periodontitis can present in a localised pattern of disease, defined as affecting less than 30% of the dentition. In chronic periodontitis, localised disease is usually the result of specific and predictable risk factors (Matthews 2004), while the term 'localised aggressive periodontitis' is used for aggressive periodontitis that typically presents in adolescents or young adults, affecting first molars and incisors, in the absence of local risk factors (Armitage 1999). While such a classification system aids clinicians in diagnosis and guides appropriate management of periodontal disease, it is recognised that a broad spectrum of disease exists that cannot be fully accounted for by dichotomous groupings (AAP 2015).

While a number of epidemiological studies have attempted to provide estimates of periodontitis prevalence, there is a lack of consensus regarding the precise definition of the disease, its severity, and its classification (Dye 2012). This is reflected in the World Health Organization Global Data Bank estimates (WHO 2004), where advanced disease is estimated to occur in 1% to 79% of the population worldwide. Despite challenges in measuring the extent of periodontitis across populations, numerous reports have demonstrated that the disease is a major burden globally (Eke 2012; Kassebaum 2014; Petersen 2012). Ultimately, untreated periodontal disease may lead to overt inflammation and progressive mobility of affected teeth, resulting in pain, difficulty eating, aesthetic concerns and tooth loss. Consequently, effective treatment modalities are required to control actively progressing disease, and maintain the dentition by preventing relapse and further disease progression.

Treatment of active periodontal disease is typically staged. Initial efforts focus on reducing or eliminating pathogenic (disease-associated) microbes. This is usually achieved through a combination of assisting patients to perform effective oral hygiene, and mechanical debridement to remove supragingival and subgingival microbial deposits (Lang 2015). In certain clinical scenarios, management of periodontal disease may include the adjunctive use of antimicrobials, at the discretion of the clinician. A number of surgical treatments may also be employed in some cases, with the aim of facilitating access for debridement by dentists and modification of the periodontal environment to permit effective patient-performed oral hygiene measures and reduce the risk of re-colonisation by periodontal pathogens. A different modality of treatment employed in specific cases and disease sites aims to regenerate lost bone and periodontal support through techniques including guided tissue regeneration.

Susceptibility to periodontal disease is difficult to predict prior to onset, and response to treatment is also unpredictable. However, patients with a history of periodontitis are at markedly increased risk of future episodes of disease, typically affecting the same sites. Consequently, following treatment of active disease, patients are routinely closely monitored through a formal programme of supportive periodontal therapy (SPT). Appointments often include debridement of any persistent periodontal pockets to ensure any colonising microbial populations are disrupted and so minimise the inflammatory response that underpins disease progression. SPT therefore offers an opportunity for clinicians to promote periodontal health, and rapidly detect and intercept recurrence or progression of periodontal disease (Heasman 2008; Ramfjord 1987).

The success of SPT has been demonstrated in a number of long-term, retrospective, epidemiological studies, which have shown that, whether in university, hospital or specialist practice settings, only 2% to 5% of teeth in patients originally treated for chronic periodontitis are lost over a 5- to 10-year period (Chambrone 2006; Fardal 2004; Loesche 2002; Wilson 1987; Wood 1989).

Additionally, tooth loss tends to cluster in a reduced population of high-risk patients (Chambrone 2006; Tonetti 2000). Studies assessing SPT have found:

- frequent-recall patients were able to maintain excellent oral hygiene standards and stable attachment levels (Axelsson 1981);
- well-maintained patients experienced reduced loss of periodontal support per annum (for example, a study by Suomi 1971 found 0.03 mm mean loss in a well-maintained group versus 0.1 mm in patients who received only one oral examination and no further reinforcement of oral hygiene instructions); and
- reductions in tooth loss over time. Becker 1979 observed a mean tooth loss per year of 0.36 in people who received neither treatment of active disease nor SPT, 0.22 in people who were treated but did not enrol in a SPT programme (Becker 1984a), and 0.11 in people who received treatment of active periodontal disease followed by SPT (Becker 1984b).

Overall, SPT appears effective in preventing recurrence of periodontitis, although SPT cannot eliminate the increased risk of attachment loss compared to periodontally healthy individuals in a preventive regimen (Teles 2008). If disease recurs during SPT, only a small subgroup of individuals is affected (AAP 1998; Echeverria 1996), and the risk of relapse is primarily affected by patient-specific factors, such as smoking (Matuliene 2008), and site-specific characteristics, such as involvement of root furcations in molar teeth (Hirschfeld 1978).

Description of the intervention

SPT (also known as maintenance therapy, supportive periodontal care or supportive periodontal treatment) follows the same principles employed in the treatment of active disease. It begins once patients are deemed periodontally stable, which is determined six to eight weeks after completion of active treatment (Morrison 1980). A thorough evaluation of the initial diagnosis and the response to periodontal treatment, and thoughtful analysis of risk factors (local, systemic and behavioural) for the recurrence of periodontal disease, are important components in assessing periodontal stability and establishing a prognosis for affected teeth (Armitage 2016). In addition to reinforcement of meticulous patient-performed oral hygiene, detailed monitoring of the periodontal tissues is routinely undertaken. Typically, this may include a record of clinical attachment and gingival probing depths at six sites per tooth (six-point pocket chart) and records of any bleeding or suppuration from each site. This well-organised data system shows the levels of insertion and of sites that are losing insertion or that remain stable (Lang 2008). The evaluation of bleeding on probing (BoP) is an accepted indicator of periodontal inflammation (Joss 1994; Lang 1986). Further means of monitoring periodontal stability include measures of tooth mobility, gingival recession, furcation involvement and radiographic examination of affected sites.

The aims of SPT are well established: minimise the recurrence of disease through periodic preventive interventions (Armitage 2016), and maintain the attachment apparatus in the most stable condition possible (Echeverria 1996). The aims of SPT are achieved through:

- preventing or minimising recurrence and progression of periodontal disease in people who have been previously treated for gingivitis, periodontitis, or peri-implantitis;
- reducing the incidence of tooth loss by monitoring the dentition, including any prostheses used to replace natural teeth;
- increasing the probability of identifying and treating, in a timely manner, other diseases or conditions found within the oral cavity (AAP 1998).

According to the American Academy of Periodontology (AAP) in order to fulfil these objectives, SPT should include:

- an update of the medical and dental history;
- examination of extraoral and intraoral soft tissues;
- dental examination and radiographic review;
- evaluation of the patient's oral hygiene performance;
- periodontal evaluation and risk assessment;
- supragingival and subgingival removal of bacterial plaque and calculus;
- re-treatment of disease when indicated (AAP 2000; AAP 2003).

While the first four points listed might be expected to form part of the routine examination appointment for periodontally healthy patients, the inclusion of thorough periodontal evaluation, risk assessment and subsequent treatment - normally including mechanical debridement of any plaque or calculus deposits - differentiates SPT from routine care.

As periodontitis is a multifactorial disease, with complex interplay between host and microbial factors, both treatment of active disease and subsequent SPT should be individualised in terms of prevention, therapeutic treatment modalities and frequency. Controversy exists about the most suitable approach to take during the maintenance visits due to difficulties encountered in accurately diagnosing disease activity and predicting disease progression. However, the importance of controlling risk factors, particularly by minimising bacterial plaque and calculus deposits, is widely accepted. Therefore, interventions focus on strategies to improve home care and motivation of the patient (Echeverria 1996), minimise bacterial deposits, reduce the risk of relapsing periodontal disease, and manage relapsed or persisting active disease sites.

The evaluation of patient risk of the progression of periodontitis is based on several clinical conditions that must be considered simultaneously. Lang 2003 described a risk assessment diagram that can serve as a tool to determine the individual risk of progression of the disease and, therefore, help the clinician make individualised decisions about the maintenance of their patients' dentition. The aspects that are analysed together are: 1) percentage of locations with BoP, 2) presence of residual bags 5 mm, 3) loss of teeth, 4)

loss of periodontal support in relation to the patient's age, 5) systemic and genetic conditions, and 6) environmental factors (e.g. tobacco). Each parameter is analysed based on a low, medium or high risk scale. Subsequently, the patient's risk is determined based on the analysis of all of them. For a patient to be categorised as high risk for periodontal disease, at least two parameters must be in the high risk zone (Lang 2003).

Whether results are superior when SPT is delivered by a periodontist, a general dentist or a hygienist is controversial. A number of studies point to better outcomes in favour of specialists (Axelsson 1981; Leavy 2017). Additionally, there is a lack of consensus regarding the effect of a range of antimicrobial therapies as adjuncts to debridement in SPT (Renvert 2004). The use of systemic antimicrobials has been shown to be effective in the active treatment of some periodontitis cases, primarily by eradicating microbes (particularly *P gingivalis)* that have invaded the gingival tissues and thus are shielded from mechanical debridement (Dakic 2016; Keestra 2015). This approach may be effective in treating persistent or refractory periodontitis sites during SPT. Locally-delivered antimicrobials or antibiotics, such as gels, the PerioChip (a chlorhexidine gluconate impregnated gelatine insert) or mouthwashes may aid SPT by eradicating any residual microbes, preventing the recolonisation of debrided tooth surfaces and through some absorption into the periodontal tissues (Mombelli 2017).

Other areas of uncertainty include:

- which strategies are best to deliver oral hygiene instructions and increase patient adherence to the SPT programme;
- the choice of approach to prevent relapse in sites that do not show signs of activity;
- clinical findings that can reliably indicate 'active' and/or 'recurrent' periodontal disease at a specific site and consequently as 'progressing'.

Risk assessment of the patient and the specific site will help determine the best strategy and schedule for the delivery of care by dental professionals. In some cases, teeth may be electively extracted during SPT. Different criteria may result in tooth extraction, from teeth presenting aesthetic concerns, being prosthetically not viable or having extensive carious or endodontic lesions (Hull 1997), to teeth with periodontal terminal prognosis (severe attachment loss that is not responding to periodontal treatment) and that may act as reservoirs for periodontal pathogens, cause discomfort or repeated infectious episodes, or may suffer excessive mobility (Matuliene 2008). Therefore, the outcome 'tooth loss' results from different scenarios, not all of them related to the failure of SPT interventions.

How the intervention might work

Relapse can be prevented or kept to a minimum in most patients, primarily through rigid surveillance at regular recall appointments (Lang 2015). It is well-recognised that periodontitis is a multifactorial disease induced by bacteria, and that differences in disease patterns between patients (and sites within the same patient) are determined by the local bacterial challenge, host response and the modifying effect of various risk factors (Ismail 1994). However, some of the factors contributing to the onset and progression of periodontal disease can be altered by the patient or the clinician to prevent the recurrence of periodontitis during SPT (Renvert 2004).

Both treatment of active disease and SPT aim to eradicate dental plaque, which is a community of microbes embedded in an extracellular polymeric substance (EPS) termed a biofilm. It is the presence of antigens in these bacterial communities, in combination with specific virulence factors from periodontal pathogens, that leads to inflammatory destruction of periodontal tissues. If plaque is retained over time without disruption or removal, the constituent population changes, with an increase in anaerobic fermenters primarily responsible for periodontal disease. Calculus (calcified plaque) does not have a major role in the pathogenesis of periodontitis, but can act as a 'retention web' for microbes, encouraging plaque accumulation (Ismail 1994). It has been demonstrated that adequate eradication of plaque and calculus deposits may be sufficient to control periodontal disease, even without modifying other risk factors involved (Lindhe 1984), and to prevent relapse (Axelsson 1981).

In concordance with the AAP position paper (AAP 2003), in order to provide the patient with close monitoring and minimise bacterial deposits, SPT should include (Lang 2015):

- examination, re-evaluation and diagnosis;
- motivation, re-instruction, instrumentation and polishing of the entire dentition;
- determination of future SPT.

Medical history should be updated and a full-mouth oral, dental and periodontal examination completed. Plaque and BoP assessment, probing depths (PDs) and clinical attachment level (CAL) should be recorded and both full-mouth and site-specific stability should be determined. Oral hygiene instruction including appropriate frequency, technique and use of aids such as interdental brushes should be tailored to patients' needs. Patients should be educated about the importance of compliance as better results are experienced when patients are compliant with the SPT schedule (Lee 2015). The specific treatment measures at each appointment, and the frequency with which SPT is scheduled should be individually formulated in accordance with the characteristics of each patient and site within the mouth. Clinical findings related to increases in attachment loss (progression) and the number of sites showing relapse are considered when establishing the maintenance schedule. The parameters commonly used to assess progression are: percentage of sites showing BoP; persistence of BoP concomitantly found with an increase in PD (Claffey 1990b); sites presenting probing pocket depths (PPD) greater than 5 mm; smoking status, and assessment of periodontal disease history (Renvert 2004). There is no consensus on which treatment regimen is most

appropriate for the majority of cases, but there is evidence to support the two most common interventions during SPT: supragingival debridement (Corbet 1993) and subgingival debridement (Heasman 2008).

It is important to differentiate stable versus progressive periodontitis, or sites showing signs of inflammation. Determination of stability is challenging without monitoring progression over time. However, measures of dental plaque levels and BoP are routinely used as proxy determinants of stability (Claffey 1990b). While bleeding sites may not necessarily progress, the absence of BoP is considered to indicate site stability (Lang 1990). Generally, sites showing stability or signs of inflammation without disease progression will undergo supragingival debridement. This can be performed with a variety of instruments and approaches. In order to minimise the volume of bacterial deposits, specific features likely to be retentive for plaque and calculus should be eliminated. In addition, there are a wide range of adjunctive measures that have been proposed to minimise the degree of plaque accumulation and inflammation, including adjunctive antimicrobials and lasers.

Indicators of active disease requiring re-treatment include signs of inflammation (BoP and suppuration) along with an increase in attachment loss (Claffey 1990b). After treatment of such sites, re-evaluation should be considered based on the extent and severity of the relapse or persistent disease, and the degree of control over site- or patient-specific risk factors. Typically, these sites are treated using subgingival debridement under local anaesthesia to accomplish effective removal of microbial deposits (Drisko 2014; Ramfjord 1987). Subgingival debridement is also recommended at sites presenting with PPD greater than 4 mm regardless of signs of inflammation or recurrent disease, as the risk of relapse increases with deeper probing depth measurements. Subgingival debridement has traditionally been delivered using a variety of hand instruments, ultrasonic and sonic scalers. Adjunctive treatments have also been proposed such as locally-delivered, controlled-release antibiotics including tetracycline (Newman 1994), minocycline (Hagiwara 1998), doxycycline (Bogren 2008a), and metronidazole (Bernimoulin 1999). Other antimicrobials including chlorhexidine (Kasaj 2007) and essential oils (Cosyn 2013) have been proposed, which can also be applied as subgingival irrigation. Additional measures such as host modulation therapy using low-dose doxycycline (Schumaker 2009), and more recently, different types of lasers (Ratka-Krüger 2012), have also been suggested to aid maintenance of periodontal health.

Why it is important to do this review

Cochrane Oral Health undertook an extensive prioritisation exercise in 2014 to identify a core portfolio of titles that were the most clinically important ones to maintain in the Cochrane Library (Worthington 2015). The periodontal expert panel identified this review as a priority (Cochrane Oral Health priority review portfolio).

Some retrospective studies have shown that active periodontal treatment followed by intensive adherence to a SPT programme may prevent the recurrence of periodontitis and further attachment loss (Axelsson 1981; Lindhe 1984; Tonetti 2000; Wood 1989), and can delay or avoid tooth loss (Becker 1984a; Lee 2015), even when considering teeth with severe periodontal involvement or patients with contributing systemic factors. Nowadays, the decision to extract a tooth with reduced periodontal support is mostly based on the so-called 'forceps level' of the dentist, and the belief that these teeth cannot be saved (Gotfredsen 2008), have a poor long-term prognosis, or that maintaining them will cause discomfort to the patient. However, the primary objective of SPT is to keep teeth functioning adequately according to each patient's needs and 'tooth loss' is considered a failure of the intervention (AAP 2000).

