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ORIGINAL ARTICLE

# A systematic review of medical interventions for oral submucous fibrosis and future research opportunities

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**Oral submucous fibrosis (OSF) is a chronic, insidious disease caused by areca nut use, and is associated with both significant morbidity (including pain and reduced oral opening) and an increased risk for malignancy. This systematic review explored and updated the current medical (i.e., non-surgical) interventions available for the management of OSF. Of the 27 published medical interventions, there were four randomized controlled trials. The overall quality of these randomized controlled studies was assessed using the GRADE approach and significant limitations that challenged the conclusions were found. However, this review was valuable in terms of identifying opportunities to provide recommendations for future research, in terms of the populations to research, the types of interventions needed, the types of outcomes to be measured, the study designs needed, and the infrastructure required to conduct studies. The next step is to initiate a pathway for a low-cost research plan leading to the development of a brief protocol for future clinical trials in this field, with an emphasis on conducting studies in regions of the world where OSF is prevalent.**

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**Keywords:** oral submucous fibrosis; systematic review; management; medical interventions; research

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## Background

Oral submucous fibrosis (OSF) is a chronic, insidious disease that is associated with significant functional morbidity and an increased risk for malignancy. It initially affects the lamina propria of the oral mucosa and as the disease progresses it involves the submucosa and the deeper tissues including muscles of the oral cavity with resulting loss of fibroelasticity. The clinical manifestations include blanching and stiffening of the oral mucosa leading to limitation in oral opening (Figure 1). The presence of fibrous bands in lips, cheeks and soft palate is a hallmark of the disease. The disease extends over time to include the oropharynx and the upper third of the esophagus. Oral submucous fibrosis predominantly affects South, South Asian and East Asian populations and is seen in India, Pakistan, Bangladesh, Nepal, Sri Lanka, southern parts of China, Taiwan, Melanesia and Micronesia and in the Pacific Islands. The disease is also reported among Asian migrant communities living in the Southern and Eastern Africa, parts of Europe, and in North America.

Oral submucous fibrosis was described by Schwartz in 1952 among five Indian females living in Kenya and he coined the term *atrophia idiopathica* (*trophica*) *mucosae oris*. Several other descriptive terms have been attributed; submucosal fibrosis of palate and pillars, diffuse oral submucous fibrosis, idiopathic scleroderma of the mouth, idiopathic palatal fibrosis, and sclerosing stomatitis. The etiology of the disease over the intervening years was thought to be multifactorial and several agents have been implicated, including the consumption of large amounts of chillies, nutritional deficiency, genetic predisposition, and auto-immune disease. Conclusive evidence now exists indicating that OSF is caused by areca nut, a masticatory substance used predominantly by peoples of South and SE Asian ethnicity, the surrounding geographical areas,

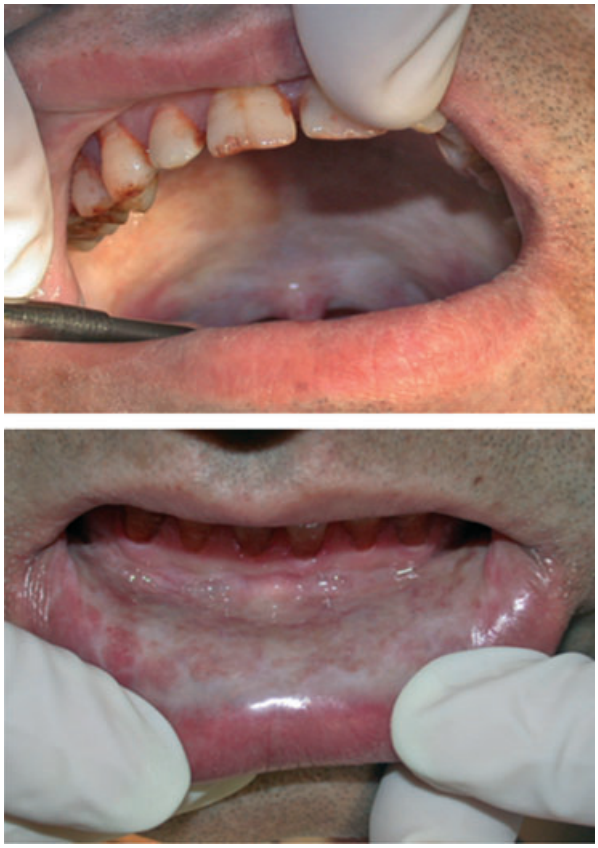

**Figure 1** Clinical photographs of a patient with moderate (Grade 2) oral submucous fibrosis (OSF). Inter-incisal opening was $<25$ mm. The lower lip demonstrated very little elasticity. Note blanching of tissues

and in the diaspora therefrom (Gupta and Warnakulasuriya, 2002; IARC, 2004). Several pathogenic mechanisms have been proposed, all based on the constituents of areca nut and genetic susceptibility to the disease (Rajalalitha and Vali, 2005; Tilakaratne *et al*, 2006). In essence, the disease could be described as primarily as a collagen metabolic disorder with changes observed in the extracellular matrix of the lamina propria and in the deeper mucosal tissues of the oral cavity because of both increased collagen synthesis and/or reduced collagen degradation. Epithelial changes are more likely to be secondary events.

Areca nut is the fourth most addictive substance in the world (Gupta and Warnakulasuriya, 2002), and is associated with a dependency syndrome (Winstock, 2002). Interventional programs have neither been adopted nor evaluated, unlike those for tobacco cessation. There is a significant variation in the prevalence of OSF in different communities, regions, and countries which is directly attributable to the patterns of areca nut use, age of onset of the habit and variations in product availability. Reports on the frequency of encountering OSF suggests that the disease has rapidly increased in India from an estimated 250 000 in 1980 to 2 million cases in 1993. The reasons for this rapid increase of the disease is believed to be attributed to the commercial marketing strategies of the pan masala industry which produces and markets freeze-dried preparations of areca nut, and the growth in uptake of this habit by young people (Gupta, 1999). The disease has also been identified in young children, with the report that a 4-year-old child had developed OSF in Canada (Hayes, 1985). Concurrently the pattern of areca nut use has also changed in other parts of south Asia. Examples are Thailand and Cambodia where areca nut use has been decreasing for several decades.

The malignant potential (for transformation to cancer) in OSF was described by Pindborg and Sirsat (1966). In a long-term follow-up study, the annual transformation rate was approximately 0.5% (Murti *et al*, 1985). OSF is now well recognized as a potentially malignant disorder of the oral cavity (Warnakulasuriya *et al*, 2007). Various classification systems for OSF based on clinical (Warnakulasuriya, 1987; Maher *et al*. 1996) and histopathological criteria (Pindborg & Sirsat, 1966) exist and reviewed by Ranganathan and Mishra (2005). There are no established markers to identify who may be predisposed to the disease nor to identify the risk of malignancy in affected individuals.

The treatment of OSF has been reviewed previously, including a narrative review by Jiang and Hu (2009) and a Cochrane review by Fedorowicz *et al* (2008). Jiang and Hu reviewed 'the role of drugs' in the treatment of OSF and included a total of 15 publications (involving 1224 patients), six of which were classed as randomized controlled trials, four as controlled clinical trials, and five as 'other experimental studies'. However, it is unclear how these papers were selected. Overall, the authors concluded that the 'effect' of various drug treatments was 'not satisfactory' and that the research in this field was insufficient.