There is a lack of consensus about the best approach to use during SPT and even which factors are the most important to consider when designing an individualised maintenance prescription for a patient. Other aspects to be considered are the number of appointments, cost, and time spent in SPT through the years.

The goal of this systematic review and meta-analysis is to evaluate the effects of SPT in the maintenance of the dentition and determine the optimal means of delivering SPT.

OBJECTIVES

To determine the effects of supportive periodontal therapy (SPT) in the maintenance of the dentition of adults treated for periodontitis.

METHODS

Criteria for considering studies for this review

Types of studies

We included randomised controlled trials (RCTs) with at least 12 months of follow-up in this review. Follow-up was considered as the period of supportive periodontal therapy (SPT) in which the interventions were compared. It started following the completion of active periodontal therapy or when participants had already been enrolled in a periodontal maintenance programme.

We excluded split-mouth studies where we considered there could be a risk of contamination (treatment in one quadrant affecting untreated quadrants); for example, locally delivered antimicrobial agents, which might leach out or diffuse through saliva to control sites.

Types of participants

We included RCTs of adult participants (18 years or older) previously treated for periodontal disease and now in the maintenance phase. Treatment of active disease should have been concluded at least six months prior to randomisation to ensure that participants were known to be periodontally stable and compliant.

Types of interventions

The key elements of SPT are supragingival and subgingival mechanical debridement in conjunction with relevant periodontal indices (for example, bleeding on probing).
We included RCTs if they compared:

- SPT performed by periodontal specialists versus non-specialist dental professionals;
- SPT versus monitoring only, or alternative interventions that do not include mechanical debridement;
- SPT with and without adjunctive interventions delivered by dental professional or self-administered;
- SPT performed using different techniques and appliances for mechanical root debridement;
- SPT provided at different time intervals.

Types of outcome measures

Primary outcomes

- Tooth loss
- Bleeding on probing (BoP)
- Clinical attachment level (CAL)
- Adverse events

Secondary outcomes

- Probing pocket depth (PPD)
- Patient-reported outcome measures; for example, satisfaction with treatment
- Cost-effectiveness of SPT related to overall dental care with or without SPT
- Cost-effectiveness of SPT related to the frequency of SPT

Our main analyses were undertaken for results reported at 12 months or nearest time point. We would also have reported outcomes measured subsequent to 12 months if these had been available.
Had tooth loss been reported in any of the included studies, we would have sought the reason for the tooth loss, to ensure discrimination between elective extractions, loss of teeth due to other dental disease, and tooth loss due to periodontal disease progression.

Search methods for identification of studies

Electronic searches

Cochrane Oral Health's Information Specialist conducted systematic searches in the following databases for RCTs and controlled clinical trials. There were no language, publication year or publication status restrictions:

- Cochrane Oral Health's Trials Register (searched 8 May 2017) (Appendix 1);
- Cochrane Central Register of Controlled Trials (CENTRAL; 2017, Issue 5) in the Cochrane Library (searched 8 May 2017) (Appendix 2);
- MEDLINE Ovid (1946 to 8 May 2017) (Appendix 3);
- Embase Ovid (1980 to 8 May 2017) (Appendix 4).

Subject strategies were modelled on the search strategy designed for MEDLINE Ovid. Where appropriate, they were combined with subject strategy adaptations of the highly sensitive search strategy designed by Cochrane for identifying randomised controlled trials and controlled clinical trials as described in the *Cochrane Handbook for Systematic Reviews of Interventions* Chapter 6 (Lefebvre 2011).

Searching other resources

The following trial registries were searched for ongoing studies:

- US National Institutes of Health Ongoing Trials Register ClinicalTrials.gov (clinicaltrials.gov; searched 8 May 2017) (Appendix 5);
- World Health Organization International Clinical Trials Registry Platform (apps.who.int/trialsearch; searched 8 May 2017) (Appendix 6).

We did not perform a separate search for adverse effects of interventions used; we considered adverse effects described in included studies only.

Data collection and analysis

Selection of studies

Three review authors (CM, ESM, JT) independently screened records retrieved from the searches. On the basis of title, abstract or keywords, we discarded records that were obviously irrelevant and obtained the full text of remaining references. Full reports obtained from electronic and other methods of searching were assessed independently and in triplicate by the same three review authors to establish whether the studies met the inclusion criteria. We used an eligibility form, which was prepared and pilot tested in advance. We resolved disagreements by discussion and when resolution was not possible, we consulted a review contributor (Professor José J Echeverría (JE)). We recorded studies that were rejected at this or

subsequent stages in the Characteristics of excluded studies tables, and specified the reasons for exclusion. If we had identified studies in foreign languages, we would have translated them prior to data extraction and risk of bias assessment.

Data extraction and management

Three review authors (CM, ESM, JT) extracted data from the included studies independently and in duplicate using a pilot-tested data extraction form. We resolved disagreements through discussion with a review contributor (JE). We contacted trial authors for clarification or gathering of missing information as required. Review authors were not blinded to the name of the authors, institutions, journal of publication or results of the studies.

Assessment of risk of bias in included studies

We followed the methods recommended for assessing the risk of bias in studies included in Cochrane Reviews (Higgins 2011a). We used a two-part tool addressing seven specific domains (sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, incomplete outcome data, selective outcome reporting and 'other issues'). We prepared a 'Risk of bias' table for each study. We first described what was reported to have had happened in the study and then assigned a judgment of the risk of bias for that entry - low, high or unclear risk of bias. We also presented the results of the 'Risk of bias' assessment graphically.
Two review authors (CM, ESM) independently undertook the 'Risk of bias' assessment as part of the data extraction process. After taking into account the additional information provided by the authors of the trials, we grouped studies into the following categories:

- overall low risk of bias (plausible bias unlikely to seriously alter the results) for all key domains;
- overall unclear risk of bias (plausible bias that raised some doubt about the results) if we had assessed one or more key domains as unclear;
- overall high risk of bias (plausible bias that seriously weakens confidence in the results) if we had assessed one or more key domains to be at high risk of bias.

Measures of treatment effect

We planned to calculate the mean difference (MD) and 95% confidence interval (CI) for continuous data. Change scores or final scores were extracted for BoP, PPD and CAL, according to the data provided by the authors. If results were expressed using different scales, we planned to use the standardised mean difference (SMD). For binary data, we planned to calculate risk ratios and 95% CI.

Unit of analysis issues

The unit of analysis in this review was the individual.
For any future cluster-RCTs analysed and reported by statistical measures that take clustering into account, we will use the reported effect estimate and standard error. If clustering is ignored, we will attempt to re-analyse study data using approximate analyses with an 'effective sample size' and we will calculate the design effect using external estimates of the intracluster correlation coefficient (ICC) from similar studies (when available) (Deeks 2011a).

Dealing with missing data

We contacted the trial authors, when possible, to clarify incompletely reported data related to trial characteristics, methodology and outcomes.
For continuous variables with missing standard deviations (SDs), we estimated the SDs using the methods described in section 7.3.3 of the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011b).

Assessment of heterogeneity

We had planned to assess heterogeneity in the results by inspection of a graphic display of the estimated treatment effect along with their 95% CI, and statistically through Chi^2 (Deeks 2011b) and I^2 statistics (Higgins 2003). As a general rule, if there had been considerable heterogeneity (i.e. when the I^2 statistic was greater than 75%), we would not have pooled data.

Assessment of reporting biases

We had planned to examine the possibility of publication bias using funnel plots (Egger 1997), as described in the *Cochrane Handbook for Systematic Reviews of Interventions* (Sterne 2011).

Data synthesis

We described the characteristics and results of the included studies in tables. We planned to analyse the effect of SPT on maintenance of the dentition in people previously treated for periodontal disease, according to: different outcome parameters (incidence of teeth lost/PD/CAL); different frequency intervals of maintenance care (three to four months, six months); and different time scales (short-term (three to six months) and long-term outcomes (12 or more months)). We planned to conduct meta-analyses if there were studies of similar comparisons reporting the same outcome measures, using random-effects models if we combined three or more trials.

Subgroup analysis and investigation of heterogeneity

- Type of periodontitis originally treated: chronic or aggressive
- Presence of risk factors: diabetes, tobacco use

- Frequency of maintenance care

It was not possible to perform subgroup analysis due to the inadequate number of studies available.
Had we had sufficient studies, we would have performed meta-regression to investigate the effect of different variables on the outcome.

Sensitivity analysis

We had planned to assess the impact of excluding studies with high risk of bias from the analysis if sufficient data were available.

Summary of results

We presented a summary of the results for each comparison and the main outcomes (tooth loss, BoP, CAL, PPD and adverse events) in 'Summary of findings' tables and we assessed the quality of the body of evidence for the main outcomes under each comparison (Schünemann 2011). We adopted the GRADE system for evaluating quality of the evidence (GRADE 2011), with the help of GRADE profiler software (GRADEpro GDT 2015). Three review authors (CM, ESM, JT) classified the quality of a body of evidence as one of four categories: high, moderate, low or very low, depending on the extent of study design limitations, indirectness, inconsistency, imprecision and risk of publication bias.

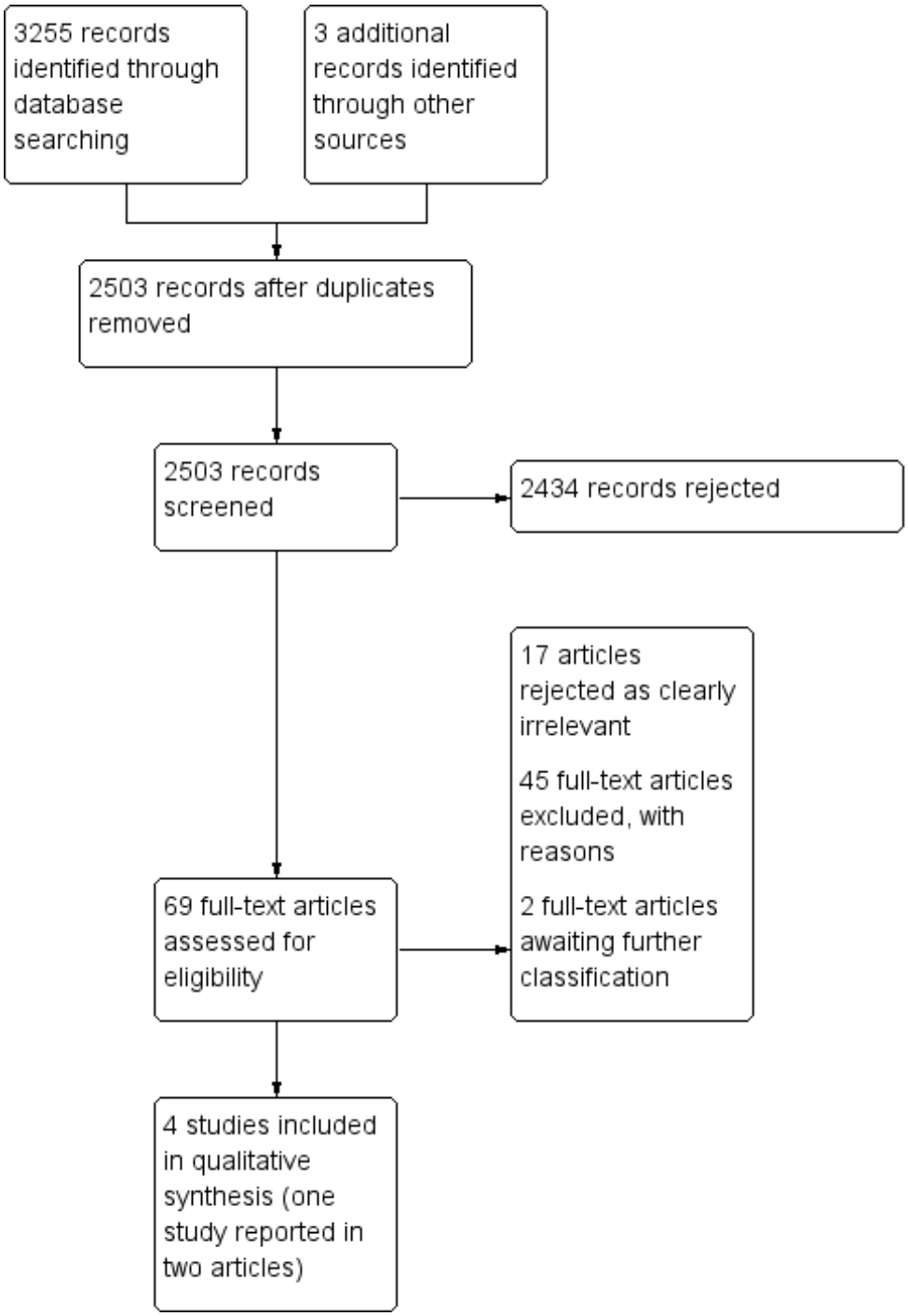
RESULTS

Description of studies

Results of the search

Searches of all sources yielded a total of 2503 records after de-duplication. After reading the titles and abstracts, we obtained the full text of 69 papers that we considered potentially relevant to the review. We rejected 18 outright and recorded our reasons for excluding 45. Two reports (one study) are awaiting classification due to insufficient information about the study design (Bogren 2008a; Bogren 2008b). We therefore identified four studies for inclusion in the review (one study had published an additional paper focused on furcation sites).
Although many of the excluded studies could have been excluded for more than one reason, we generally recorded only the main reason for exclusion in the Characteristics of excluded studies tables. We excluded nine studies as they were not or were unlikely to be RCTs (Costa 2012; De Carvalho 2010; Doherty 1988; Franke 2015; Garcia 2011; Guarnelli 2010; Meinberg 2002; Renvert 2011; Silva 2009); 14 because the follow-up was less than 12 months (Escribano 2010; Guarnelli 2010; Haffajee 2009; Hu 2015; Hägi 2015; Iwasaki 2016; Moëne 2010; Müller Campanile 2015; Nakajima 2012; Ratka-Kruger 2012; Rühling 2010; Slots 2012; Tomasi 2011; Wennström 2011); seven because participants were not in a maintenance programme (Aimetti 2004; Clarkson 2013; Goodson 2012; Jönsson 2009; Jönsson 2012; Krück 2012; Teles 2008); one because of the risk of influence of prior active periodontal treatment (possible cross-over effect) (Carvalho 2015); four because they did not measure relevant outcomes (Da Cruz Andrade 2017; Golub 2010; Payne 2011; Reinhardt 2010); eight because they used a split-mouth design with risk of contamination from the experimental intervention (Correa 2016; Heasman 2001; Kargas 2015; Krohn-Dale 2012; Müller 2014; Nguyen 2015; Simon 2015; Zhao 2015); and one because no control group data were available (Nakajima 2016).
We did not identify any ongoing studies. Figure 1 shows the flow of studies.

Figure 1. Study flow diagram



Included studies

After detailed assessment of the potentially relevant papers, we found four studies that fulfilled the review eligibility criteria (Killeen 2016; Lulic 2009; Preshaw 2005; Tonetti 2012). See Characteristics of included studies table for further details.

Characteristics of the trial settings and investigators

Killeen 2016 and Lulic 2009 were university-based studies. Killeen 2016 was conducted at the Department of Surgical Specialties at the University of Nebraska Medical Center College of Dentistry, Omaha, NE, USA; Lulic 2009 was conduced at the Department of Periodontology and Fixed Prosthodontics of University of Berne, Switzerland. Preshaw 2005 and Tonetti 2012 were multicentre studies. Preshaw 2005 was conducted in a specialist periodontal clinic and general dental practices in Newcastle, UK. Tonetti 2012 was conducted in several European centres (Belgium, Germany, Greece, the Netherlands and Switzerland), three university centres and three private practices.

Treatment was provided by a calibrated and trained therapist at each clinic in Tonetti 2012. In Killeen 2016, treatment was initiated by a dental student, refined by a faculty member and revisited by a single dental hygienist, who also applied the medication in the experimental sites. In Preshaw 2005, the clinician performing the treatment was the independent variable; thus, treatment was performed either by a hygienist in a periodontal specialist practice or the referring general dental practitioner (under specialist prescription). Lulic 2009 did not state who performed the intervention.