The Cochrane review by Fedorowicz *et al* had the objective to 'assess the effectiveness of interventions in the management of pain and restricted jaw opening or movement occurring as a result of oral submucous fibrosis'. Only randomized controlled clinical trials of patients with trismus or restricted jaw movement and a confirmed diagnosis of OSF (by clinical examination and biopsy) were considered. Prespecified primary outcomes the reviewers set out to assess included (i) resumption of normal eating, chewing and speech, (ii) change or improvement in maximal jaw opening, measured as interincisal distance, (iii) improvement in range of jaw movement utilizing any validated assessment tool, and (iv) change in severity of oral/mucosal burning pain using any recognized validated pain scale. Secondary outcome measures included (i) postoperative discomfort or pain as a result of the intervention: patient assessed using any validated pain scale, (ii) length of hospital admission, (iii) quality of life (QOL) as assessed by any validated questionnaire, either generic or oral health specific and (iv) patient satisfaction assessed by validated questionnaire. In addition, healthcare costs and adverse effects were considered. After review of potentially eligible studies, only two studies involving 87 participants were included. The validity of both of the included studies was rated as having a high risk of bias,

i.e., plausible bias that seriously reduces confidence in the results. In terms of results regarding the primary outcome measures, both trials included measurements of the change of interincisal distance. However, incomplete reporting of results hampered the ability of reviewers to draw quantitative conclusions or to corroborate the reported scores. No data on resumption of normal eating, chewing and speech, or range of jaw movement were reported in either of the included studies. Changes in severity of oral/mucosal burning pain were not assessed using validated pain scales and the data were considered of insufficient quality to draw any conclusions. No data concerning any of the secondary outcome measures or costs, and no quantitative data regarding adverse events were reported in either of the studies. The authors concluded that the uncertain validity of a limited amount of available data could not support the view that any of the evaluated interventions were effective, beneficial, or safe. The authors also highlighted several concerns regarding the design and reporting of future trials, including recommendations for stratified randomization or minimization for treatment allocation established on baseline disease severity; rigorous blinding and improved methods of outcome assessments and the use of validated instruments to ascertain relevant outcomes; and reporting of trials in accordance with CONSORT standards (Moher *et al*, 2001). However, the authors acknowledged the challenges and difficulties faced by investigators in low and middle income countries in which OSF is prevalent.

Review of the natural history of OSF indicates that it is an insidious disorder which progresses with time. In clinical practice, there are a number of treatments for OSF, ranging from medical and surgical interventions, physical therapy, and of course habit control (i.e. cessation of areca nut use). Often a combination of strategies is used.

People with OSF characteristically complain of two problems: inability to open their mouths and function normally, and a burning sensation and intolerance to spicy foods that are often the mainstay of the Asian diet, leaving an individual disadvantaged both physically and psychologically. The severity and permutation of signs and symptoms of OSF are highly variable. Patients with mild early disease, marked by a strong inflammatory component, are less likely to have fibrosis and more prone to complain of burning. This is in marked contrast to those with severe advanced disease where irreversible fibrosis and loss in function predominates. The aims of treatment were therefore to reverse or ameliorate these signs and symptoms, stop disease progression, and in addition, to minimize the risk for malignant transformation. There is a dizzying array of reported medical interventions including dietary supplementation (vitamins, anti-oxidants), anti-inflammatory agents (principally corticosteroids) and proteolytic agents (such as hyaluronidase and placental extracts), and anti-cytokines. Such agents may be administered orally, topically or via submucosal injection. Surgical interventions are generally reserved for more advanced cases of OSF. Physical therapy may be used as a single modality or combined with other interventions.

## Objectives

Our objectives were:

a. To develop a systematic map of the current medical (i.e. non-surgical) interventions available for the management of OSF.
b. To update the evidence on the medical interventions used for the management of OSF.
c. To initiate a pathway for a low-cost research plan and lead to the development of a brief protocol for future clinical trials in this field, with an emphasis on conducting studies in regions of the world where OSF is prevalent.

## Review methodology

*Search strategy*

Detailed automated searches of PubMed were conducted using 'oral submucous fibrosis' as the key words up to September 2010. Additional searches of the Indian and Chinese literature were manually conducted. Chinese studies of interest were translated into English. Titles and abstracts of potentially relevant studies were selected. Afterwards, we ordered the full texts of these studies and evaluated whether they matched our inclusion criteria. The initial pool of primary studies and review articles were searched for references leading to additional papers missed in the automated searches. Articles that were case reports and statements of expert opinion were only included if they offered some possible insight.

*Inclusion criteria*

Interventional studies were then categorized by study type, including randomized controlled studies (RCTs), observational studies, or case series reports. To meet the criteria for RCTs, the study had to be prospective, include a control group and state that subjects were randomly assigned to the control and interventional groups. Remaining studies included uncontrolled (or poorly controlled) and/or non-randomized prospective study of a single intervention, retrospective studies comparing two or more different interventions, or observational studies. A case series constituted a retrospective series of cases based on a single intervention. Participants included individuals in any age group with a confirmed diagnosis, by clinical examination and/or biopsy of OSF. Types of interventions included habit intervention, surgical procedures, medical treatments (i.e. systemic, submucosal injection or topical agents, or physical therapy. The primary outcomes explored were the (i) objective change or improvement in maximal jaw opening, measured as the inter-incisal distance, (ii) subjective change in severity of oral/mucosal burning pain using any recognized validated pain scale, (iii) subjective change in quality of life using any questionnaire, whether validated or not,

and (iv) reduction in the rate of malignant transformation.

The secondary outcomes explored were any other objective or subjective changes, such as adverse events, and improvement of anemias and co-morbidities.

*Data collection and extraction*

Studies selected were evaluated independently by three reviewers (RK, TD and AM), and a data extraction table was developed for this purpose. For each study, the following data were captured: study period, publication language, country, study setting, number of subjects, study type, intervention types, design details (i.e. control group, randomization, blinding, and timing of visits), description of population (gender, age, diagnostic criteria for OSF, baseline disease severity, and habit profile), outcomes measured (subjective and objective), follow-up information, and details about statistical analyses.

*Data synthesis*

As a result of heterogeneity of the studies and missing data, we were not able to pool the data of the included RCTs and provided a narrative synthesis of the data.

*GRADING the overall quality of evidence*

The overall quality of evidence of RCTs for each outcome was assessed and reported using the GRADE approach (Guyatt *et al*, 2008), (Jaeschke *et al*, 2008), (Higgins, Green, 2009). For further information, please visit the http://www.gradeworkinggroup.org website. Factors that might reduce the quality of evidence were assessed, including: (i) study limitations, (ii) inconsistency, (iii) indirectness, (iv) imprecision, and others such as publication bias.

*Developing recommendations*

The quality of evidence for the questions was presented and discussed in the consensus group. The balance between risk and benefits, necessary cost and resources and patients' views and local contexts has been taken into consideration. The final recommendations were graded from strong or weak based on the judgment of all participating experts.

## Results

Fifty publications were included in the pool of investigations on the treatment of OSF, of which 23 were surgical in focus (and will be reported elsewhere by our group). Of the remaining studies, 22 were medical, three were medical/surgical, one was medical/physical, and one was medical/surgical/physical. The earliest study was reported in 1980 from India, and approximately half were undertaken after the year 2000. Three were reported in Chinese and the rest in English. Of these 27 studies, about half were conducted in India, about a third in Taiwan/China, a small number in other South Asian countries, and two among immigrants living abroad (one each in the UK and USA). All of the reported investigations were hospital/institution based and none were conducted in community settings.

In most of the 27 investigations, the diagnosis of OSF was based on the classic clinical presentation. Histopathology was used to confirm diagnosis in 12 of the investigations. Enrolled populations had a wide spectrum of OSF (i.e. from early to advanced), and yet stratification of the study group by OSF stage/severity rating was defined at baseline in only approximately half of the studies, most of these by reporting baseline mouth opening, although some studies grouped subjects by range of opening (Ariyawardana *et al*, 2005), (Maher *et al*, 1997) and (Lai *et al*, 1995), or by using various rating scales (Khanna and Andrade, 1995), (Gupta *et al*, 1992), (Talsania *et al*, 2009) and (Singh *et al*, 2010).

Baseline demographic information, such as age and gender, was reported in 60% of studies. Baseline patterns of areca nut use were reported in 30% of investigations, and those of alcohol and/or tobacco were reported in 22%. Baseline assessment of nutritional or dietary habits was reported in a single study (Tai *et al*, 2001), and laboratory assessment of hematologic status was made in 30% of studies.

Only four studies (Rajendran *et al*, 2006; Kumar *et al*, 2007; Jirge *et al*, 2008; and Cox and Zoellner, 2009) met our criteria for an RCT [including the two (Rajendran *et al*, 2006) and (Kumar *et al*, 2007) previously reported in the Cochrane review], and all were single center studies. There was one other prospective controlled study that lacked randomization (Lin and Lin, 2007). The rest were rated as observational or retrospective studies.

Tables 1 and 2 highlight the different interventions and how the therapies are alleged to work. There were no studies that looked at the effect of habit control alone as the primary endpoint, i.e. cessation of areca nut habits. The methodology of 14 studies included the advice to quit the habit, although only two of these described specific measures for cessation. In these studies, subjects were given a dental cleaning at baseline to remove staining and then re-examined at follow-up visits for any new staining (Ariyawardana *et al*, 2005 and Kumar *et al*, 2007). No serum markers for metabolites of areca nut were utilized.

A total of 15 studies used a single agent, and the rest studied combinations of agents. A total of 22 studies included the use of nutrients, micronutrients and/or anti-oxidants, 21 studies included the use of immunomodulatory agents that reduced the inflammatory component, principally injected corticosteroids (16 studies); 19 studies included the use of proteolytic enzymes to reduce fibrosis of which seven used hyaluronidase; and four studies included agents to promote blood flow. Agents were delivered orally for systemic absorption, intra-lesionally, or topically.

Outcome measures reported in these studies were highly variable both in the type and the manner in which they were measured. In terms of objective measures, mouth opening (generally measured as inter-incisal opening) was the most frequently measured outcome across all studies. Although the level of reliability (e.g.

**Table 1** Summary of studies including physical therapy

| *Group* | *Rationale* | *Examples of interventions* | *Example references* | |
|---|---|---|---|---|
| Physical therapy | Modify tissue remodeling through promotion of physical movements and localized heat | Physiotherapy | Physical exercise regimen (including postsurgery) | (Lai *et al*, 1995), (Cox and Zoellner, 2009) |
| | | | Splints or other devices (including postsurgery) | (Patil and Parkhedkar, 2009), (Nayak *et al*, 2009), (Le *et al*, 1996), (Huang *et al*, 2008) |
| | | | Microwave diathermy | (Gupta *et al*, 1980), (Gupta *et al*, 1992) (Chen 2006) |

validation of measurements) was not clearly defined. Other objective measures included changes in tongue movement (i.e. ability to protrude), degree of suppleness of the tissues, amount of blanching of the mucosa, presence of ulceration/vesicle formation, and amount of dorsal tongue papillation, although the methodology for measuring these other objective outcomes was poorly defined and of questionable reliability. In terms of subjective measures, oral burning/pain was the most consistently measured subjective outcome, although very few studies reported using validated pain assessment instruments, such as a visual analog pain rating scale. Other subjective measures included change in taste, oral dryness, and ability to chew, swallow, or speak. None of the studies used validated instruments evaluating quality of life of subjects with OSF nor could we find any such instruments in the published literature.

A total of 22 investigations did not specify whether or not subjects completed a given treatment regimen. Of the remaining studies, 17 reported >75% of the subjects completed the study regimen. Follow-up of subjects after treatment was highly variable, with only 19 studies reporting follow-up beyond 1 year.

*Randomized controlled studies*

There was one RCT evaluating the effectiveness of physical therapy (Cox and Zoellner, 2009) and three RCTs evaluating the effectiveness of medical interventions: pentoxifylline (Rajendran *et al*, 2006), lycopene (Kumar *et al*, 2007) and levamisole with anti-oxidants (Jirge *et al*, 2008). Evaluation by the working group of the published data from these four RCTs using the GRADE criteria identified significant limitations with each report and challenged the conclusions reached by the authors (Table 3). However, we narratively report the information that the trialists reported but advice caution in interpreting the results as there was not enough information available to extract necessary data to re-analyze the results and verify the conclusions reached.

Rajendran *et al*, 2006 divided the 29 participants into two groups that took either oral pentoxifylline or multivitamins. All those enrolled completed the 7-month study period. The authors reported statistically significant improvements in the oral pentoxifylline group ($n = 14$) compared with controls with respect to objective criteria (mouth opening, tongue protrusion and relief from circum-oral fibrotic bands) and subjective criteria (intolerance to spices, burning sensations, tinnitus, difficulty in swallowing, and difficulty in speech).

Kumar *et al*, 2007 recruited 83 participants who were divided between study groups that received either oral lycopene ($n = 21$; group A), oral lycopene with intralesional corticosteroids ($n = 19$; group B) or an oral placebo ($n = 18$; group C). The 2-month intervention period was completed by 58 people. Objective measurement of mouth opening was reported to be significantly improved with an average increase of 3.4 mm, 4.6 mm, and 0 mm for groups A, B, and C, respectively. The increases were maintained at 3 and 6-months review. All patients who took lycopene reported relief from burning sensations within 2 weeks, whereas only one patient from the placebo group reported a similar improvement.

The 45 participants reported by Jirge *et al*, 2008 were divided equally between three study groups: oral levamisole (group I), an oral antioxidant [ANTOXID – containing beta carotene, selenium oxide, zinc sulfate, manganese and copper] (group II), or oral levamisole with antioxidant (group III). On conclusion of the intervention period (approximately 15 weeks), there was improvement of mouth opening of 7.1%, 6.7%, and 8.0% in groups I, II, and III, respectively. These gains were maintained on further evaluation 2 months later. There was also a significant reduction in burning sensations in all study groups.

Cox and Zoellner, 2009 enrolled 54 Nepali subjects into three groups: physiotherapy, injections with combination hyaluronidase/steroids, and a control group. After 4 months, subjective and objective measures were compared with baseline. The physiotherapy group showed a significant increase in opening but had no superior effect on subjective measures.