Characteristics of the participants

The age of the participants included in the trials varied. Participants were at least 31 years old in Preshaw 2005, 35 years old in Tonetti 2012, and 40 years old in Lulic 2009 and Killeen 2016.

Before randomisation, all participants had previously received periodontal treatment. Lulic 2009 reported that the participants had all been previously treated for chronic periodontitis. Killeen 2016,and Preshaw 2005 specified that the participants had been previously treated for moderate to advanced chronic periodontitis, while Tonetti 2012 detailed that participants were undergoing regular maintenance care and were suffering from persistent or recurrent moderate to severe periodontitis.

All participants included in the studies were recruited from a SPT programme. However, no information was provided about the degree of stability at the time of the re-evaluation in any of the studies. In addition, none of the studies provided information about the progression or the absence of progression of the disease during maintenance, that is, changes observed since re-evaluation.

The duration of SPT prior to enrolment was not specified in Lulic 2009. SPT duration was of at least six months in Preshaw 2005 and Tonetti 2012, while Killeen 2016 reported that participants had a history of regular PMT (Periodontal Maintenance Therapy) defined as at least two sessions of PMT per year prior to enrolment. All studies included smokers. Lulic 2009 limited the number of cigarettes to 10 or fewer per day in their study population.

Preshaw 2005 required participants to have at least eight sites with a probing depth (PD) of 5 mm to 8 mm, bleeding on probing (BoP) and radiographic evidence of alveolar bone loss. One of the inclusion criteria in Tonetti 2012 was the presence of at least four teeth with PD 5 mm or more, with presence of BoP, while Killeen 2016 required the presence of at least one posterior site with a PD 5 mm or more, with history of BoP. The only difference between Killeen 2016 and Lulic 2009 was that participants had to have residual PD 5 mm or more, with or without concomitant BoP. Tonetti 2012 had inclusion criteria that included FMPS (full-mouth plaque score).

As can be observed from the description provided above and from the Characteristics of included studies tables, characteristics of the participants in the studies differed in terms of age, severity of periodontitis, and smoking habits.

Characteristics of the interventions

See Characteristics of included studies for further details.

The interventions applied in the included studies were:

- specialist provision of SPT (including mechanical debridement) compared to SPT performed by general dental practitioners under specialist prescription (Preshaw 2005);
- locally delivered antibiotics as adjuncts to mechanical debridement (Killeen 2016; Tonetti 2012);
- photodynamic therapy as an adjunct to mechanical debridement (Lulic 2009).

SPT performed in specialist practice or by general dental practitioners (GDPs)

In Preshaw 2005, the intervention was SPT, including mechanical debridement of affected sites. One group of participants received treatment by a hygienist in specialist practice, while the alternate group received a written prescription of SPT requirements for the referring general dental practitioner.

Locally-delivered, topical antimicrobials as adjuncts to mechanical debridement in SPT

In Tonetti 2012, root instrumentation was undertaken at baseline, followed immediately by placement of doxycycline gel or placebo.

At three-monthly follow-up appointments, root instrumentation was completed but there was no further application of the investigational product. Results for furcation sites in a subset of participants were presented in an additional paper, but we have not presented these in this review. In Killeen 2016, the experimental sites received routine SPT, including mechanical root instrumentation, with 1 mg of minocycline HCl microspheres applied to test sites. Treatment was repeated at 6- and 12-month follow-up appointments.

Photonics as an adjunct to mechanical debridement in SPT

Lulic 2009 evaluated the effect of repeated adjunctive photodynamic therapy (PDT) (five times in two weeks: days 0, 1, 2, 7, 14) (test) following debridement. The control sites followed the same schedule using non-activated, placebo, laser applications. No further root instrumentation or repeat of treatments was undertaken at follow-up appointments up to 12 months.

Characteristics of the outcomes

Details of the different outcome indices used in each trial are presented in the Characteristics of included studies tables.

Tooth loss

Our primary outcome 'tooth loss', was not measured in any of the included studies.

Bleeding on probing (BoP)

Bleeding on probing was measured at baseline, 3, 6 and 12 months in Lulic 2009, and at baseline, 6 and 12 months in Killeen 2016 and Preshaw 2005. In Preshaw 2005 full-mouth bleeding scores were reported, while Killeen 2016 and Lulic 2009 reported BoP for experimental sites only. We could not use data from Lulic 2009 as they only reported the percentage of sites with bleeding, with no participant-based measures. Tonetti 2012 measured BoP, but did not report it.

Clinical attachment level (CAL)

Attachment level was measured at baseline, 3, 6 and 12 months in Lulic 2009, and at baseline, 6 and 12 months in Killeen 2016. Lulic 2009 and Killeen 2016 measured in millimetres. Tonetti 2012 did not measure CAL but considered probing attachment level. Preshaw 2005 did not measure CAL; they estimated attachment levels from radiographs of affected sites, but used volumetric estimates rather than linear attachment loss.

Adverse events

Tonetti 2012 reported adverse events while Killeen 2016 instructed the participants to record any adverse events noted.

Secondary outcomes

Probing pocket depth (PPD)

This was measured at baseline, 3, 6 and 12 months in Lulic 2009 and Tonetti 2012; and at baseline, 6 and 12 months in Killeen 2016 and Preshaw 2005.

There was considerable heterogeneity in reporting of PPD. Preshaw 2005 reported both test site and full-mouth mean PPD in mm. Killeen 2016 and Lulic 2009 also reported mean PPD in mm for test sites only. Tonetti 2012 provided the number and percentage of sites for PPDs of 4 mm, 5 mm, 6 mm, 7 mm and 8 mm or more.

Patient perception of treatment

This was not measured in the included studies.

Cost effectiveness

No outcomes based on the expense of the treatment (cost-effectiveness analysis) were reported, but Tonetti 2012 reported the treatment time spent at each visit and Killeen 2016 included information about the extra time spent in the periodontal maintenance appointment when delivering the local antibiotic.

Excluded studies

Although most of the 45 excluded studies could have been excluded for more than one reason (see Characteristics of excluded studies tables), we have recorded below the main reason for exclusion.

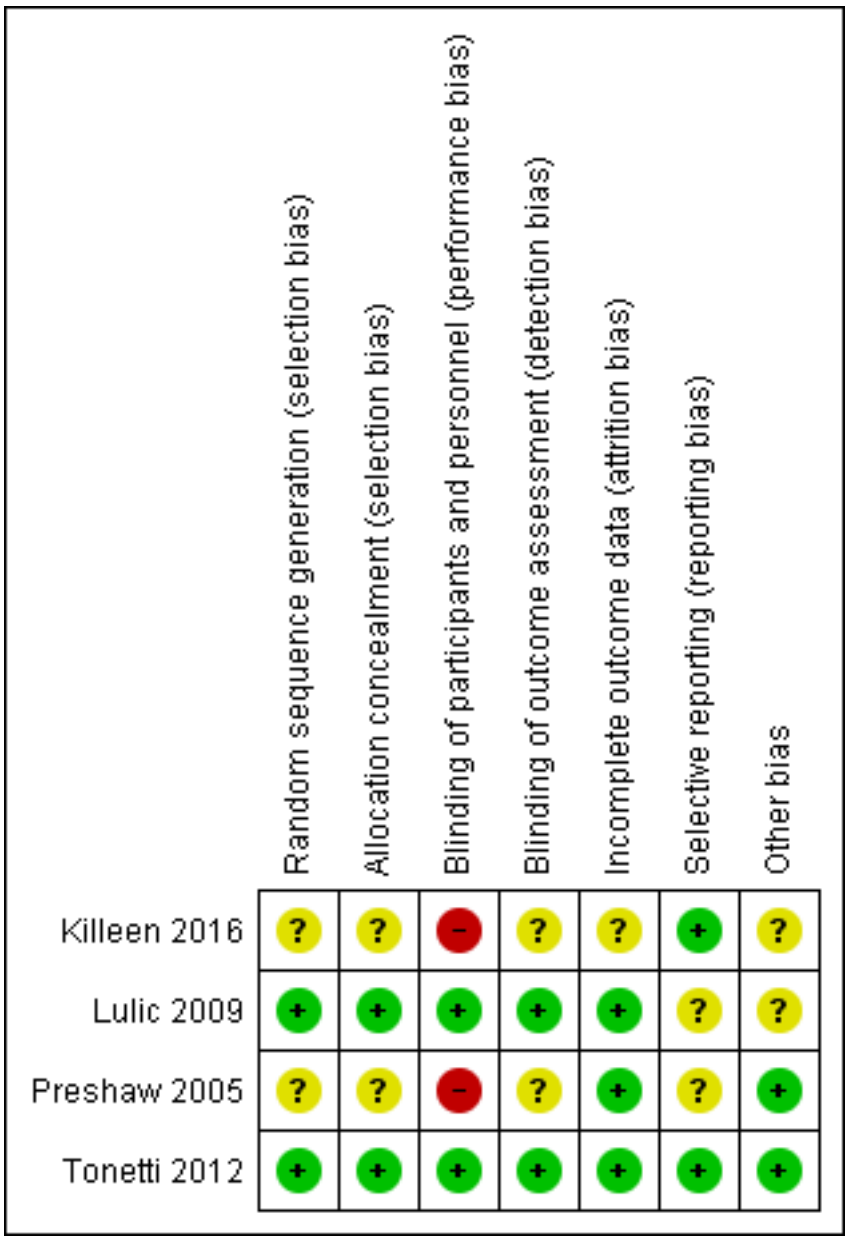
The majority of studies excluded were not RCTs (Costa 2012; De Carvalho 2010; Doherty 1988; Franke 2015; Garcia 2011; Guarnelli 2010; Meinberg 2002; Renvert 2011; Silva 2009); the intervention was not provided as part of SPT (Aimetti 2004; Clarkson 2013; Goodson 2012; Jönsson 2009; Jönsson 2012; Krück 2012; Teles 2008) or the follow-up was less than 12 months (Escribano 2010; Guarnelli 2010; Haffajee 2009; Hu 2015; Hägi 2015; Iwasaki 2016; Moëne 2010; Müller Campanile 2015; Nakajima 2012; Ratka-Kruger 2012; Rühling 2010; Slots 2012; Tomasi 2011; Wennström 2011). We excluded two studies because active periodontal treatment was not completed more than six months before study commencement (Carvalho 2015; McColl 2006); four studies because the relevant outcomes were

not measured (Da Cruz Andrade 2017; Golub 2010; Payne 2011; Reinhardt 2010); seven of them because the design used 'split-mouth' (Correa 2016; Kargas 2015; Krohn-Dale 2012; Müller 2014; Nguyen 2015; Simon 2015; Zhao 2015); one because no control group data were available (Nakajima 2016); and finally Dannewitz 2009 because it was an interim analysis of another paper, focused on the analysis of the furcation locations (see Tonetti 2012).

Risk of bias in included studies

We present details of the assessment of the risk of bias for each included study in the Characteristics of included studies table and Figure 2. We judged one study to be at overall low risk of bias (Tonetti 2012), and one study to be at high risk of bias (Killeen 2016). We considered Lulic 2009 and Preshaw 2005 to be at unclear risk of bias.

Figure 2. Risk of bias summary: review authors' judgements about each risk of bias item for each included study



Allocation

We classified two studies as presenting with a low risk of selection bias (Lulic 2009; Tonetti 2012). In Lulic 2009, the therapist (a registered dental hygienist) was blinded to the activation of the laser and random assignment of groups was performed by a dental nurse otherwise not involved in the study. Randomisation was performed using a randomisation table. Tonetti 2012 used a computer-generated sequence to randomise participants and information about allocation group was not revealed to the therapist (it was kept in an opaque envelope) until the time of treatment.
Two studies were at unclear risk of selection bias (Killeen 2016; Preshaw 2005). In Killeen 2016, randomisation was by coin toss, subsequent to patient stratification by sex and smoking status. Allocation concealment was not described. Preshaw 2005 did not specify how randomisation was performed, and allocation concealment was not possible in this study as the operator performing SPT was the test variable.

Blinding

We assessed two studies as being at low risk of both performance and detection bias. In Lulic 2009 and Tonetti 2012, participants, treatment providers and assessors were blinded to the intervention. Lulic 2009 reported "masked switching of the power setting of the laser". In Tonetti 2012, the investigator providing the intervention ('therapist') was blinded to the intervention during the initial stages of treatment, until application of the adjunctive intervention. A second investigator, who was blind to allocation, performed the examinations. Tonetti 2012 mentioned that statisticians were blinded to treatment when performing the statistical analysis while none of the other studies provided this information.
Preshaw 2005 did not report blinding of participants and it is likely they would have known their group assignment. Clinical examinations were performed by an individual blinded to allocation, but it is not clear if this is the case for radiographic analysis. We assessed Preshaw 2005 as being at high risk of performance bias and unclear risk of detection bias.
Killeen 2016 was described as a single-blinded study. We assessed it as being at high risk of performance bias as neither participants or clinicians were blinded to treatment allocation during the study. The risk of detection bias in Killeen 2016 was unclear; the outcomes were assessed by a blinded examiner, but data analysis methods were not described and it is uncertain if treatment allocation was known at that stage.
Killeen 2016 and Tonetti 2012 presented data on calibration of the examiners.

Incomplete outcome data

We assessed Lulic 2009, Preshaw 2005 and Tonetti 2012 as being at low risk of attrition bias, as each study had no, or very low, loss to follow-up and reported any reasons for incomplete outcome data. We assessed Killeen 2016 as being at unclear risk of attrition bias because intention to treat analysis was not performed (although loss to follow-up was well reported).

Selective reporting

We assessed Killeen 2016 and Tonetti 2012 as being at low risk of reporting bias, as all planned outcomes were reported fully. The other two studies were unclear: Lulic 2009 reported all outcomes at 12 months, but did not report earlier prespecified time points; Preshaw 2005 did not provide compliance data for one group.

Other potential sources of bias

We were not aware of any other potential sources of bias for three of the studies. We considered Killeen 2016 to be unclear because experimental sites had been determined from screening data and assigned at baseline.

Effects of interventions

See: **Summary of findings for the main comparison** Supportive periodontal therapy (SPT) performed by specialists versus SPT performed by non-specialist clinicians; **Summary of findings 2** Mechanical debridement plus local antimicrobial versus mechanical debridement; **Summary of findings 3** Photonics plus mechanical debridement versus mechanical debridement
The following results focus on the 12-month results (minimum of 12 months follow-up was an inclusion criterion of the review).

SPT performed by specialists or non-specialist clinicians

Preshaw 2005 evaluated the effectiveness of SPT performed by a hygienist in a specialist periodontal clinic, compared with SPT performed by general dental practitioners under specialist prescription, in 35 participants.

Tooth loss

This outcome was not measured in the study.

Bleeding on probing (BoP)

The mean percentage of sites with BoP at each time point was reported with, but standard error was displayed only graphically. Full-mouth scores, rather than test sites only were provided. There was no statistically significant difference between treatment groups at 12 months (MD 7.40, 95% CI -8.12 to 22.92; Analysis 1.1).

Clinical attachment level (CAL)

This outcome was not measured in the study.
Radiographs were analysed and changes in attachment level inferred as volumetric changes in bone levels. The trial authors reported there was no evidence of a difference in bone-loss estimates from analysis of serial radiographs.

Adverse events

Adverse events were not measured in this study.

Secondary outcomes

Probing pocket depth (PPD)

PPD measurement (mm) of test sites was reported in addition to full-mouth measurements at baseline and 12 months. Measurements were reported with mean PPD values presented numerically, but standard error displayed only graphically. There was no evidence of a difference in PPD at 12 months between the group treated by a specialist and the group treated by a non-specialist (MD 0.20, 95% CI -0.40 to 0.80; Analysis 1.2).

SPT with and without adjunctive interventions delivered by dental professional or self-administered

Mechanical debridement plus local antimicrobial versus mechanical debridement only

Two studies provided clinical data for this comparison (Killeen 2016; Tonetti 2012). Tonetti 2012 used a single application of topical slow-release 14% doxycycline gel; Killeen 2016 used 1 mg minocycline microspheres, applied at baseline and six months.