Re-analysis by the working group of the published data from these four RCTs using the GRADE criteria identified significant limitations with each report and challenged the conclusions reached by the authors (Table 3).

## Future studies

The review team, echoing the sentiments of other reviewers, appreciates the opportunity and importance to offer suggestions and recommendations for future research. Clinical research methodology has evolved rapidly in some parts of the world, yet elsewhere there is neither the experience, nor the necessary infrastructure,

**Table 2** Summary of studies including medical therapy

| *Group* | *Rationale* | *Examples of interventions* | | | *Example references* |
|---|---|---|---|---|---|
| Nutrients, micronutrients and anti-oxidants | Correct deficiency states and promote normal cellular processes present in health that help to protect against adverse events including carcinogenesis | Systemic | Vitamin A (chewable tablets also give some topical application) | | (Borle and Borle, 1991), (Kumar *et al*, 1991) |
| | | | Vitamin A and vitamin B complex | | (Khanna and Andrade, 1995) |
| | | | Vitamin B complex | | (Lai *et al*, 1995) |
| | | | Vitamin B complex (with iodine injection) | | (Gupta *et al*, 1992) |
| | | | Vitamins A, B complex, C, D and E plus minerals iron, copper, zinc, magnesium and others | | (Maher *et al*, 1997) |
| | | | Ferrous fumarate | | (Borle and Borle, 1991) |
| | | | Zinc | | (Kumar *et al*, 1991) |
| | | | Antioxidants ($\beta$-carotene, vitamins A, C and E, zinc, copper, manganese and selenium) | | (Jirge *et al*, 2008) |
| | | | Glucosidorum tripterygii totorum, vitamins A and E, nicotinic acid | | (Liu *et al*, 1999) |
| | | | Tea pigment, vitamins A, B complex, D and E | | (Li and Tang, 1998) |
| | | | Lycopene | | (Kumar *et al*, 2007) |
| | | | Placental extract | | (Kakar *et al*, 1985), (Gupta and Sharma, 1988), (Katharia *et al*, 1992), (Rananjaneyulu and Rao, 1980), (Gupta *et al*, 1992) |
| Biogenic stimulation | Homograft stimulates favorable metabolic processes that promote non-fibrotic tissue regeneration | Intralesional injections | Placental extract | | (Kakar *et al*, 1985), (Gupta and Sharma, 1988), (Katharia *et al*, 1992), (Rananjaneyulu and Rao, 1980), (Gupta *et al*, 1992) |
| Proteolytic enzymes | Proteolytic enzymes breakdown the inappropriate connective tissue fibrosis | Intralesional injections | Papain (cysteine protease) with keratolytic action of urea: | | Gupta *et al* (1992) |
| | | | Collagenase | | (Chen and Lin, 1986), (Lin and Lin, 2007) |
| | | | Hyaluronidase | | (Kakar *et al*, 1985), (Gupta and Sharma, 1988), (Borle and Borle, 1991), (Lai *et al*, 1995), (Cox and Zoellner, 2009), (Singh *et al*, 2010) |
| | | | Chymotrypsin | | (Gupta and Sharma, 1988) |
| Immune modulation | Immune modulation that diminishes pro-fibrotic inflammation and enhances pro-fibrolytic immune-mediated pathways | Topical | Corticosteroid | Betamethasone | (Borle and Borle, 1991) |
| | | | | Triamcinolone acetonide | (Lai *et al*, 1995) |
| | | Intralesional injections | Corticosteroid | Dexamethasone | (Kakar *et al*, 1985), (Gupta and Sharma, 1988), (Borle and Borle, 1991), (Lai *et al*, 1995), (Liu *et al*, 1999) |
| | | | | Triamcinolone diacetate | (Lin and Lin, 2007), (Borle and Borle, 1991), (Khanna and Andrade, 1995), (Chen and Lin, 1986), (Singh *et al*, 2010) |
| | | | | Methylprednisolone | (Ariyawardana *et al*, 2005) |
| | | | | Betamethasone | (Kumar *et al*, 2007) |
| | | | | Hydrocortisone | (Cox and Zoellner, 2009), (Kumar *et al*, 1991), (Singh *et al*, 2010) |
| | | | Other | Interferon gamma (IFN-$\gamma$) | (Haque *et al*, 2001) |
| | | Systemic | Levamisole | | (Jirge *et al*, 2008) |
| | | | Immune milk from cows immunized with multiple human intestinal bacteria | | (Tai *et al*, 2001) |
| Promotion of blood flow | Promote blood flow to ischemic tissues via multiple mechanisms including vasodilatation and mild anti-coagulant effects with other biological actions including immunomodulation and anti-oxidant functions | Systemic | Pentoxifylline | | (Rajendran *et al*, 2006) |
| | | | Nylidrin hydrochloride | | (Sharma *et al*, 1987) |
| | | | Buflomedial hydrochloride | | (Lai *et al*, 1995), |
| | | | Danxuan Koukang (DXKK) | | (Tan *et al*, 2006) |

**Table 3** GRADE summary of randomized controlled studies

*Question: Should oral lycopene vs placebo be used for oral submucous fibrosis? (Kumar et al, 2007)*

| *Quality assessment of study* | | | | | | | *Summary of findings* | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | | *No. patients* | | *Effect* | | | |
| *No. studies* | *Design* | *Limitations* | *Inconsistency* | *Indirectness* | *Imprecision* | *Other considerations* | *Oral lycopene* | *Placebo* | *Relative (95% CI)* | *Absolute* | *Quality* | *Importance* |
| Clinical assessment of maximum opening (follow-up 2 months; measured with: interincisal distance (mm); better indicated by higher values) | | | | | | | | | | | | |
| 1 | Randomized trials | Very serious[a] | No serious inconsistency | No serious indirectness | Serious[b] | None | 21 | 18 | – | MD 1.15 higher (4.42 lower to 6.72 higher) | ⊕OOO Very low | Critical |
| Burning sensation (follow-up 2 months; subjective reporting by the patients) | | | | | | | | | | | | |
| 1 | Randomized trials | Very serious[a] | No serious inconsistency | No serious indirectness | Serious[b] | None | 1/21 (4.8%)[c] | 17/18 (94.4%)<br>94.4%[d] | RR 0.05 (0.01 to 0.34) | 897 fewer per 1000 (from 623 fewer to 935 fewer)<br>897 fewer per 1000 (from 623 fewer to 935 fewer) | ⊕OOO Very low | Important |

[a]The method of randomization was not clear. It was not blinded. It was not clear whether the allocation was concealed. The study has 30% dropout.
[b]The sample size was very small. The participants were first 83 patients and a number were lost to follow-up and only 58 continued to participate in the trial.
[c]The authors report that in the lycopene group and the lycopene with betamethasone group, only one patient had still burning sensation. It was not clear whether the patients was from the lycopene or the lycopene with betamethasone group, therefore, we assumed the worse case scenario for this comparison and put 1 event for the lycopene group.
[d]This is derived from the mean baseline risk in the control group of this study and assumes that there is a high baseline risk (94.4) that patients with oral submucous fibrosis would have burning sensation.