Tooth loss

This outcome was not measured in either study.

Bleeding on probing (BoP)

Killeen 2016 reported the mean percentage (both final scores and change in scores) for BoP at the experimental site of each participant at 12 months. The authors reported that the odds of having BoP were not significantly different between groups at 12 months (OR 0.45, 95% CI 0.14 to 1.52, 50 participants; Analysis 2.1).
Tonetti 2012 reported the full-mouth bleeding score (95% CI) for the control and test group separately at baseline. BoP was used later in the results as an indicator of healing, expressed as the OR for treatment difference in the rate of healing of sites with PPD 5 mm or more, or 4 mm with BoP to a category of non-bleeding sites with PPD 4 mm or more, with no evidence of a difference between groups at 12 months.

Clinical attachment level (CAL)

Killeen 2016 provided data at 12 months for CAL measurements (mm), mean and ratio of change in CAL at experimental sites. CAL decreased from baseline in the test and control groups, but the study found no significant difference between groups (MD 0.10 mm, 95% -0.42 to 0.62; 53 participants, Analysis 2.2).
Tonetti 2012 used PAL (probing attachment level) as a measurement for CAL. Results were expressed as adjusted mean changes in PAL between test and control treatments by baseline pocket depth (4 mm, 5 mm, 6 mm, 7 mm and 8+ mm) at 3-, 6- and 12-month follow-up. Tonetti 2012 presented the results as supplemental diagrams and reported no evidence of a benefit in probing attachment level at 12 months.

Adverse events

No participants reported any adverse events at follow-up examinations in Killeen 2016. Tonetti 2012 reported there were, "83 participants (out of 203) reporting 131 adverse events, 49 participants with 75 adverse events in the control group and 34 participants with 56 adverse events in the test group. No adverse events were rated as serious and none required special treatment. The number of adverse events rated as possibly related to the medication was three events in two subjects. A test of significance was not carried out."

Secondary outcomes

Probing pocket depth (PPD)

Killeen 2016 provided data at 12 months for PPD measurements (mm), the mean, and ratio of change at 12 months. No significant differences between groups from baseline at any time point, nor between smokers compared with non-smokers were observed. There was no evidence of a difference between groups in PPD

scores at 12 months (MD -0.10, 95% CI -0.59 to 0.39; 51 participants, Analysis 2.3).
Tonetti 2012 reported mean changes in PPD at 12 months. However, only mean changes experienced for each of the initial PPDs (4 mm, 5 mm, 6 mm 7 mm and 8 mm or more) were reported, rather than absolute numerical values. Tonetti 2012 reported reductions in PPD from baseline but no evidence of a difference between groups.

Cost effectiveness

Killeen 2016 noted that the addition of the local antibiotic to the overall treatment time for the periodontal maintenance appointment was less than five minutes per appointment. Tonetti 2012 stated in their discussion that the adjunctive administration of slow-release doxycycline gel took an average of 13 minutes.

Mechanical debridement plus photonics versus mechanical debridement only

One very small study (10 participants) evaluated photodynamic therapy (PDT) as an adjunct to mechanical debridement compared to mechanical debridement only (with placebo PDT treatment) (Lulic 2009). Mechanical debridement was performed on all participants at baseline, followed by application of either PDT or placebo treatment at baseline, 1, 2, 7 and 14 days.

Tooth loss

This outcome was not measured in the study.

Bleeding on probing (BoP)

The study did not provide participant-based measures; it only reported the percentage of sites with bleeding.

Clinical attachment level (CAL)

CAL was measured in mm for test sites only. There were no statistically significant changes in CAL from baseline to 12 months in either test or control participants. There was no evidence of a difference between groups at 12 months (MD -0.97, 95% CI -3.51 to 1.57; Analysis 3.1).

Adverse events

The study did not report adverse events.

Secondary outcomes

Probing pocket depth

No statistically significant decreases in mean PPD were observed between baseline and 12 months for test or control participants. There was no evidence of a difference between groups at 12 months (MD -0.09, 95% CI -1.41 to 1.23; Analysis 3.2).

SPT performed using different techniques and appliances for mechanical root debridement

No studies evaluated this comparison.

SPT provided at different time intervals

No studies evaluated this comparison.

ADDITIONAL SUMMARY OF FINDINGS [*Explanation*]

Mechanical debridement plus local antimicrobial compared with debridement only

Population: adults treated for periodontitis and receiving supportive periodontal therapy
Settings: dental clinic
Intervention: minocycline or doxycycline gel plus mechanical debridement
Comparison: mechanical debridement

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	Number of participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	Control	Antimicrobial (minocycline)				
Tooth loss	Not measured					
Bleeding on probing (ratios) at 12-month follow-up			OR 0.45 (0.14 to 1.52)	1 study (50 participants)	⊕◯◯◯ **very low**[a]	
Clinical attachment level (mm) at 12-month follow-up	Change score 4.6 mm	Change score was 0.10 mm higher (from 0.42 lower to 0.62 higher)		1 study (53 participants)	⊕⊕◯◯ **low**[a]	Tonetti 2012 assessed the effect of adjunctive doxycycline and reported no evidence of a benefit for probing attachment level
Pocket depth (mm) at 12-month follow-up	4.3 mm	PD was 0.10 mm lower (from 0.59 lower to 0.39 higher)		1 study (51 participants)	⊕⊕◯◯ **low**[a]	Tonetti 2012 assessed the effect of adjunctive doxycycline and reported no evidence of a benefit for pocket depth reduction

Adverse events	See comment	2 studies (251 participants)	Killeen 2016 reported no adverse events at follow-up examinations in either study arm Tonetti 2012 reported that there were no serious adverse events.

*The basis for the **assumed risk** (e.g. the median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).
CI: confidence interval; **MD**: mean difference; **OR**: odds ratio

GRADE Working Group grades of evidence
High quality: we are very confident that the true effect lies close to that of the estimate of the effect
Moderate quality: we are moderately confident in the effect estimate; the true effect is likely to be close to the estimate of effect, but there is a possibility that it is substantially different
Low quality: we are moderately confident in the effect estimate; the true effect is likely to be close to the estimate of effect, but there is a possibility that it is substantially different
Very low quality: we have very little confidence in the effect estimate; the true effect is likely to be substantially different from the estimate of effect

[a] Single study at high risk of bias, small sample size and serious imprecision in the effect estimate - downgraded three levels
[b] Study (Killeen 2016) at high risk of bias and small sample size - downgraded two levels

Photodynamic therapy plus mechanical debridement compared with mechanical debridement

Patient or population: adults treated for periodontitis and receiving supportive periodontal therapy
Settings: dental clinic
Intervention: photodynamic therapy plus mechanical debridement
Comparison: mechanical debridement

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	Number of participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	Control	Experimental				
Tooth loss	Not measured					
Bleeding on probing	Not measured in usable way					
Clinical attachment level (mm) at 12-month follow-up	7.76 mm	0.97 mm lower (from 3. 51 lower to 1.57 higher)		1 study (10 partici- pants)	⊕◯◯◯ **very low**[a]	
Probing pocket depth (mm) at 12-month follow-up	5.9 mm	0.09 mm lower (from 1. 41 lower to 1.23 higher)		1 study (10 partici- pants)	⊕◯◯◯ **very low**[a]	
Adverse events	Not measured					

The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).
CI: confidence interval; **MD**: mean difference

GRADE Working Group grades of evidence
High quality: we are very confident that the true effect lies close to that of the estimate of the effect
Moderate quality: we are moderately confident in the effect estimate; the true effect is likely to be close to the estimate of effect, but there is a possibility that it is substantially different
Low quality: we are moderately confident in the effect estimate; the true effect is likely to be close to the estimate of effect, but there is a possibility that it is substantially different

Very low quality: we have very little confidence in the effect estimate; the true effect is likely to be substantially different from the estimate of effect

[a]Study at unclear risk of bias and very small sample size - downgraded three levels

DISCUSSION

Summary of main results

In this review, we included four RCTs, three of which were at high or unclear risk of bias. The studies had a total of 307 participants who had been previously treated for periodontitis and were receiving SPT. We included a small (n = 35), multicentre study with no sample size calculation (Preshaw 2005); a larger multicentre study (n = 202), in which sample calculations were performed (Tonetti 2012); and two studies in which the sample size was small but sufficient according to the power calculations (Lulic 2009, n = 10; Killeen 2016, n = 60, respectively). Studies differed in pre-randomisation duration of maintenance, severity of sites, treatments tested and protocols followed. All studies had a follow-up of at least 12 months and assessed the effect of different periodontal maintenance protocols on BoP, PPD and CAL. Killeen 2016 and Tonetti 2012 measured adverse events. Tonetti 2012 also measured overall treatment time (an indirect measure of cost effectiveness). None of the studies measured our primary outcome 'tooth loss'.

Preshaw 2005 compared a standard SPT programme in a specialist setting or general dental practice, and found no difference in outcomes between the two care settings. Tonetti 2012 compared the administration of topical doxycycline as a single application adjunctive to mechanical debridement versus debridement alone, and treated all sites presenting PD 4 mm or more. It concluded that a single subgingival application of doxycycline as an addition to mechanical debridement had only a short-term benefit on pocket depth reduction, but no differences between groups at 12 months. Killeen 2016 treated test sites with minocycline at baseline and at six months, and no differences in either clinical, microbiological or gingival crevicular fluid parameters were observed at the 12-month follow-up between the groups. Lastly, Lulic 2009 repeated photodynamic therapy (five times in two weeks) as an adjunct to debridement and found short-term improvement in PD and CAL, but no difference between test and control groups after 12 months.

Overall completeness and applicability of evidence

The aim of this systematic review was to determine the effects of supportive periodontal therapy (SPT) in the maintenance of the dentition. The included studies tested different approaches to treat persistent/recurrent periodontitis in people enrolled in a SPT programme. Specific objectives of this systematic review were to compare:

- SPT performed by periodontal specialists versus non-specialist dental professionals;
- SPT versus monitoring only, or alternative interventions that do not include mechanical debridement;
- SPT with and without adjunctive interventions delivered by dental professionals or self-administered;
- SPT performed using different techniques and appliances for mechanical root debridement;
- SPT provided at different time intervals.

We found four studies that met the eligibility criteria for this review. We found no eligible studies that evaluated SPT versus monitoring only, SPT performed using different techniques and appliances for mechanical root debridement, or SPT provided at different time intervals. As only a limited number of studies relevant to the objectives of this review were available, all of which had small sample sizes and featured diverse designs, interventions and outcome reporting, any inferences made from this review must be guarded.

Preshaw 2005 evaluated the effect of SPT performed by a dental hygienist working in a specialist periodontal clinic, compared with SPT performed by general dental practitioners under specialist prescription. Of the primary outcomes specified for this review, only BoP was evaluated. A secondary outcome in the review, PPD, was the main outcome for this study. The study was limited by a low sample size, lack of formal power calculation, and incomplete information relating to compliance of the general dental practitioner cohort. The authors note that the response to treatment in both arms of this study was comparable to previous reports in the literature, which lends some support to their veracity. However, it is clear that further studies are required in future with sample sizes determined by power calculation, and inclusion of all relevant clinical outcomes (tooth loss, CAL, and any adverse events) to evaluate the impact of specialist practitioners in delivering SPT.

Three studies compared SPT with and without adjunctive interventions delivered by dental professionals (Lulic 2009; Tonetti 2012; Killeen 2016). Lulic 2009 evaluated the effectiveness of adjunctive photodynamic therapy to mechanical debridement in SPT, while both Tonetti 2012 and Killeen 2016 assessed the use of adjunctive local antibiotic formulations (doxycycline gel and minocycline microspheres, respectively). All studies reported CAL, a primary outcome for this review. BoP was reported in Killeen 2016 (and in Lulic 2009, but not in a useable way), while adverse events were reported in Tonetti 2012 and Killeen 2016. No studies provided data on tooth loss experienced by participants. PPD, a secondary outcome of this review, was reported in all studies, although Tonetti 2012 reported PPD data grouped rather than numerical aggregate data.

Evidence for adjunctive interventions in SPT is limited by the heterogeneous interventions and limited number of studies evaluating this objective. In total, the three studies provided outcome data for 261 participants at 12 months. Lulic 2009 included 10 participants, and because the nature of the intervention (photodynamic therapy) was highly dissimilar to Tonetti 2012 and Killeen 2016, we could not pool outcomes. While both Tonetti 2012 and

Killeen 2016 evaluated the impact of adjunctive, locally-delivered tetracycline-class antibiotics, each used a different formulation (gel versus microspheres). There is a lack of evidence regarding the use of alternative locally-delivered antibiotics (e.g. metronidazole) or other antimicrobial agents (e.g. chlorhexidine).

With the exception of Preshaw 2005, studies were based in university dental hospitals or specialist clinics, likely due to the logistics of sampling a large cohort of compliant SPT patients. However, this limits the applicability of the evidence to patients in general practice, who may be less compliant with traditional SPT modalities and thus experience greater benefit from alternative or adjunctive treatments.

Importantly, tooth loss was not reported in any included studies. It may be that substantially longer follow-up periods are required to adequately evaluate this outcome.

Overall, there is no evidence available to assess the effects of SPT compared to monitoring only or alternatives to mechanical debridement, or the effects of different frequencies of SPT provision. The evidence informing the choice of practitioner to perform SPT and effects of adjunctive treatments is very limited.

Quality of the evidence

We assessed the quality of the body of evidence using GRADE (GRADE 2011) and present this in Summary of findings for the main comparison, Summary of findings 2 and 'Summary of findings 3'. The quality of evidence for the included comparisons and outcomes is low or very low, and limited by the small number of studies, and differences in study design, SPT protocols and reporting of outcomes.

Potential biases in the review process

We made a number of post hoc changes to our planned methods, partly because of the time lag between the publication of our protocol and the completion of this review. We excluded trials where participants were described as presenting with gingivitis only. We excluded trials where participants were in the active periodontal treatment phase or where their active treatment had ended less than six months from randomisation into the SPT study. We excluded split-mouth studies where we considered there to be a risk of contamination between study arms. See Differences between protocol and review for full details of our changes.

Agreements and disagreements with other studies or reviews

A number of in vitro and clinical studies have demonstrated short-term beneficial effects following adjunctive treatments, such as locally-delivered antimicrobials, in combination with mechanical debridement during SPT. However, clinically relevant effectiveness of such therapies is difficult to determine due to the limited follow-up of most of the published research, which typically extends to a maximum of six months. As SPT is employed to help maintain teeth over a lifetime, evaluation over at least 12 months (comprising several recall appointments) is important, and may explain the lack of evidence for effectiveness of interventions included in this review compared to a number of other published studies.

Local application of chlorhexidine has previously shown positive results. Heasman 2001 compared mechanical debridement alone versus mechanical debridement with a gelatine chip impregnated with chlorhexidine gluconate 2.5 mg (PerioChip™). This was a randomised, split-mouth, single-blind study in 26 participants with a minimum of one pocket per quadrant with a PD 5 mm or more and BoP, having completed SRP treatment at least three months prior to baseline. SRP + PerioChip was placed in the selected sites of two quadrants, while control sites in the remaining quadrants were treated with debridement only. Participants were re-examined at one, three and six months, but no further PerioChips were placed. At the end of the study, the potential benefit of adjunctive use of PerioChip was noticeable at six months with respect to PPD, CAL and BoP. These results did not meet the threshold of statistical significance however, and we speculate that it is likely that follow-up examination of 12 months or greater would yield no significant benefit, as was found in the trials comparing locally-delivered antibiotics included in this review (Tonetti 2012; Killeen 2016).

A 12-month study was carried out by Aimetti 2004 to evaluate the clinical, radiological and microbiological response to the local delivery of tetracycline (TE) of sites with persistent periodontal lesions. This was an unblinded split-mouth design in 19 participants with at least four bilateral pockets 4 mm to 5 mm and BoP. The pockets were treated with mechanical debridement plus TE or with mechanical debridement alone. Clinical and radiological measures were taken at baseline and 6 and 12 months. Both treatments found a reduction in PPD, BoP and gain of CAL, with a clear statistically significant benefit to the adjunctive use of tetracycline fibres over mechanical debridement alone. The findings of this study contrast with the two studies we included that evaluate locally-delivered antibiotics as adjuncts to mechanical debridement (Tonetti 2012; Killeen 2016), which found no significant benefit for such adjuncts to treatment. While the antibiotics compared are all tetracyclines, differences in the method of delivery (gel, microspheres or fibres) and consequent retention and release profile of antibiotic over time may have influenced the outcome. Such apparent differences in effectiveness highlight the need for further evaluation of both different classes of antibiotics and antimicrobials, as well as vehicles for delivery.

Although local and systemic antimicrobials combined with mechanical debridement show significant improvement in PPD reduction and/or gains in CAL on a short-term basis, both in active

or maintenance periodontal therapy, there remains insufficient evidence to recommend their routine use, particularly as monotherapy ((Feres 2015; Greenstein 1993; Greenstein 2006). Many authors agree on the need for conservative prescribing of antibiotics, due to their frequent side-effects (Herrera 2008). This is further compounded by dental plaque, which exists as a biofilm, protecting its inhabitant micro-organisms from disruption, immune-clearance or the effects of antimicrobials. Unless mechanical debridement is established alongside antibiotic therapy, there is limited likelihood of successful treatment. Additional concerns over the routine use of antibiotics for SPT are raised due to the growing threat of antimicrobial resistance (Mombelli 2006).

There were some studies that we excluded from this review solely because of their split-mouth design. Müller 2014 tested the use of subgingival air polishing with erythritol (test sites) versus ultrasonic debridement with piezon (control sites) and Krohn-Dale 2012 compared the use of repeated Er:YAG laser to conventional maintenance therapy (curette/ultrasonic instrumentation with piezon). Neither of the studies showed superiority of the test treatments over controls in terms of reduction of sites with PPD 4 mm or more (Müller 2014), PPD reduction, or microbiological findings (Krohn-Dale 2012). In a systematic review and meta-analysis of the diode laser, no significant effect on PPD, CAL or plaque index compared to conventional mechanical debridement alone was found. Laser treatment was found to lead to improvements in bleeding index scores, although the clinical relevance of this finding is questionable (Slot 2014). In addition, another meta-analysis found that diode laser treatment as an adjunct to non-surgical periodontal therapy did not provide an additional clinical benefit (Sgolastra 2013). No differences were found between various types of lasers compared to debridement alone (Cobb 2006). However, in a recent RCT, the efficacy of combining full-mouth subgingival debridement with Er: YAG laser application in the treatment of periodontal patients was evaluated (Sanz-Sánchez 2015). After one year, the test group showed significant reductions in the percentage of moderate-to-deep PPDs and a clear trend of reduced open pockets, compared to the control group. However, the study authors pointed out that this study failed to demonstrate any clinically significant benefit when the adjunctive laser therapy was added to ultrasonic root debridement.

AUTHORS' CONCLUSIONS

Implications for practice

There is no evidence available to determine the merits of supportive periodontal therapy (SPT) versus monitoring alone, or SPT provided at different time intervals. There is a very limited amount of evidence, of low to very low quality, suggesting that adjunctive treatments may not provide any additional benefit for SPT compared with mechanical debridement alone. Evidence of very low quality suggests that SPT performed by general dentists under specialised prescription may be as effective as specialised treatment. Overall, definitive clinical protocols are still lacking as the evidence is insufficient to draw any reliable conclusions about the equality or superiority of different approaches to SPT.

Implications for research

There is a need for well-conducted trials on SPT in order to answer the four questions that were considered for this systematic review: the effectiveness of SPT compared to monitoring/standard dental care, different timings of SPT, adjuncts to SPT and different approaches for mechanical debridement as part of SPT.

A serious limitation in the clinical application of adjunctive therapy or different time intervals in SPT is the lack of clear guidelines and protocols, as pointed out by many authors. Basing treatment on broad guidelines in the era of personalised medicine seems undesirable. Further knowledge regarding susceptibility and progression of periodontal disease in a specific site, based on individual patient risk factors will ensure optimal outcomes and cost-effective institution of a SPT regime.

Overall, the quality of evidence is low to very low, due to the limited number of studies, relatively small numbers of participants, and high or unclear risk of bias in three out of the four included RCTs.

Greater attention should be given to the methodology used to assess SPT. Duration of follow-up is of paramount importance when adding adjunctive treatments to SPT, as many adjuncts demonstrate short-term effectiveness but fail to demonstrate long-term improvement in clinical outcomes. Studies should focus on the clinical significance of results, in order to place the effectiveness of adjunctive therapy in perspective. Tooth loss should be considered as an outcome because of its clinical importance. In future, rigorous trials with adequate sample sizes should be planned with a minimum of 12 months' follow-up, and should also consider patient-orientated outcomes (costs, dentine hypersensitivity, comfort, satisfaction), which are likely to influence adherence to SPT programmes.

ACKNOWLEDGEMENTS

The review authors would like to thank Prof. Dr. José J Echeverría for his mentorship and help and The Spanish Society of Periodontology (SEPA) for their support, especially Dr. Adrian Guerrero and Dr. David Herrera.

We acknowledge Anne Littlewood (Cochrane Oral Health) for her assistance with literature searching; and are grateful to Laura C.I. MacDonald for her support and comments during the preparation of this review. We thank Professor Helen Worthington, Thomas Lamont (editor with Cochrane Oral Health), and external referees

Dr. John Zaki and Soodabeh Behboodi for their feedback, and Denise Mitchell for final copy editing. We acknowledge the contribution of Luisa Fernandez Mauleffinch and Phil Riley for their earlier help with preparation of the protocol.

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* *Indicates the major publication for the study*

CHARACTERISTICS OF STUDIES

Characteristics of included studies *[ordered by study ID]*

Killeen 2016

Methods	Design: 2-arm, parallel-group, single-masked RCT Location: USA Number of centres: 1 (University of Nebraska Medical Center (UNMC) College of Dentistry, Omaha, Nebraska clinics) Recruitment period: not specified. Study conducted from October 2012-December 2014 Clinical exam performed with a manual UNC15 tip (Hu-Friedy) probe at experimental sites. No information provided about rounding of measurements. Inflammatory markers were analysed in GCF (gingival crevicular fluid) through enzyme-linked immunosorbent assay
Participants	Adults (40-85 years old) with a history of regular PMT ≥ twice a year before enrolment with ≥ 1 posterior ≥ 5 mm interproximal pocket with BoP. Diagnosis of moderate-severe chronic periodontitis. Men n = 35; women n = 16. Smokers n = 12. Mean number of teeth per participant: 23.5 ± 5.1 (test group) and 25.3 ± 3.9 (control group) Experimental site of the individuals was assigned from screening data (most posterior interproximal ≥ PD with history of BOP). Only 6 participants had an experimental site with 7 mm pockets Number of participants: 270 individuals screened; 60 randomised and 51 finished study (24 test, 27 control) and results analysed (12-month evaluation)
Interventions	**Test group**: **application of 1 mg of minocycline HCl microspheres (MM) according to the instructions of the manufacturer (Arestin, OraPharma, Bridgewater, NJ) + SRP (at baseline and 6 months)** n = 30 allocated; and n = 24 analysed at 12 months (3 participants excluded due to inadequate experimental site after randomisation; 3 participants withdrawn due to having the tooth extracted, presenting with conflicting medical treatment and the last one due to failed appointments) **Control group: mechanical debridement (at baseline and 6 months)** n = 30 allocated; n = 27 analysed at 12 months (2 participants excluded due to inadequate experimental site after randomisation; 1 participant withdrawn due to having the tooth extracted) The adjacent site to the experimental/control site was also treatment according to randomisation (debridement + MM if adjacent site was assigned to the experimental group) or debridement only (if adjacent site was assigned to the control group) Participants underwent routine periodontal maintenance with full-mouth debridement and root planing of the inflamed pockets (provided by a dental student and revised by a faculty member). In order to ensure standardisation of the experimental sites, a single dental hygienist finished the root planing (< 5 min) and applied the MM in the test and adjacent sites
Outcomes	Two calibrated examiners without knowledge of the experimental group assignment Outcomes measured at 6- and 12-month follow-up Primary outcome: improvement in **CAL** (mm). CALs were calculated as recession plus PPDs.

	Secondary outcomes: **PPD** (mm), plaque (%), and **BoP** (%) and inflammatory markers (inflammation index ratio of interleukin (IL)-1b/IL-1 receptor antagonist (ra)) All the results were based on the examination of experimental site (1 site per participant) (not full-mouth results provided for any of the outcome measures) See Additional Table 1 for further details of indices used in trials to measure outcomes Clinical and inflammatory biomarker outcomes were presented at baseline, 6 months and 12 months and expressed as means ± SD or n (%). Change after 6 months and change after 12 months presented as means (means ± SD for the post-treatment change or n (%) of participants/sites experiencing reduction in the clinical parameter/biomarker) and ratios (the mixed model or generalised linear mixed models with autoregressive correlation for repeated measures were fitted from the same participants were fitted) Information regarding **adverse events** was also gathered and a subanalysis of number (%) of sites improving PPD and CAL (mm) in ≥ 2 mm presented
Notes	No sample calculation performed but 2 power analyses presented: 1. taking into account the largest SD of CAL change after 6 or 12 months in either treatment group-based data 2. the mean of SD of change in the four CAL change results (at 6 and 12 months in either group) The sample size available at the end of the study deemed an 80% power to detect a difference in the CAL post-treatment of: a) a minimum difference of 0.7-0.8 mm using a 2-sided Wilcoxon signed-rank test at a significance level of 0.025 (when using the first model of power analysis) b) a minimum difference of 0.6 mm post-treatment (when using the second model of power analysis) No information available regarding the way the data were entered and stored Funding source: the Dr. D.H. Reinhardt Scholar Program. Additional funding was provided by the late Dr. Mick Dragoo and his wife, Mary, and the Nebraska Dental Association Foundation CONSORT flow diagram recording reasons for loss to follow-up Details about randomisation and blinding provided Per-protocol analysis of data

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Randomisation provided by a coin toss. Randomisation stratified by sex and smoking status
Allocation concealment (selection bias)	Unclear risk	No information provided about the allocation concealment
Blinding of participants and personnel (performance bias) All outcomes	High risk	Single-blinded study - examiners only. Non-blinded therapist. Participants not blinded

Killeen 2016 (*Continued*)

Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Two calibrated and blinded-to-treatment examiners. Manual probe used No information about who analysed the data, masking and statistical programme used
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	CONSORT flow diagram fully explains the reasons for participant withdrawal/ drop-outs and the number of participants included in the analysis No ITT principle applied No full-mouth data provided
Selective reporting (reporting bias)	Low risk	Primary and secondary outcomes reported
Other bias	Unclear risk	Experimental sites determined from screening data. Sites assigned to a group at baseline

Lulic 2009

Methods	Design: double-blind design RCT Location: Switzerland Number of centres: 1 (Department of Periodontology and Fixed Prosthodontics of University of Berne) Recruitment period: during regular SPT visits, March 2005-July 2006
Participants	Adults (40-74 years old) in maintenance previously treated for chronic periodontitis and displaying residual PPD 20% of the participants were active smokers ($\leq$ 10 cigarettes/day) Presence of 24 remaining teeth during SPT and with $\geq$ 1 residual pocket with PPDs of $\geq$ 5 mm, with or without concomitant BoP Number of participants: 10 participants screened; 10 examined; 10 analysed
Interventions	**Group 1 (test): photodynamic therapy (PDT) + mechanical debridement** n = 5 participants with 39 residual pockets **Group 2 (control):mechanical debridement (with hand instruments) + placebo** n = 5 participants with 31 residual pockets It is not specified who performed the intervention On day 0, all participants were re-instructed in oral hygiene practices. Debridement of all sites with PPD $\geq$ 5 mm was performed under local anaesthesia using hand instruments. Additionally, all experimental sites were treated with the set-up for PDT including the dye/photosensitiser. In the randomly assigned control sites, the laser was set in a light mode that was no compatible with the photosensitiser. The procedure was repeated in the same manner after 1, 2, 7 and 14 days

Lulic 2009 (*Continued*)

Outcomes	A single examiner blind to intervention undertook the outcome assessment in this study Outcomes measured at day 0 (baseline) and at days 7 and 14 as well as at months 1, 3, 6 and 12 Primary outcome: PPD Secondary outcomes: CAL, BoP See Additional Table 1 for further details of indices used in trials to measure outcomes Plaque: PlI (Silness 1964) **Bleeding**: BoP **Probing depth**: PPD **Clinical attachment level:** CAL Clinical exam (PPD, CAL, BoP) performed with a calibrated periodontal probe (HAWE Click Probe(R), KerrHawe SA, Bioggio TI, Switzerland) with a point diameter of 0. 45 mm and standardised to a probing pressure of 0.25 N. Measurements performed at residual pockets
Notes	Sample size calculation Funding source: in part supported by HIELBOs Photodynamic Systems GmbH, Grieskirchen, Austria, and by the Clinical Reaserch Foundation (CRF) for the Promotion of Oral Health, Brienz BE, Switzerland No CONSORT flow diagram of participants No intra-examiner calibration data provided No ITT analysis of data Number of participants recruited based on sample calculation (if an effect of change in PPD of 1 mm is expected, assuming that the common SD is 0.5 mm)

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	The allocation to either the test or the control group was performed by random assignment using a randomisation table
Allocation concealment (selection bias)	Low risk	The determination of whether photosensitiser was applied or not was performed by a dental nurse, who was unaware of the study objectives, on the basis of the randomisation table
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Both the participant and the treatment provider were blinded through masked switching of the power setting of the laser
Blinding of outcome assessment (detection bias) All outcomes	Low risk	The examiner was blinded to treatment

Lulic 2009 (*Continued*)

Incomplete outcome data (attrition bias) All outcomes	Low risk	All participants completed the 12-month follow-up period
Selective reporting (reporting bias)	Unclear risk	Primary and secondary outcomes reported, but not at all time points assessed by the examiner as stated in the text. No clinical outcome data are reported for days 7, 14 and the first month
Other bias	Unclear risk	No intra-examiner calibration data provided although a calibrated periodontal probe (HAWE Click Probe, KerrHawe SA) was used The study authors declare no conflict of interest, although the study was in part supported by HIELBOs Photodynamic Systems GmbH

Preshaw 2005

Methods	Design: 2-arm, parallel-group, single-masked RCT Location: Newcastle, UK Number of centres: several (specialist clinic and unspecified number of referring general dental practices) Recruitment period: not specified
Participants	35 participants (15 men and 20 women) with moderate-severe chronic periodontitis
Interventions	**Group A: periodontal maintenance provided within the specialist clinic** n = 18 **Group B: periodontal maintenance provided by the referring general dentist under specialist prescription** n = 17 Interventions were matched between groups, although compliance of GDPs with specialist prescription was not monitored. Independent variable was person performing the intervention
Outcomes	A single, calibrated examiner blind to allocation undertook the outcome assessment in this study Outcomes measured at baseline, 6 and 12 months Primary outcome: PPD Secondary outcomes: plaque index and BoP See Additional Table 1 for further details of indices used in trials to measure outcomes Plaque: full-mouth plaque index (Silness 1964) **Bleeding**: full-mouth BoP **Probing depth**: full-mouth and test site PPDs Clinical exam (PPD, BoP) performed with a True Pressure Sensitive Probe (VivaCare) with 20 g probing force

Preshaw 2005 (*Continued*)