*Question: Should oral lycopene vs oral lycopene and betamethasone be used for oral submucous fibrosis? (Kumar et al, 2007)*

| *Quality assessment of study* | | | | | | | *Summary of findings* | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | | *No. patients* | | *Effect* | | | |
| *No. studies* | *Design* | *Limitations* | *Inconsistency* | *Indirectness* | *Imprecision* | *Other considerations* | *Oral lycopene* | *Oral lycopene and betamethasone* | *Relative (95% CI)* | *Absolute* | *Quality* | *Importance* |
| Clinical assessment of maximum opening (follow-up 2 months; measured with: interincisal distance (mm); better indicated by higher values) | | | | | | | | | | | | |
| 1 | Randomized trials | Very serious[a] | No serious inconsistency | No serious indirectness | Serious[b] | None | 21 | 19 | – | MD 6.35 higher (1.04 to 11.66 higher) | ⊕OOO Very low | Critical |
| Burning sensation (follow-up 2 months; subjective reporting by the patients) | | | | | | | | | | | | |
| 1 | Randomized trials | Very serious[a] | No serious inconsistency | No serious indirectness | Serious[b] | None | 0/21 (0%)[c] | 0/19 (0%) | Not estimable[d] | 0 fewer per 1000 (from 0 fewer to 0 fewer) | ⊕OOO Very low | Important |

[a]The method of randomization was not clear. It was not blinded. It was not clear whether the allocation was concealed. The study has 30% dropout.
[b]The sample size was very small. The participants were first 83 patients and a number were lost to follow-up and only 58 continued to participate in the trial.
[c]The authors report that in the lycopene group and the lycopene with betamethasone group, only one patients had still burning sensation. It was not clear whether the patients were from the lycopene or the lycopene with betamethasone group, therefore, we did not put any data in this comparison.
[d]Both groups had burning sensation before the treatment and this disappeared after the treatment.

**Table 3** (Continued)

*Question: Should oral lycopene and betamethasone vs placebo be used for oral submucous fibrosis? (Kumar et al, 2007)*

| *Quality assessment of study* | | | | | | | *Summary of findings* | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | | *No. patients* | | *Effect* | | | |
| *No. studies* | *Design* | *Limitations* | *Inconsistency* | *Indirectness* | *Imprecision* | *Other considerations* | *Oral lycopene and betamethasone* | *Placebo* | *Relative (95% CI)* | *Absolute* | *Quality* | *Importance* |
| Clinical assessment of maximum opening (follow-up 2 months; measured with: interincisal distance (mm); better indicated by higher values) | | | | | | | | | | | | |
| 1 | Randomized trials | Very serious[a] | No serious inconsistency | No serious indirectness | Serious[b] | None | 19 | 18 | – | MD 5.20 lower (9.85 to 0.55 lower) | ⊕OOO Very low | Critical |
| Burning sensation (follow-up 2 months; subjective reporting by the patients) | | | | | | | | | | | | |
| 1 | Randomized trials | Very serious[a] | No serious inconsistency | No serious indirectness | Serious[b] | None | 1/19 (5.3%)[c] | 17/18 (94.4%) 94.4%[d] | RR 0.06 (0.01 to 0.38) | 888 fewer per 1000 (from 586 fewer to 935 fewer) 887 fewer per 1000 (from 585 fewer to 935 fewer) | ⊕OOO Very low | Important |

[a]The method of randomization was not clear. It was not blinded. It was not clear whether the allocation was concealed. The study has 30% dropout.
[b]The sample size was very small. The participants were first 83 patients and a number were lost to follow-up and only 58 continued to participate in the trial.
[c]The authors report that in the lycopene group and the lycopene with betamethasone group, only one patient had still burning sensation. It was not clear whether the patients were from the lycopene or the lycopene with betamethasone group, therefore, we assumed the worse case scenario for this comparison and put 1 event for the lycopene + betamethasone group.
[d]This is derived from the mean baseline risk in the control group of this study and assumes that there is a high baseline risk (94.4) that patients with oral submucous fibrosis would have burning sensation.

*Question: Should levamisole vs antioxidant (multivitamin) be used for oral submucous fibrosis? (Jirge et al, 2008)*

| *Quality assessment of study* | | | | | | | *Summary of findings* | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | | *No. patients* | | *Effect* | | | |
| *No. studies* | *Design* | *Limitations* | *Inconsistency* | *Indirectness* | *Imprecision* | *Other considerations* | *Levamisole* | *Antioxidant (multivitamin)* | *Relative (95% CI)* | *Absolute* | *Quality* | *Importance* |
| Clinical assessment of maximal opening (changes in interincisal distance) end of the treatment (follow-up 6 weeks[a]; measured with: cm; better indicated by higher values) | | | | | | | | | | | | |
| 1 | Randomized trials | Very serious[b] | No serious inconsistency | No serious indirectness | Serious[c] | None | 15 | 15 | – | MD 0 higher (0.11 to 0.11 higher) | ⊕OOO Very low | Critical |
| Clinical assessment of maximal opening (changes in interincisal distance) after 60 days follow-up (follow-up 60 days; measured with: cm; better indicated by higher values) | | | | | | | | | | | | |
| 1 | Randomized trials | Very serious[b] | No serious inconsistency | No serious indirectness | Serious[c] | None | 15 | 15 | – | Mean 0.10 higher (0.03 to 0.17 higher) | ⊕OOO Very low | Critical |
| Burning sensation (follow-up 6 weeks[a]; measured with: VAS scale; better indicated by lower values) | | | | | | | | | | | | |
| 1 | Randomized trials | Very serious[b] | No serious inconsistency | No serious indirectness | Serious[c] | None | 15 | 15 | – | Mean 9.10 lower (16.23 to 1.9 lower) | ⊕OOO Very low | Important |

[a]Six weeks was the treatment (5th visit after starting the treatment) and 60 days follow up with two visits each 30 days (7th visit).
[b]No clear description of methods of randomization, concealment of allocation or blinding.
[c]The sample size was small and included only 45 patients.

**Table 3** (Continued)

*Question: Should pentoxifylline and local heat therapy vs multivitamin capsule and local heat therapy be used for oral submucous fibrosis? (Rajendran et al, 2006)*

| *Quality assessment of study* | | | | | | | *Summary of findings* | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | | *No. patients* | | *Effect* | | | |
| *No. studies* | *Design* | *Limitations* | *Inconsistency* | *Indirectness* | *Imprecision* | *Other considerations* | *Pentoxifylline and local heat therapy* | *Multivitamin capsule and local heat therapy* | *Relative (95% CI)* | *Absolute* | *Quality* | *Importance* |
| Clinical assessment of maximum opening (follow-up 6–12 months) | | | | | | | | | | | | |
| 1 | Randomized trials | Very serious[a] | No serious inconsistency | No serious indirectness | Very serious[b] | None | 14 | 15 | – | MD lower (0 to 0 higher)[c] | ⊕OOO Very low | Critical |
| Burning sensation (follow-up 6–12 months; unclear) | | | | | | | | | | | | |
| 1 | Randomized trials | Very serious[a] | No serious inconsistency | No serious indirectness | Serious[b] | None | 0/14 (0%)[c] | 0/15 (0%)[c]<br>0% | RR 0 (0 to 0) | 0 fewer per 1000 (from 0 fewer to 0 fewer)<br>0 fewer per 1000 (from 0 fewer to 0 fewer) | ⊕OOO Very low | Important |

[a]Methods of randomization, concealment of allocation and blinding is unclear. Not all of the patients were included in the analysis.
[b]The study only included 29 patients. The sample size was very small.
[c]The data were not transparently reported and we were not able to do further calculation.