	Examination at months 0 (corresponding to 6 months after completion of non-surgical therapy), 6 and 12	
Notes	Compliance not evaluated for group B	
Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	"...subjects were randomly allocated to one of two groups" No mention of method of randomisation
Allocation concealment (selection bias)	Unclear risk	No mention of allocation concealment
Blinding of participants and personnel (performance bias) All outcomes	High risk	Participant blinding not mentioned and unlikely
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Clinical assessments - "all measurements were recorded by one calibrated individual (dental hygienist), who was blind to the group allocation." Radiographic assessments - unclear
Incomplete outcome data (attrition bias) All outcomes	Low risk	Group A - 1 dropout Group B - 2 dropouts Low number of participants lost to follow-up, similar between groups
Selective reporting (reporting bias)	Unclear risk	No compliance data for group B. No measures used to deal with truncated data (e.g. ITT analysis)
Other bias	Low risk	Nothing remarkable

Tonetti 2012

Methods	Design: 2-arm, parallel-group, multicentre RCT Location: Switzerland, Belgium, Germany, Greece and the Netherlands Number of centres: 5 (Periodontology, Centre for Dental, Oral, and Maxillofacial Medicine (Carolinum), Johann Wolfgang Goethe-University, Frankfurt; Department of Periodontology School of Dentistry, Athens; Private Practice, Munster; Private Practice, Den Haag; Private Practice, Langenthal) Recruitment period: 3 months Clinical exam performed with a manual pressure sensitive probe at 0.3 N (Brodontic(R) pressure sensitive device (Dentramar), equipped with a PCP - UNC 15 tip (Hu-Friedy)) at 6 sites per tooth. Values rounded up to the nearest mm
Participants	Adults (≥ 35 years old) undergoing regular SPT for ≥ 6 months and suffering from persistent or recurrent moderate to severe periodontitis. The areas in need of treatment did not undergo periodontal treatment in the previous 12 months Participants included had ≥ 4 teeth with residual PPD ≥ 5 mm and positive BoP Number of participants: 203 enrolled; 202 randomised; 181 examined and 200 analysed (12th month)
Interventions	**Group 1 (test)**: **doxycycline (SRD: Ligosan Slow Release®; Heraeus Kulzer GmbH, Germany) hyclate gel (equivalent to 14% doxycycline base) (single application) + debridement** ((**mechanical instrumentation; ultrasonic/sonic instruments (USI))** n = 100 allocated; n = 89 examined and n = 100 analysed at 12 months **Group 2 (control): mechanical debridement (USI)** n = 102 allocated; n = 92 examined and n = 100 analysed at 12 months "Two trained and calibrated investigators were available at each trial site. One investigator performed the actual treatment according to the randomisation scheme therapist. The second investigator was blind to treatment and acted as examiner." All sites presenting PPD ≥ 4 mm at 3, 6 and 9 months were retreated by SRP
Outcomes	A trained, calibrated and blinded investigator in each site acted as examiner Outcomes measured at 3-, 6- and 12-month follow-up Primary outcome: inter-group difference in absolute change of probing pocket depth (PPD) 3, 6 and 12 months after intervention Secondary endpoints: rate of healing (defined as the transition of sites with PPD ≥ 5 mm or 4 mm with BOP to non bleeding sites with PPD ≤ 4 mm), changes in PAL. Safety assessment was also performed See Additional Table 1 for further details of indices used in trials to measure outcomes Plaque: FMPS **Bleeding**: FMBS **Probing depth**: PPD, rate of healing (transitions of sites with PPD ≥ 5 mm or 4 mm with BOP to nonbleeding sites with ≤ 4 mm), ORs of rate of healing Manual pressure-sensitive probe used with a force of 0.3 N (Brodontic® pressure sensitive device, Dentramar, the Netherlands, equipped with a PCP-UNC 15 tip; Hu-Friedy, Leimen, Germany) **Probing attachment level**: changes in PAL All parameters recorded at 6 sites/tooth **Adverse events:** recorded following the MedDRA specifications **Treatment time** Need for re-treatment

	Number and frequency distribution of sites with different baseline probing depths in the test and control groups. Adjusted mean changes in PPD reduction between both groups by baseline pocket depth at the different follow-up appointments (at 3, 6 and 12 months). Adjusted OR for treatment difference in rate of healing of sites with PPD $\geq$ 5 mm or 4 mm + BOP to a category of non-BOP with PPD $\leq$ 4 mm. Adjusted OR and frequency of healing for treatment difference in pockets $\geq$ 5 mm at 3-, 6-, 12-month follow-up
Notes	Sample calculation: yes. Sample size adjusted after a planned interim analysis (2-stage sequential adaptive design) Data entered into the database using double data entry techniques Funding source: European Reserch Group on Periodontology (ERGOPerio) and Ivoclar Vivadent, Schaan, Liechtenstein CONSORT flow diagram recording reasons for loss to follow-up Details about randomisation and blinding provided ITT analysis of data

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Randomisation provided by computer-generated table
Allocation concealment (selection bias)	Low risk	Treatment allocation at baseline (administration of SRD test vs. no further intervention - control) was revealed to the therapist after completion of supragingival and subgingival ultrasonic/sonic instrumentation and was applied in test cases in pockets depths 4 mm or deeper
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Two trained and calibrated investigators were available at each trial site. One investigator (therapist) performed the treatment according to the randomisation scheme and the other one performed the exam and collection of data blinded to treatment
Blinding of outcome assessment (detection bias) All outcomes	Low risk	The examiner was blinded to treatment. Calibrated. Clinical examination performed at 3, 6, 12 months. Manual pressure-sensitive probe used
Incomplete outcome data (attrition bias) All outcomes	Low risk	Consort flow diagram fully explains the reasons for participant withdrawal/dropouts and the number of participants included in the analysis

Tonetti 2012 (*Continued*)

Selective reporting (reporting bias)	Low risk	Primary and secondary outcomes reported.
Other bias	Low risk	Nothing remarkable

BoP: bleeding on probing; **CAL**: clinical attachment level; **FMBS**: full-mouth bleeding scores; **FMPS**: full-mouth plaque scores; **GDP**: General Dental Practitioner; **ITT**: intention-to-treat; MM: 1mg of minocycline HCl microspheres (MM) according to the instructions of the manufacturer (Arestin, OraPharma, Bridgewater, NJ; SRP (scaling and root planing); **OR**: odds ratio; **PAL**: probing attachment level; **PD**: probing depth; **PDT**: photodynamic therapy; **PII**: Plaque Index; **PMT**: periodontal maintenance therapy; **PPD**: probing pocket depth; **RCT**: randomised controlled trial; **SD**: standard deviation; **SPT**: supportive periodontal therapy; **VAS**: visual analogue scale

Characteristics of excluded studies *[ordered by study ID]*

Study	Reason for exclusion
Aimetti 2004	RCT in which the intervention was given as part of active treatment phase. 3 months after mechanical treatment, participants who presented with pockets and bleeding on probing were enrolled in the study. This split-mouth study evaluates the effect of the application of tetracycline-loaded fibres after 12 months
Carvalho 2015	RCT where participants finished the periodontal active phase just 45 days prior to the initial examination and allocation of participants into two modalities of SPT
Clarkson 2013	This multicentre RCT included healthy periodontal participants with gingivitis and moderate periodontitis (basic periodontal examination score 0-3). The aim of the study was to assess the relative effectiveness of oral hygiene advice and periodontal instrumentation in a primary dental care setting
Correa 2016	Length of follow-up < 12 months
Costa 2012	Not an RCT. Retrospective cohort study
Da Cruz Andrade 2017	None of the primary outcomes specified in our review were measured in this study
De Carvalho 2010	Not an RCT. Participants were classified according to their level of compliance with past maintenance visits as complete compliance, irregular compliance or noncompliance
Doherty 1988	Not an RCT
Escribano 2010	Length of follow-up less than 12 months
Franke 2015	Not an RCT - questionnaire-based survey
Garcia 2011	Unclear if randomised. The authors refer to an earlier paper (Miley 2009) for further details. The same cohort was studied over a 1-year period. In Miley 2009 study, participants had previously completed

(*Continued*)

	questionnaires to determine their levels of oral supplementation to determine the group to which they would be assigned
Golub 2010	None of the primary outcomes specified in our review were measured in this study. This study evaluated the effectiveness of SDD versus placebo in the reduction of periodontal disease progression in 2 random groups of postmenopausal osteopenic women as adjunct to periodontal maintenance therapy over 2 years. Results are given in terms of serum bone biomarkers, dental radiographs, microbiological samples and gingival crevicular fluid. The authors refer to an earlier paper (Payne 2007) for further details about materials and methods
Goodson 2012	RCT that compared the effect of scaling and root planing in combination with an adjunctive therapy (systemic antibiotics, local antibiotics, and/or periodontal surgery), during periodontal active therapy phase in participants with moderate periodontitis. Different periodontal treatments were evaluated longitudinally at 3, 6, 12, 18 and 24 months. Intervention was given during periodontal active treatment phase and the participants were followed up for 24 months (that included a 12-month period of periodontal maintenance phase)
Guarnelli 2010	Not an RCT and insufficient follow-up period
Haffajee 2009	Length of follow-up < 12 months
Heasman 2001	Split-mouth RCT with risk of contamination
Hu 2015	Length of follow-up < 12 months
Hägi 2015	Length of follow-up < 12 months
Iwasaki 2016	Length of follow-up < 12 months
Jönsson 2009	Intervention was given during periodontal active treatment phase although the results were evaluated up to 12 months. This RCT evaluated the effect of an individually tailored oral health educational programme for oral hygiene self care vs. standard approach, during periodontal active therapy phase in patients with moderate-advanced chronic periodontitis. The effects of both programmes were evaluated at 3 and 12 months
Jönsson 2012	This study is an "interim report" from the previous RCT conducted by Jönsson 2009. In this article the aim was to compare cost-effectiveness of an individually tailored oral health educational programme based on cognitive behavioural strategies integrated in non surgical periodontal treatment compared with the standard treatment programme
Kargas 2015	Length of follow-up < 12 months
Krohn-Dale 2012	Split-mouth RCT evaluating laser versus scaling and root planing
Krück 2012	Study that compared, after 12 months, the effect of scaling and root planing in combination with and without adjunctive therapy (different irrigation solutions) during periodontal active therapy phase in patients with moderate chronic periodontitis. Participants never entered in a periodontal maintenance programme

(*Continued*)

McColl 2006	RCT evaluating minocycline only versus subgingival mechanical debridement. Participants had completed active treatment less than six months before the RCT began
Meinberg 2002	Not an RCT. Prospective cohort study
Moëne 2010	Length of follow-up < 12 months
Müller 2014	Split-mouth RCT evaluating air polishing with erythritol versus SRP - risk of contamination
Müller Campanile 2015	Length of follow-up < 12 months
Nakajima 2012	Length of follow-up < 12 months
Nakajima 2016	RCT without control group or SPT alone. Participants were randomly assigned to experimental groups to evaluate short-term and long-term clinical and microbiological effect of systemic Sitafloxacin or Azithromycin on active periodontal pockets during SPT
Nguyen 2015	Length of follow-up < 12 months
Paraskevas 2004	Both groups received an active intervention (antimicrobial mouthrinse)
Payne 2011	None of the outcomes specified in our review were measured in this RCT. This study evaluated the effectiveness of SDD versus placebo in the reduction of periodontal disease progression in two random groups of post-menopausal osteopenic women as an adjunct to periodontal maintenance therapy over 2 years. Results were measured in terms of serum biomarkers of bone formation and radiological alveolar bone height change. The authors refer to an earlier paper (Payne 2007) for further details about materials and methods
Ratka-Kruger 2012	Length of follow-up < 12 months
Reinhardt 2010	None of the primary outcomes specified in our review were measured in this RCT. It evaluated the effectiveness of SDD versus placebo in the reduction of periodontal disease progression in two random groups of postmenopausal osteopenic women as adjunct to periodontal maintenance therapy lasting 2 years. Results were measured in terms of gingival crevicular fluid (GCF) and its correlation with periodontal attachment and bone loss (radiography measurements). The authors refer to an earlier paper (Payne 2007) for further details about materials and methods
Renvert 2011	Not an RCT. This cohort study was conducted based on participants of the Swedish National Study on Aging and Care (SNAC). Four centres in Sweden were involved; the participants were invited by mail to take part in medical, psychological and dental examination
Rühling 2010	Length of follow-up < 12 months
Silva 2009	Not an RCT. Cross-sectional study
Simon 2015	Length of follow-up < 12 months

(*Continued*)

Slots 2012	Length of follow-up < 12 months
Teles 2008	The aim of this RCT was to determine the rate of attachment loss in periodontal healthy participants in a prevention regimen and the rate of disease progression in periodontitis participants enrolled in a maintenance programme
Tomasi 2011	Length of follow-up < 12 months
Wennström 2011	Length of follow-up < 12 months
Zhao 2015	Length of follow-up < 12 months

RCT: randomised controlled trial; **SDD**: subantimicrobial-dose of doxycycline; **SPT**: supportive periodontal therapy

Characteristics of studies awaiting assessment *[ordered by study ID]*

Bogren 2008a

Methods	Design: 4-arm, single-masked, multicentre RCT (2 arms reported) Location: Skövde and Göteborg, Sweden; and The Forsyth Institute, Massachusetts, USA Number of centres: 3 specialist clinics Recruitment period: January 2000-February 2002
Participants	128 adult periodontal maintenance patients (≥ 1 year enrolment in SPT programme)
Interventions	**Experimental group: mechanical debridement with adjunctive 8.8% doxycycline gel administered to all test sites at baseline only** n = 63 **Control group: mechanical debridement only** n = 65 Loss to follow-up for 2 participants at 12 months (1 test, 1 control) and 4 participants (3 test, 1 control) at end of study (3 years)
Outcomes	Calibrated examiners (reproducibility and inter-examiner correlation data reported) who were blinded to intervention allocation assessed clinical outcome data Outcomes measured at 3 months and 1, 2 and 3 years Primary outcome: PPD measurements (mm) and CAL (reported as relative attachment level gain) in mm **Plaque:** FMPS **BoP:** FMBS **Microbiological findings:** mean counts of a panel of 40 bacterial species
Notes	Study is part of a 4-arm RCT, but overall study design and outcome measures not clear from published data alone

Bogren 2008b

Methods	Design: 4-arm, single-masked, multicentre RCT (2 arms reported) Location: Skövde and Göteborg, Sweden; and The Forsyth Institute, Massachusetts, USA Number of centres: 3 specialist clinics Recruitment period: January 2000-February 2002
Participants	128 adult periodontal maintenance patients (≥ 1 year enrolment in SPT programme)
Interventions	**Experimental group: mechanical debridement with home use of a rotating-oscillating powered toothbrush (Oral-B, Gillette, Boston, MA, USA) and a triclosan/copolymer/fluoride-containing dentifrice (Colgate Total, Piscataway, NJ, USA)** n = 65 **Control group: mechanical debridement with soft, multi-tufted manual toothbrush and fluoride-containing dentifrice (Colgate Protection Caries)** n = 63 Loss to follow-up for 2 participants at 12 months (0 test, 2 control) and 4 participants (1 test, 3 control) at end of study (3 years)
Outcomes	Calibrated examiners (reproducibility and inter-examiner correlation data reported) who were blinded to intervention allocation assessed clinical outcome data Outcomes measured at 3 months and 1, 2 and 3 years Primary outcome: PPD measurements (mm) and CAL (reported as relative attachment level gain) in mm **Plaque:** FMPS **BoP:** FMBS **Change in % sites with PPD < 4 mm, 4 mm-5.5 mm or ≥ 6 mm** **Microbiological findings:** mean counts of a panel of 40 bacterial species
Notes	Study is part of a 4-arm RCT, but overall study design and outcome measures not clear from published data alone

CAL: clinical attachment level; **FMBS**: full-mouth bleeding scores; **FMPS**: full-mouth plaque scores; **RCT**: randomised controlled trial; **PPD**: probing pocket depth; **SPT**: supportive periodontal therapy

DATA AND ANALYSES

Comparison 1. Supportive periodontal therapy (SPT) performed by specialists versus non-specialist clinicians

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Bleeding on probing (%)	1		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
1.1 12 months	1	35	Mean Difference (IV, Fixed, 95% CI)	7.40 [-8.12, 22.92]
2 Full-mouth mean probing depths mm (final scores)	1		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
2.1 12 months	1	35	Mean Difference (IV, Fixed, 95% CI)	0.20 [-0.40, 0.80]

Comparison 2. Antimicrobial + mechanical debridement versus mechanical debridement

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Bleeding on probing (one site per patient)	1	50	Odds Ratio (M-H, Fixed, 95% CI)	0.45 [0.14, 1.52]
2 Clinical attachment level mm (change scores)	1	53	Mean Difference (IV, Fixed, 95% CI)	0.10 [-0.42, 0.62]
3 Pocket depth mm (final scores)	1		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
3.1 12 months	1	51	Mean Difference (IV, Fixed, 95% CI)	-0.10 [-0.59, 0.39]

Comparison 3. Photonics + mechanical debridement versus mechanical debridement

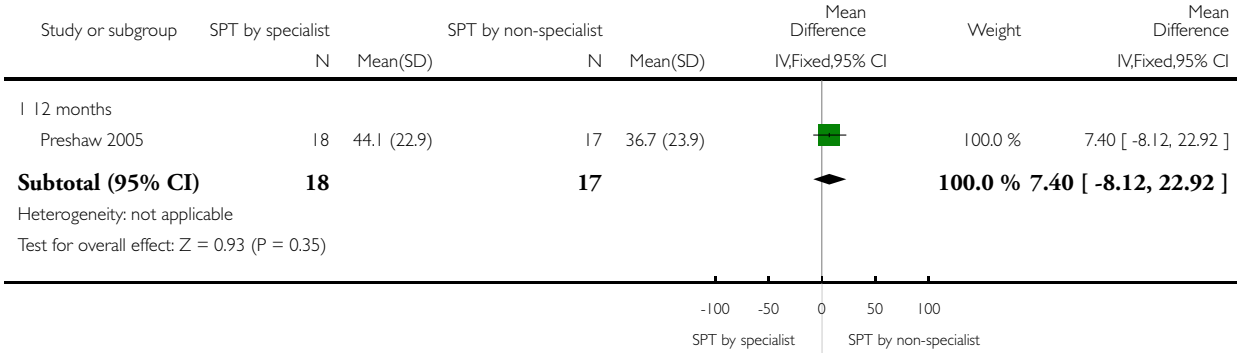
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Full-mouth mean clinical attachment level mm (final scores)	1		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
1.1 12 months	1	10	Mean Difference (IV, Fixed, 95% CI)	-0.97 [-3.51, 1.57]
2 Full-mouth mean probing depths mm (final scores)	1		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
2.1 12 months	1	10	Mean Difference (IV, Fixed, 95% CI)	-0.09 [-1.41, 1.23]

Analysis 1.1. Comparison 1 Supportive periodontal therapy (SPT) performed by specialists versus non-specialist clinicians, Outcome 1 Bleeding on probing (%).

Review: Supportive periodontal therapy (SPT) for maintaining the dentition in adults treated for periodontitis

Comparison: 1 Supportive periodontal therapy (SPT) performed by specialists versus non-specialist clinicians

Outcome: 1 Bleeding on probing (%)

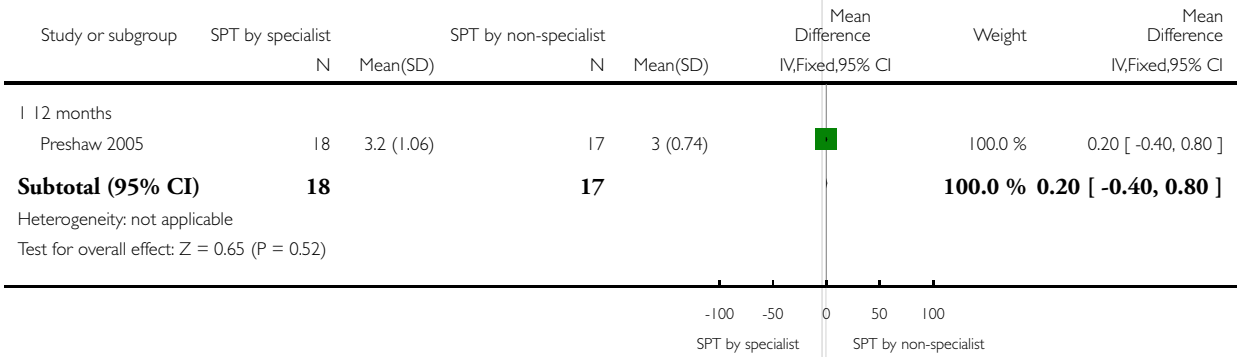


Analysis 1.2. Comparison 1 Supportive periodontal therapy (SPT) performed by specialists versus non-specialist clinicians, Outcome 2 Full-mouth mean probing depths mm (final scores).

Review: Supportive periodontal therapy (SPT) for maintaining the dentition in adults treated for periodontitis

Comparison: 1 Supportive periodontal therapy (SPT) performed by specialists versus non-specialist clinicians

Outcome: 2 Full-mouth mean probing depths mm (final scores)



Analysis 2.1. Comparison 2 Antimicrobial + mechanical debridement versus mechanical debridement, Outcome 1 Bleeding on probing (one site per patient).

Review: Supportive periodontal therapy (SPT) for maintaining the dentition in adults treated for periodontitis

Comparison: 2 Antimicrobial + mechanical debridement versus mechanical debridement

Outcome: 1 Bleeding on probing (one site per patient)

Study or subgroup	Experimental n/N	Control n/N	Odds Ratio M-H,Fixed,95% CI	Weight	Odds Ratio M-H,Fixed,95% CI
Killeen 2016	6/24	11/26		100.0 %	0.45 [0.14, 1.52]
Total (95% CI)	**24**	**26**		**100.0 %**	**0.45 [0.14, 1.52]**
Total events: 6 (Experimental), 11 (Control)					
Heterogeneity: not applicable					
Test for overall effect: Z = 1.28 (P = 0.20)					
Test for subgroup differences: Not applicable					

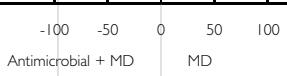
Analysis 2.2. Comparison 2 Antimicrobial + mechanical debridement versus mechanical debridement, Outcome 2 Clinical attachment level mm (change scores).

Review: Supportive periodontal therapy (SPT) for maintaining the dentition in adults treated for periodontitis

Comparison: 2 Antimicrobial + mechanical debridement versus mechanical debridement

Outcome: 2 Clinical attachment level mm (change scores)

Study or subgroup	Antimicrobial + MD N	Mean(SD)	MD N	Mean(SD)	Mean Difference IV,Fixed,95% CI	Weight	Mean Difference IV,Fixed,95% CI
Killeen 2016	24	4.7 (1)	29	4.6 (0.9)		100.0 %	0.10 [-0.42, 0.62]
Total (95% CI)	**24**		**29**			**100.0 %**	**0.10 [-0.42, 0.62]**
Heterogeneity: not applicable							
Test for overall effect: Z = 0.38 (P = 0.70)							
Test for subgroup differences: Not applicable							

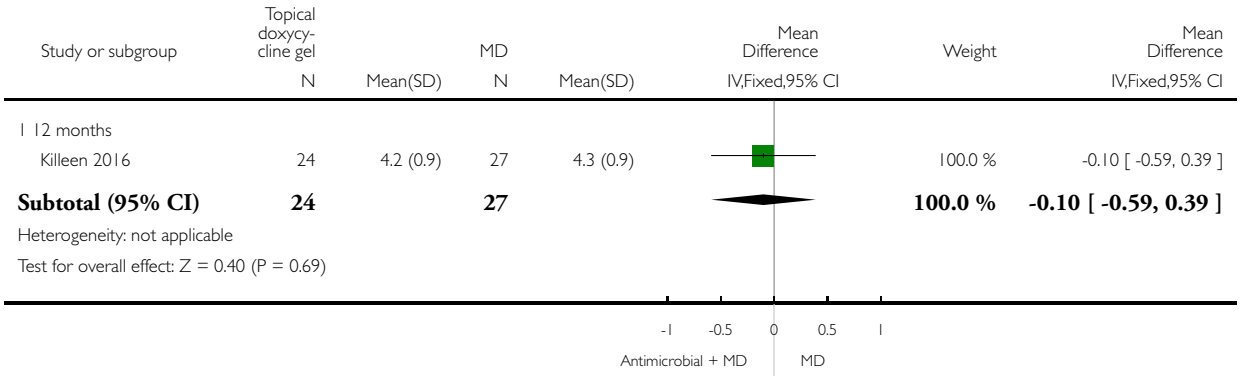


Analysis 2.3. Comparison 2 Antimicrobial + mechanical debridement versus mechanical debridement, Outcome 3 Pocket depth mm (final scores).

Review: Supportive periodontal therapy (SPT) for maintaining the dentition in adults treated for periodontitis

Comparison: 2 Antimicrobial + mechanical debridement versus mechanical debridement

Outcome: 3 Pocket depth mm (final scores)

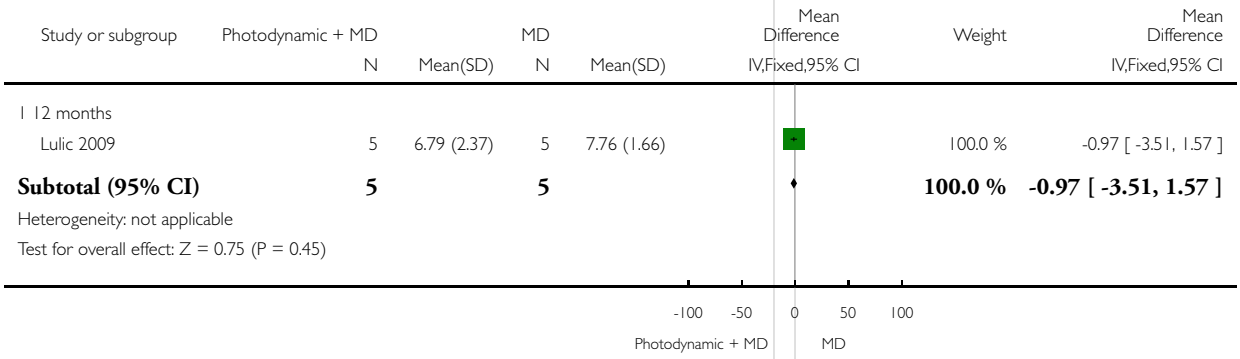


Analysis 3.1. Comparison 3 Photonics + mechanical debridement versus mechanical debridement, Outcome 1 Full-mouth mean clinical attachment level mm (final scores).

Review: Supportive periodontal therapy (SPT) for maintaining the dentition in adults treated for periodontitis

Comparison: 3 Photonics + mechanical debridement versus mechanical debridement

Outcome: 1 Full-mouth mean clinical attachment level mm (final scores)

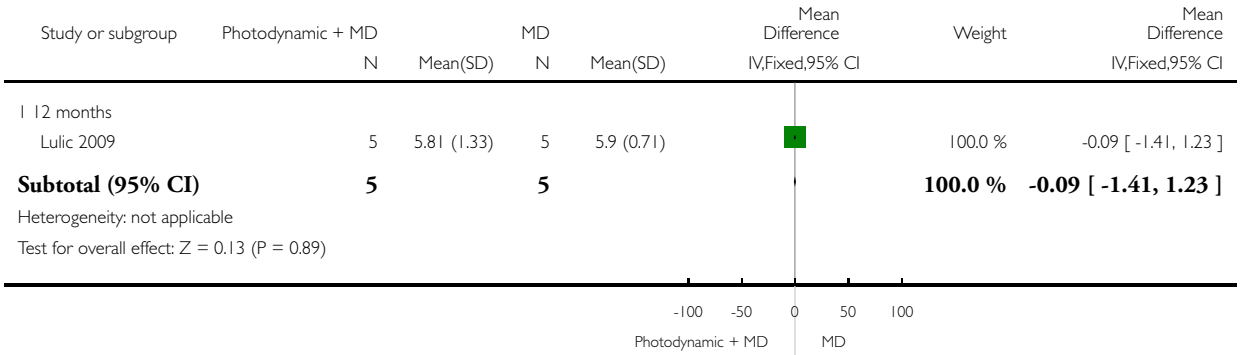


Analysis 3.2. Comparison 3 Photonics + mechanical debridement versus mechanical debridement, Outcome 2 Full-mouth mean probing depths mm (final scores).

Review: Supportive periodontal therapy (SPT) for maintaining the dentition in adults treated for periodontitis

Comparison: 3 Photonics + mechanical debridement versus mechanical debridement

Outcome: 2 Full-mouth mean probing depths mm (final scores)



APPENDICES

Appendix 1. Cochrane Oral Health's Trials Register search strategy

From February 2013, searches of the Cochrane Oral Health Trials Register for this review were undertaken using the Cochrane Register of Studies and the search strategy below:
#1 ((periodont* or gingiva* or gingivi*)) AND (INREGISTER)
#2 ((check-up* or "check up*" or inspect* or "dental exam*" or attend* or recall* or visit* or radiograph* or xray* or x-ray* or scaling or scale* or curettage or plane* or planing or debride* or instuct* or advise* or educat* or teach* or train* or "oral hygiene*" or "mouth care" or "dental care" or "mouth hygiene" or "dental hygiene" or "plaque control" or antibiotic or anti-biotic or antiseptic or anti-septic or antibacterial or anti-bacterial or antimicrobial or anti-microbial or tetracycline or chlorhexidine or doxycycline or metronidazole or minocycline or roxithromycin or moxifloxacin or ciprofloxacin)) AND (INREGISTER)
#3 ((SPT or "supportive periodontal therapy")) AND (INREGISTER)
#4 ((periodont* and maintain*)) AND (INREGISTER)
#5 ((periodont* and mainten*)) AND (INREGISTER)
#6 ((posttreat or post-treat or "preventive maintenance" or "supportive periodontal care" or "recall maintenance")) AND (INREGISTER)
#7 (#3 or #4 or #5 or #6) AND (INREGISTER)
#8 (#1 and #2 and #7) AND (INREGISTER)
Previous searches of the Oral Health Group Trials Register were undertaken using the Procite software and the search strategy below:
((periodont* or gingiva* or gingivi*) AND (check-up* or "check up*" or inspect* or "dental exam*" or attend* or recall* or visit* or radiograph* or xray* or x-ray* or scaling or scale* or curettage or plane* or planing or debride* or instuct* or advise* or educat* or teach* or train* or "oral hygiene*" or "mouth care" or "dental care" or "mouth hygiene" or "dental hygiene" or "plaque control" or antibiotic or anti-biotic or antiseptic or anti-septic or antibacterial or anti-bacterial or antimicrobial or anti-microbial or tetracycline

or chlorhexidine or doxycycline or metronidazole or minocycline or roxithromycin or moxifloxacin or ciprofloxacin) AND (SPT or "supportive periodontal therapy" or (periodont* and maintain*) or (periodont* and mainten*) or posttreat or post-treat or "preventive maintenance" or "supportive periodontal care" or "recall maintenance"))

Appendix 2. Cochrane Central Register of Controlled Trials (CENTRAL) search strategy