*Question: Should physiotherapy be used for oral submucous fibrosis? (Cox and Zoellner, 2009)*

| *Quality assessment of study* | | | | | | | *Summary of findings* | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | | *No. patients* | | *Effect* | | | |
| *No. studies* | *Design* | *Limitations* | *Inconsistency* | *Indirectness* | *Imprecision* | *Other considerations* | *Physiotherapy* | *Control* | *Relative (95% CI)* | *Absolute* | *Quality* | *Importance* |
| Clinical assessment of maximum opening (follow-up 4 months) | | | | | | | | | | | | |
| 1 | Randomized trials | Very serious[a] | No serious inconsistency | No serious indirectness | Serious[b] | None | 16 | 8 | – | MD 0 higher (0 to 0 higher)[c] | ⊕OOO Very low | Critical |

[a]The study did not adequately conceal the allocation of patients in two groups, it was not blinded and 52% of the patients were lost to follow-up.
[b]The study included 54 patients at the beginning and only 28 came for the final evaluation. The sample size is small.
[c]The data were not adequately reported and we could not include them in further calculation.

**Table 3** (Continued)

*Question: Should physiotherapy vs hyaluronidase and steroid injections be used for oral submucous fibrosis? (Cox and Zoellner, 2009)*

| *Quality assessment of study* | | | | | | | *Summary of findings* | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | | *No. patients* | | *Effect* | | | |
| *No. studies* | *Design* | *Limitations* | *Inconsistency* | *Indirectness* | *Imprecision* | *Other considerations* | *Physiotherapy* | *Hyaluronidase and steroid injections* | *Relative (95% CI)* | *Absolute* | *Quality* | *Importance* |
| Clinical assessment of maximum opening (follow-up 4 months) | | | | | | | | | | | | |
| 1 | Randomized trials | Very serious[a] | No serious inconsistency | No serious indirectness | Serious[b] | None | 16 | 4 | – | MD 0 higher (0 to 0 higher)[c] | ⊕OOO Very low | Critical |

[a]The study did not adequately conceal the allocation of patients in two groups, it was not blinded and 52% of the patients were lost to follow-up.
[b]The study included 54 patients at the beginning and only 28 came for the final evaluation. The sample size is small.
[c]The data were not adequately reported and we could not include them in further calculation.

*Question: Should hyaluronidase and steroid injections be used for oral submucous fibrosis? (Cox and Zoellner, 2009)*

| *Quality assessment of study* | | | | | | | *Summary of findings* | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | | *No. patients* | | *Effect* | | | |
| *No. studies* | *Design* | *Limitations* | *Inconsistency* | *Indirectness* | *Imprecision* | *Other considerations* | *Hyaluronidase and steroid injections* | *Control* | *Relative (95% CI)* | *Absolute* | *Quality* | *Importance* |
| Clinical assessment of maximum opening (follow-up 4 months) | | | | | | | | | | | | |
| 1 | Randomized trials | Very serious[a] | No serious inconsistency | No serious indirectness | Serious[b] | None | 4 | 8[c] | – | MD 0 higher (0 to 0 higher) | ⊕OOO Very low | Critical |

[a]The study did not adequately conceal the allocation of patients in two groups, it was not blinded and 52% of the patients were lost to follow-up.
[b]The study included 54 patients at the beginning and only 28 came for the final evaluation. The sample size is small.
[c]The data were not adequately reported and we could not include them in further calculation.

**Table 4** Proposed disease Grading System – Oral submucous fibrosis

- Grade 1 – Mild: Any features of the disease triad for OSF (burning, depapillation, blanching or leathery mucosa) may be reported – and inter-incisal opening >35 mm
- Grade 2 – Moderate: Above features of OSF + inter-incisal limitation of opening 20–35 mm
- Grade 3 – Severe: Above features of OSF + inter-incisal opening <20 mm
- Grade 4A – OSF + other potentially malignant disorder on clinical examination
- Grade 4B – OSF with any grade of oral epithelial dysplasia on biopsy
- Grade 5 – OSF + oral squamous cell carcinoma (SCC)

OSF, oral submucous fibrosis.

to design let alone run randomized controlled trials. While the methodological issues in the published literature we reviewed offer weak evidence at best to make recommendations for the management of patients with OSF, there is much valuable insight to be gained from the studies we reviewed.

Moving away from the perspective of a systematic review, and focusing on mining the studies for information to help direct future research, we developed a list of objectives [adapted from (Brown *et al*, 2006)], and summarized the proposed recommendations in Table 5.

a. What populations should be researched?
b. What types of interventions are needed?
c. What types of outcomes should be measured?
d. What study designs are needed?
e. What infrastructure is required to conduct studies?

*Populations*

The populations for research on OSF are dictated by where the areca nut habit is prevalent. Studies should be conducted in South and South East Asia (e.g. India, Pakistan, Nepal, Bangladesh, and Sri Lanka), and in Chinese populations (Taiwan and Southern China) where studies have already been performed and the research infrastructure is developing. Numerous other countries have high rates of areca nut use (e.g. Myanmar, parts of Malaysia, Pacific Islands and others), although we are unaware that clinical studies are ongoing or planned. Additional studies conducted in immigrant populations, such as in Europe, USA or Australasia, have the potential to overcome some of the methodological limitations inherent in countries where clinical research infrastructure is less developed.

Given the variable spectrum of the signs and symptoms of OSF, subpopulations of patients grouped by disease severity/stage should be studied separately because different interventions may be effective at different stages of the disease. For simplicity, there are two distinct populations: those with advanced-stage disease hallmarked by irreversible and debilitating fibrosis, and those who have not reached advanced-stage (Table 4). Studies must define specific inclusion and exclusion criteria to foster the enrollment of subjects suited to the type of intervention (Table 5). In terms of demographics, studies are needed not only in adult populations, but also in children who are regularly using areca nut products (particularly gutkha) (Gupta and Ray, 2003). There may also be differences in OSF

**Table 5** Recommendations for future studies

| *Researcher recommendation* | *Proposed medical management of oral submucous fibrosis (Grades 1 and 2 in Table 4)* |
|---|---|
| Population/setting (*taking context/equity/social determinants of health into consideration for defining future subgroups in the study*) | Studies in countries with high prevalence of OSF: India, Sri Lanka, Nepal, Taiwan/China<br>Studies in immigrant populations from high prevalence areas (Europe, USA or Australia)<br>Studies in adults and children<br>Studies based on stage of disease (Table 4) |
| Intervention (*taking values and preferences into consideration*) | Habit control/prevention<br>Targeting early-intermediate stages<br>Use of systemic agents (alone or in combination) e.g. curcumin<br>Anti-inflammatory agents, anti-oxidants, anti-fibrinolytics, targeted (molecular) therapies<br>Development of QOL scale |
| Comparison | Compare medical agent(s) to placebo controls<br>Compare medical agents to habit control<br>Develop 'standard of care' therapy and compare other therapies to it. |
| Outcomes (*taking patient views into consideration*) | Subjective<br>QOL scale<br>Pain/burning<br>Objective<br>Inter-incisal opening (corrected for those with loss of incisors)<br>Presence of potentially malignant oral disorders<br>Habit cessation success rates at 1 year |
| Timing | Variable depending on type of trial |
| Study design | Double-blinded RCT (multicenter-clustered)<br>In case of habit controls not blinded |
| Sample size | Variable depending on type of trial. It is essential to conduct a power calculation to ensure the sample size for each treatment arm is adequate |

OSF, oral submucous fibrosis; QOL, quality of life; RCT, randomized controlled study.

populations related to the habits and types of areca-nut preparations used.