#1 MeSH descriptor Periodontal Diseases explode all trees
#2 periodonti* in All Text
#3 (gingiva* in All Text near/3 pocket* in All Text)
#4 (periodontal in All Text near/3 pocket* in All Text)
#5 "periodont* attachment loss" in All Text
#6 ((blood in All Text near/4 prob* in All Text) or (bleed* in All Text near/4 prob* in All Text))
#7 (#1 or #2 or #3 or #4 or #5 or #6)
#8 MeSH descriptor Diagnosis, Oral explode all trees
#9 ((dental in All Text near/4 check-up* in All Text) or (dental in All Text near/4 "check up*" in All Text) or (dental in All Text near/4 inspect* in All Text) or (dental in All Text near/4 exam* in All Text) or (dental in All Text near/4 attend* in All Text) or (dental in All Text near/4 recall* in All Text) or (dental in All Text near/4 visit* in All Text) or (dental in All Text near/4 diagnos* in All Text) or (oral in All Text near/4 check-up* in All Text) or (oral in All Text near/4 "check up*" in All Text) or (oral in All Text near/4 inspect* in All Text) or (oral in All Text near/4 exam* in All Text) or (oral in All Text near/4 attend* in All Text) or (oral in All Text near/4 recall* in All Text) or (oral in All Text near/4 diagnos* in All Text) or (tooth in All Text near/4 check-up* in All Text) or (tooth in All Text near/4 "check up*" in All Text) or (tooth in All Text near/4 inspect* in All Text) or (tooth in All Text near/4 exam* in All Text) or (tooth in All Text near/4 attend* in All Text) or (tooth in All Text near/4 recall* in All Text) or (tooth in All Text near/4 diagnos* in All Text) or (teeth in All Text near/4 check-up* in All Text) or (teeth in All Text near/4 "check up*" in All Text) or (teeth in All Text near/4 inspect* in All Text) or (teeth in All Text near/4 exam* in All Text) or (teeth in All Text near/4 attend* in All Text) or (teeth in All Text near/4 recall* in All Text) or (teeth in All Text near/4 diagnos* in All Text))
#10 ((dental in All Text or oral in All Text or teeth in All Text or tooth in All Text) and (radiograph* in All Text or x-ray in All Text or xray in All Text))
#11 MeSH descriptor Dental Prophylaxis explode all trees
#12 ((dental in All Text or oral in All Text or teeth in All Text or tooth in All Text or supragingival in All Text or subgingival in All Text) and (scaling in All Text or scale* in All Text or curettage in All Text))
#13 ("dental prophylaxis" in All Text or "oral prophylaxis" in All Text)
#14 (root* next plane* in All Text or root* next planing in All Text)
#15 periodontal next debridement* in All Text
#16 MeSH descriptor Oral hygiene explode all trees
#17 MeSH descriptor Health education, dental explode all trees
#18 ((health in All Text near/5 promot* in All Text) and (dental in All Text or teeth in All Text or mouth in All Text or periodont* in All Text or gingival in All Text or oral in All Text))
#19 ((instruct* in All Text or advis* in All Text or advice* in All Text or educat* in All Text or teach* in All Text or train* in All Text) and (dental in All Text or teeth in All Text or mouth in All Text or periodont* in All Text or gingival in All Text or oral in All Text))
#20 ("oral hygiene" in All Text or (mouth in All Text near/3 care in All Text) or (dental in All Text near/3 care in All Text) or (care in All Text near/3 teeth in All Text) or (mouth in All Text near/3 hygiene in All Text) or "plaque control*" in All Text)
#21 MeSH descriptor Anti-Infective Agents, Local explode all trees
#22 (antibiotic* in Title, Abstract or Keywords or anti-biotic* in Title, Abstract or Keywords or "anti biotic*" in Title, Abstract or Keywords or antiseptic* in Title, Abstract or Keywords or anti-septic* in Title, Abstract or Keywords or "anti septic*" in Title, Abstract or Keywords or antibacterical* in Title, Abstract or Keywords or anti-bacterial* in Title, Abstract or Keywords or "anti bacterial*" in Title, Abstract or Keywords or antimicrobial* in Title, Abstract or Keywords or anti-microbial* in Title, Abstract or Keywords or "anti microbial*" in Title, Abstract or Keywords)
#23 (tetracycline in All Text or chlorhexidine in All Text or doxycycline in All Text or metronidazole in All Text or minocycline in All Text or roxithromycin in All Text or moxifloxacin in All Text or ciprofloxacin in All Text)
#24 ((intraoral in All Text or intra-oral in All Text or extraoral in All Text or extra-oral in All Text) and (check-up* in All Text or "check up*" in All Text or inspect* in All Text or exam* in All Text or attend* in All Text or recall* in All Text or visit* in All Text or diagnos* in All Text))

#25 (#8 or #9 or #10 or #11 or #12 or #13 or #14 or #15 or #16 or #17 or #18 or #19 or #20 or #21 or #22 or #23 or #24)
#26 MeSH descriptor Dental care explode all trees
#27 SPT in Title, Abstract or Keywords
#28 ("periodontal maintenance" in All Text or "supportive periodontal therap*" in All Text or "preventive maintenance" in All Text or "supportive periodontal care" in All Text or "recall maintenance" in All Text)
#29 ((periodont* in All Text near/4 maintain* in All Text) or (periodont* in All Text near/4 maintenance in All Text) or (periodont* in All Text near/4 post-treat* in All Text) or (periodont* in All Text near/4 posttreat* in All Text) or (periodont* in All Text near/4 "post treat*" in All Text) or (periodont* in All Text near/4 prevent* in All Text))
#30 ((dentition in All Text near/4 maintain* in All Text) or (dentition in All Text near/4 maintenance in All Text) or (dentition in All Text near/4 post-treat* in All Text) or (dentition in All Text near/4 posttreat* in All Text) or (dentition in All Text near/4 "post treat*" in All Text) or (dentition in All Text near/4 prevent* in All Text))
#31 ((dental in Title, Abstract or Keywords near/4 maintain* in Title, Abstract or Keywords) or (dental in Title, Abstract or Keywords near/4 maintenance in Title, Abstract or Keywords) or (dental in Title, Abstract or Keywords near/4 post-treat* in Title, Abstract or Keywords) or (dental in Title, Abstract or Keywords near/4 posttreat* in Title, Abstract or Keywords) or (dental in Title, Abstract or Keywords near/4 "post treat*" in Title, Abstract or Keywords) or (dental in Title, Abstract or Keywords near/4 prevent* in Title, Abstract or Keywords))
#32 ((tooth in All Text near/4 maintain* in All Text) or (tooth in All Text near/4 maintenance in All Text) or (tooth in All Text near/4 post-treat* in All Text) or (tooth in All Text near/4 posttreat* in All Text) or (tooth in All Text near/4 "post treat*" in All Text) or (tooth in All Text near/4 prevent* in All Text))
#33 ((teeth in All Text near/4 maintain* in All Text) or (teeth in All Text near/4 maintenance in All Text) or (teeth in All Text near/4 post-treat* in All Text) or (teeth in All Text near/4 posttreat* in All Text) or (teeth in All Text near/4 "post treat*" in All Text) or (teeth in All Text near/4 prevent* in All Text))
#34 (#26 or #28 or #29 or #30 or #31 or #32 or #33)
#35 (#7 and #25 and #34)

Appendix 3. MEDLINE Ovid search strategy

1. exp Periodontal Diseases/
2. periodonti$.mp.
3. (gingiva$ adj3 pocket$).mp.
4. (periodontal adj3 pocket$).mp.
5. "periodont$ attachment loss".mp.
6. ((blood or bleed$) adj4 prob$).mp.
7. (periimplantitis or peri-implantitis or "peri implantitis").mp.
8. or/1-7
9. exp Oral Diagnosis/
10. ((dental or oral or tooth or teeth) adj3 (check-up$ or "check up$" or inspect$ or exam$ or attend$ or recall$ or visit$ or diagnos$)).mp.
11. ((intraoral or intra-oral or extraoral or extra-oral) adj4 (check-up$ or "check up$" or inspect$ or exam$ or attend$ or recall$ or visit$ or diagnos$)).mp.
12. ((dental or oral or teeth or tooth) adj3 (radiograph$ or x-ray or xray)).mp.
13. exp Dental Prophylaxis/
14. ((dental or oral or teeth or tooth or supragingival or subgingival) adj6 (scaling or scale$ or curettage)).mp.
15. ("dental prophylaxis" or "oral prophylaxis").mp.
16. (root adj (plane$ or planing)).mp.
17. (periodontal adj debridement$).mp.
18. exp Oral hygiene/
19. Health education, dental/
20. ((Health adj5 promot$) and (dental or teeth or mouth or periodont$ or gingival or oral)).mp.
21. ((instruct$ or advis$ or advice$ or educat$ or teach$ or train$) and (dental or teeth or mouth or periodont$ or gingival or oral)).mp.
22. ("oral hygiene" or (mouth adj3 care) or (dental adj3 care) or (care adj3 teeth) or (mouth adj3 hygiene) or "plaque control$").mp.
23. exp Anti-infective agents/

24. (antibiotic$ or anti-biotic$ or "anti biotic$" or antiseptic$ or anti-septic$ or "anti septic$" or antibacterical$ or anti-bacterial$ or "anti bacterial$" or antimicrobial$ or anti-microbial$ or "anti microbial$").mp.
25. (tetracycline or chlorhexidine or doxycycline or metronidazole or minocycline or roxithromycin or moxifloxacin or ciprofloxacin).mp.
26. or/9-25
27. Dental care/
28. SPT.ti,ab.
29. ((periodont$ or dentition or dental or tooth or teeth) adj4 (maintain$ or maintenance or post-treat$ or posttreat$ or "post treat$" or prevent$)).mp.
30. ("periodontal maintenance" or "supportive periodontal therap$" or "preventive maintenance" or "supportive periodontal care" or "recall maintenance").mp.
31. or/27-30
32. 8 and 26 and 31

This subject search was linked to the Cochrane Highly Sensitive Search Strategy (CHSSS) for identifying randomised trials in MEDLINE: sensitivity- maximising version (2008 revision) as referenced in Chapter 6.4.11.1 and detailed in box 6.4.c of *The Cochrane Handbook for Systematic Reviews of Interventions,* Version 5.1.0 [updated March 2011](Lefebvre 2011).

1. randomized controlled trial.pt.
2. controlled clinical trial.pt.
3. randomized.ab.
4. placebo.ab.
5. drug therapy.fs.
6. randomly.ab.
7. trial.ab.
8. groups.ab.
9. or/1-8
10. exp animals/ not humans.sh.
11. 9 not 10

Appendix 4. Embase Ovid search strategy

1. exp Periodontal Diseases/
2. periodonti$.mp.
3. (gingiva$ adj3 pocket$).mp.
4. (periodontal adj3 pocket$).mp.
5. "periodont$ attachment loss".mp.
6. ((blood or bleed$) adj4 prob$).mp.
7. or/1-6
8. exp Preventive Dentistry/
9. ((dental or oral or tooth or teeth) adj3 (check-up$ or "check up$" or inspect$ or exam$ or attend$ or recall$ or visit$ or diagnos$)).mp.
10. ((intraoral or intra-oral or extraoral or extra-oral) adj4 (check-up$ or "check up$" or inspect$ or exam$ or attend$ or recall$ or visit$ or diagnos$)).mp.
11. ((dental or oral or teeth or tooth) adj3 (radiograph$ or x-ray or xray)).mp.
12. exp Dental Prophylaxis/
13. ((dental or oral or teeth or tooth or supragingival or subgingival) adj6 (scaling or scale$ or curettage)).mp.
14. ("dental prophylaxis" or "oral prophylaxis").mp.
15. (root adj (plane$ or planing)).mp.
16. (periodontal adj debridement$).mp.
17. exp Oral hygiene/
18. Health education, dental/
19. ((Health adj5 promot$) and (dental or teeth or mouth or periodont$ or gingival or oral)).mp.
20. ((instruct$ or advis$ or advice$ or educat$ or teach$ or train$) and (dental or teeth or mouth or periodont$ or gingival or oral)).mp.
21. ("oral hygiene" or (mouth adj3 care) or (dental adj3 care) or (care adj3 teeth) or (mouth adj3 hygiene) or "plaque control$").mp.

22. exp Anti-infective agents/
23. (antibiotic$ or anti-biotic$ or "anti biotic$" or antiseptic$ or anti-septic$ or "anti septic$" or antibacterical$ or anti-bacterial$ or "anti bacterial$" or antimicrobial$ or anti-microbial$ or "anti microbial$").mp.
24. (tetracycline or chlorhexidine or doxycycline or metronidazole or minocycline or roxithromycin or moxifloxacin or ciprofloxacin).mp.
25. or/8-24
26. Dental care/
27. SPT.ti,ab.
28. ((periodont$ or dentition or dental or tooth or teeth) adj4 (maintain$ or maintenance or post-treat$ or posttreat$ or "post treat$" or prevent$)).mp.
29. ("periodontal maintenance" or "supportive periodontal therap$" or "preventive maintenance" or "supportive periodontal care" or "recall maintenance").mp.
30. or/26-29
31. 7 and 25 and 30

The above subject search was linked to adapted version of the Cochrane Embase Project filter for identifying RCTs in EMBASE Ovid (see http://www.cochranelibrary.com/help/central-creation-details.html for information):

1. Randomized controlled trial/
2. Controlled clinical study/
3. Random$.ti,ab.
4. randomization/
5. intermethod comparison/
6. placebo.ti,ab.
7. (compare or compared or comparison).ti.
8. ((evaluated or evaluate or evaluating or assessed or assess) and (compare or compared or comparing or comparison)).ab.
9. (open adj label).ti,ab.
10. ((double or single or doubly or singly) adj (blind or blinded or blindly)).ti,ab
11. double blind procedure/
12. parallel group$1.ti,ab.
13. (crossover or cross over).ti,ab.
14. ((assign$ or match or matched or allocation) adj5 (alternate or group$1 or intervention$1 or patient$1 or subject$1 or participant$1)).ti,ab.
15. (assigned or allocated).ti,ab.
16. (controlled adj7 (study or design or trial)).ti,ab.
17. (volunteer or volunteers).ti,ab.
18. trial.ti.
19. or/1-18
20. (exp animal/ or animal.hw. or nonhuman/) not (exp human/ or human cell/ or (human or humans).ti.)
21. 19 not 20

Appendix 5. US National Institutes of Health Trials Register (ClinicalTrials.gov) search strategy

Advanced search:
Condition: periodontitis
Intervention: maintenance
Condition: periodontitis
Intervention: supportive

Appendix 6. WHO International Clinical Trials Registry Platform search strategy

Advanced search:
Condition: periodontitis
Intervention: maintenance
Condition: periodontitis
Intervention: supportive

CONTRIBUTIONS OF AUTHORS

- Carolina Manresa: drafting of the protocol, search strategy design, search screening and study selection, correspondence with authors of papers if additional information required, data extraction and analysis, 'Risk of bias' and quality assessment, final review drafting
- Elena Sanz-Miralles: drafting of the protocol, search strategy design, search screening and study selection, data extraction and analysis, 'Risk of bias' and quality assessment, final review drafting
- Joshua A Twigg: study selection, 'Risk of bias' and quality assessment, data extraction and analysis, final review drafting
- Manuel Bravo: data analysis, final review drafting

DECLARATIONS OF INTEREST

- Carolina Manresa: none known
- Elena Sanz-Miralles: none known
- Joshua A Twigg: none known
- Manuel Bravo: none known

Through a poster competition, Carolina Manresa and Elena Sanz-Miralles were awarded a scholarship by SEPA to the course "Evidence Based Dentistry" (Prof. Ian Needleman, Madrid, 7 to 8 November 2008).

SOURCES OF SUPPORT

Internal sources

- No sources of support supplied

External sources

- National Institute for Health Research (NIHR), UK.

This project was supported by the NIHR, via Cochrane Infrastructure funding to Cochrane Oral Health. The views and opinions expressed therein are those of the authors and do not necessarily reflect those of the Systematic Reviews Programme, NIHR, NHS or the Department of Health.

- Cochrane Oral Health Global Alliance, Other.

The production of Cochrane Oral Health reviews has been supported financially by our Global Alliance since 2011 (ohg.cochrane.org/partnerships-alliances). Contributors over the past year have been: American Association of Paediatric Dentistry?, USA; British Association for the Study of Community Dentistry, UK; British Society of Paediatric Dentistry, UK; the Canadian Dental Hygienists Association, Canada; Centre for Dental Education and Research at All India Institute of Medical Sciences, India; National Center for Dental Hygiene Research & Practice, USA; New York University College of Dentistry, USA; NHS Education for Scotland, UK; Swiss Society of Endontology, Switzerland.

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

The protocol was published in 2011 and we have revised it substantially. We modified the title, rewrote the Background, focused the objective, refined the inclusion criteria, added an outcome (probing pocket depth), reduced the number of planned subgroup analyses and added a plan to conduct sensitivity analyses in future updates if there are sufficient data. We did not conduct the handsearching that we had originally planned.