*Interventions needed*

We hypothesize that habit cessation alone as an intervention may have a large effect, more so on the symptoms of OSF rather than reversing fibrosis. The almost complete lack of studies incorporating successful quitting rates suggests that investigators have difficulty managing the dependence on areca nut products. Indeed the introduction of gutkha into the marketplace in India has led to even higher rates of dependence and OSF (Gupta, 1999). Future interventions must incorporate a standardized preventive plan even if a high relapse rate is anticipated, and include methodology to allow investigators to control for relapse during the study and follow-up during data analysis. Serial measures of serum/salivary areca alkaloids might be the gold standard to detect relapse or continued use of areca products during the studies, although simple strategies such as performing a baseline dental prophylaxis to remove extrinsic staining and re-evaluate for new staining might be an effective surrogate.

Our current understanding of the pathogenesis of OSF (Tilakaratne *et al*, 2006) includes overlapping phases, an early inflammatory phase and the later fibrosis phase, suggesting that interventions can be tailored to the severity of disease. At one end of the spectrum, new studies for the treatment of advanced disease are needed. We know that surgical excision of fibrosis will provide short-term improvement in function. However, there are a number research questions remaining. At what stage of fibrosis is surgery indicated? Would habit control and preoperative physical therapy lead to a subset of advanced staged patients not requiring surgery? Which postoperative interventions lead to favorable long-term outcomes? Which surgical procedures offer excellent immediate postoperative outcomes and with minimal hospitalization, complications and cost? These surgical questions will be reviewed by our group elsewhere. At the other end of the spectrum, early and intermediate stage disease may be amenable to a combination of existing and novel medical therapies. Which medical therapies are best indicated for which stage of disease? Does a combination of medical therapies provide the best outcomes? Which agents can slow down (or even reverse) fibrosis? What are the best delivery systems for medical therapies (i.e. topical *vs* submucosal injection *vs* systemic agents) in terms of compliance/adherence to treatment? What role do antioxidants or nutritional supplements play? The injection of corticosteroids was the most frequently studied medical therapy and in clinical practice in many centers it remains the first line of treatment for symptomatic patients with OSF, and yet unfortunately there is not a single controlled clinical trial using steroids.

Another major area of research is to consider specific anti-inflammatory agents (e.g. COX-2 inhibitor, Celecoxib) and molecular targets to stabilize the disease in early stages and to impact on the malignant potential of OSF. Scientific rationale for such potential interventions are based on laboratory findings in OSF that are reviewed elsewhere (Tilakaratne *et al*, 2006); (Rajalalitha and Vali, 2005). As seen in Figure 2, one of the key molecules in the initiation of fibrosis is TGF-$\beta$, a multifunctional cytokine known to be activated in fibrotic disorders. In addition to its key role in fibrosis, TGF-$\beta$ has a range of biological effects including cell proliferation and differentiation, immune regulation, production and deposition of extracellular matrix, and effects on inflammation. Given the integral role of TGF-$\beta$ in fibrosis as well as later malignant transformation, various components of the TGF-$\beta$ signaling pathway offer potentially attractive therapeutic targets for treatment of OSF. Treatment with anti-TGF-$\beta$ drugs would inhibit the function of this cytokine and may decrease inflammation, fibrosis, and malignant potential. Both small and large molecule drugs are currently in development to target TGF-$\beta$, its receptor and down stream steps along its signaling pathway that may result in novel therapies for OSF. Such clinical trials could form the basis of a high-cost approach suitable for use in some settings on selected migrant populations with OSF now resident in developed countries. Other molecular targets may be of relevance to inhibit malignant potential. $\alpha V\beta 6$ integrin is highly expressed in OSF and $\alpha V\beta 3$ in other cancers. Therapeutic trials are underway to target $\alpha V\beta 3$ integrin (Cai and Chen, 2006) in other cancers and may be applicable in the exploration of new avenues of therapy in OSF.

Curcumin (diferuloymethane) found in turmeric, which is derived from a rhizomatous plant and is widely used in Asian cooking exhibits anti-oxidant, anti-inflammatory and anti-cancer properties (Chainani-Wu, 2003), (Epstein *et al*, 2010). Curcumin has recently

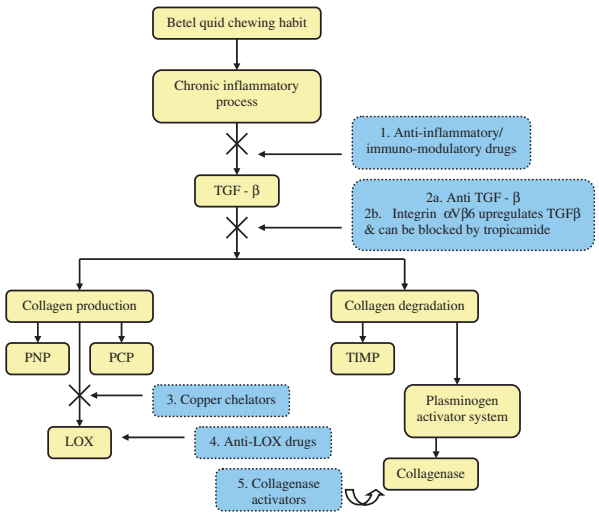


**Figure 2** Pathogenesis of oral submucous fibrosis (OSF) – A schematic illustration of the collagen production pathway and potential elements of molecular interventions. Data from Rajalalitha and Vali (2005) PCP & PNP- The enzymes known as the procollagen C and N proteinases (PCP and PNP) are involved in the processing of fibrillar procollagen precursors to mature collagens. TIMP- The matrix metalloprotinases are inhibited by specific endogenous issue inhibitors of metalloproteinasesá(TIMPs), which comprise a family of four protease inhibitors.

been advocated in phase ll and lll clinical trials for a variety of cancers including multiple myeloma, pancreatic and colon cancer (Shehzad *et al*, 2010), and for peptic ulcers using a dose of 3 g per day (Prucksunand *et al*, 2001). Sixteen clinical trials on curcumin are currently listed in the National Cancer Institute web site. As such it may fulfill two roles in the putative treatment of OSF, both as an anti-inflammatory agent and as a chemopreventive agent. It also provides the basis for a simple, safe, acceptable and cost effective intervention for earlier stage OSF. Using nine healthy volunteers, the safety of administration of tumeric oil has been established (Joshi *et al*, 2003). The same group reported a pilot trial in patients with OSF (Hastak *et al*, 1998). After completion of this systematic review and while writing this report, a paper describing the use of curcumin in the treatment of oral precancer including 25 patients with OSF was retrieved. This study again was not an RCT but reported that OSF was 'cured by curcumin'; an increase of local and systemic antioxidative status was also reported (Rai *et al*, 2010).

*Outcome measures*

In terms of important outcome measures, one must first consider the perspective of the patient. The morbidity associated with OSF is related to pain/burning, intolerance to spicy foods/beverages, and as the fibrosis progresses it is related to inability to function, such as opening wide enough to masticate, speak, and in some cases swallow. We have acknowledged the absence of any qualitative research on quality of life measures in this patient population, and the need to develop and validate such instruments. Little is known about the social implications associated with OSF. Are there issues in the workplace or at home? Are there specific issues with children and youth with OSF? Until QOL instruments are developed and validated, subjective outcome measures should include validated pain scales, such as numerical visual analog scales or pain-intensity scales (Wewers & Lowe, 1990). There are various biases associated with outcome measures. Consideration must be given to the cultural differences in pain perception and tolerance, and existing validated instruments need to be modified to the population being studied.

Inter-incisal opening is the single most reproducible objective measure for OSF. Whether measured by Vernier calipers or a metal ruler, the only room for error is if the patient is missing anterior teeth, in which case an adjustment must be made to account for tooth height. Ideally, measurements should be made by investigators blinded to the intervention and with intra and inter-rater reliability assessments. Other previously reported measurements, e.g. tongue protrusion, the extent of cheek puffing, palpation of fibrous banding, degree of tissue blanching are extremely difficult to measure with the required rigor. Development of new objective measures may have a role and could potentially include sensors to assess tightness of banding or vascular changes.

Many of the OSF patients present with anemias and nutritional deficiencies (Maher *et al* 1997; Gupta *et al* 1998). It is not clear how these conditions are related to OSF, although it seems prudent to consider laboratory testing as a secondary objective measure, particularly if designing a medical intervention involving the use of micronutrients, vitamins, or nutritional supplements. Some patients with OSF will have potentially malignant oral mucosal lesions at baseline or develop these over time. Protocols for standardized examinations to detect potentially malignant oral diseases, followed by a diagnostic algorithm leading to a histopathological diagnosis are of paramount importance (Warnakulasuriya *et al*, 2007).

The issue of areca nut dependence is a major public health issue. It is necessary to use evidence from the literature on the effectiveness of pharmacological, psychological, and public health interventions in the management of other substance use disorders to inform potential innovative therapeutic interventions for those who habitually and harmfully consume inexpensive and widely available areca nut products. Legislation and education by appropriately targeted health campaigns and mass media communication will underlie any effective strategy to reduce its overall use in the community and associated morbidity. Potential approaches for cohort studies may include, individual, family and group interventions based upon, relapse prevention and aspects of motivational enhancement therapy (e.g. in combination with potential substitute therapies and flavored chewing gums) or cognitive behavioral therapy.

*Study design*

Study design will depend on the research question and its objectives. Moreover, the type of intervention might facilitate or complicate the conduct of the studies. We recommend that all experimental studies would consider evaluating the areca nut habit during the study and also include a cessation component to control for relapse during the treatment. Depending on budget and infrastructure, cessation could range from a brief intervention repeated at all visits, to intensive counseling (and/or pharmacotherapy). Separate studies are needed to assess which strategies might work and is beyond the scope of this review.

Randomized double-blinded placebo-controlled study design is ideally suited to explore the efficacy of medical agents, particularly studies testing agents taken orally where it is feasible to manufacture placebos. It is rather more difficult to control for injected intralesional agents, although one could control for the agent by mixing it with local anesthetic and having the placebo injection with local anesthetic alone. Other acceptable designs could be comparison RCTs in which two or more different agents are compared. In such cases, power calculations are important to generate conservative sample sizes depending on expected outcomes to account for differences between active group and controls. Assigning subjects to a 'no treatment' arm (i.e. habit control alone) may also be useful, although such a design is not double-blinded.

Establishing specific inclusion and exclusion criteria is important. How to diagnose and grade OSF? Is histopathology needed or could a set of validated

clinical criteria suffice, thereby saving patient discomfort, time and cost? Defining the population depending on the agent being investigated, such as excluding advanced cases, including those patients with a range of restricted opening, or those with a certain threshold of pain, or those who use gutkha *vs* betel quid or other non-industrialized preparations. Preparation of the research infrastructure with Institutional Review Board (IRB) approval should include a study protocol, consent forms, data entry forms, a budget, and hiring of personnel with training in human subjects research. Enrollment requires informed consent. Ethics situations vary among different cultures, but the fundamental framework enshrined in the Declaration of Helsinki applies to all, Potential issues that may act as barriers to informed consent such as language, literacy, capacity to consent or culture need to be addressed at the time of study design.

Randomization, by various acceptable techniques, may be simple or stratified for various severity groups (i.e. early/mild *vs* moderate/intermediate OSF) or other variables such as presence of dysplasia. Subjects would then receive a dental cleaning and oral hygiene and dietary instruction before receiving the treatment. All investigators performing procedures (measuring outcomes) must be also be blinded to the treatment arms. Subject incentives are an important consideration and should be sensitive to the setting and within acceptable practice within the ethics approval. In studies with multiple visits, a bonus for completing the trial may help reduce dropouts. Studies with long-term follow-up are critical to assess relapse and development of potentially malignant or malignant oral lesions. Loss to follow-up is a major issue and creative approaches are needed. A checklist for these and other steps for running a clinical trial may be found through CONSORT (Moher *et al*, 2001).

None of the interventions reported so far have examined any improvement in oral health-related quality of life among patients treated for OSF. Both burning and trismus can affect oral function, oro-facial appearance and social interaction. We propose that future studies should include questionnaires designed specifically to evaluate how well those treated for OSF can perform common functions. Study questionnaires could be devised from existing QOL questionnaires, such as the following:

- EORTC QLQ – H&N 35 (Bjordal *et al*, 2000)
- International Classification of Functioning, Disability and Health (ICF) questionnaire for patients with Head and Neck Cancer (Tschiesner *et al*, 2010)
- Performance Status Scale (List *et al*, 1996)

Other new questions added to gain more information in relation to specific aspects related to OSF and oral function. However, any adapted questionnaire should be pilot tested among a cohort of OSF patients before research use.

The World Workshop on Oral Medicine V (WWOM V) Working Group will be pleased to help investigators develop research protocols for the management of OSF and facilitate centralized data collection and analysis. We propose to convene a consortium of interested investigators to design and run multi-center studies in high incidence countries.

## Conclusions

We found a low grade of evidence to support recommendations for the management of OSF. However, using the information from the review, our working group developed a framework to propose multi-center research in countries where OSF remains a serious public health issue.

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Dr. Anura Ariyawardena (Sri Lanka) was invited to participate at the WWOM but could not attend. His comments to an initial draft are acknowledged. Dr Yi-Hsin Yang helped us with translations of Chinese papers to English.

### Author contributions

S. Warnakulasuriya led the group, A. R. Kerr, A. J. Mighell and T. Dietrich were the main reviewers, J. Rimal and A. Jalil were the assistant reviewers. All other authors served as consultants and attended the 2-day workshop in London to help frame and edit this manuscript.

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