# Interventions for Managing Oral Submucous Fibrosis – Commentary to a Systematic Review

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## Statement of clinical relevance

Coinciding with our recently published Cochrane systematic review: Interventions for managing oral submucous fibrosis, our article underscores the need for improved patient-centred research and standardised trials in Oral Submucous Fibrosis (OSMF) management. Emphasising patient-reported outcomes and promoting cultural change are crucial steps in advancing effective interventions for OSMF.

## Abstract

Oral submucous fibrosis (OSMF) is a chronic, debilitating condition characterised by fibrosis of the oral mucosa, leading to impaired mouth opening, chewing, and speech functions. The aetiopathogenesis is not fully understood, but factors such as chewing betel nut, nutritional deficiencies, immunological and hereditary factors, and overconsumption of spicy foods may play a role. Recently, Jones[1] et al. (2023) published an update of the Cochrane Review titled "Interventions for managing oral submucous fibrosis," which identified 30 relevant randomised controlled trials (RCTs), including 28 new trials since the initial review in 2008.

The primary objective of this review was to evaluate patient-reported outcomes (PROs) in the management of OSMF, with a particular emphasis on restoring normal eating, chewing, and speech functions. However, our findings revealed limited reporting of PROs, with only four studies assessing relevant outcomes. Instead, most studies measured inter-incisal distance and burning sensation intensity. Moderate certainty evidence showed that antioxidants improved interincisal distance and burning sensation, but no other intervention demonstrated consistent benefits over non-active control treatments.

Adverse effects were reported in 50% of the studies, and most trials lacked rigorous blinding and allocation concealment, resulting in unclear or high risk of bias in several domains. Additionally, reporting of participant demographics was inconsistent, which hindered external validity assessment. Only four studies reported surgical interventions, which also carried a high potential for complications.

The review emphasises the need for more comprehensive research on OSMF management. Prioritising basic preclinical research to identify plausible interventions and mechanisms of action before conducting clinical trials is crucial. Furthermore, standardising trial methodologies, giving priority to PROs alongside objective outcomes, and gaining a better understanding of OSMF pathogenesis are essential steps towards improving management strategies. Additionally, emphasising behaviour change interventions to prevent OSMF through education and cultural shift away from areca nut consumption is of utmost importance.

**Keywords:** Antioxidants; Dexamethasone; Drug-Related Side Effects and Adverse Reactions; Oral Submucous Fibrosis [therapy]; Pentoxifylline; Vasodilator Agents;

## Introduction

Oral submucous fibrosis (OSMF) is a chronic debilitating disease of the oral cavity characterised by inflammation and progressive fibrosis of the submucosal tissues, resulting in a marked restriction and an eventual inability to open the mouth. Worldwide, estimates of oral submucous fibrosis indicate that 2.5 million people are affected, with most cases concentrated on the Indian subcontinent, especially southern India (Cox[2] et al., 1996). The precise cause is unknown but chewing of betel nut, overconsumption of spicy foods, nutritional deficiencies, immunological and hereditary factors have a potential role in the pathogenesis. Unfortunately, most patients with OSMF present with moderate-to-severe disease, which is irreversible at this stage (Thakur[3] et al., 2020). Currently, there is no gold standard of care for OSMF, and available treatment options focus mainly on managing symptoms and improving mouth movements.

## Discussion

Our team has recently conducted an update of the Cochrane Review titled "Interventions for managing oral submucous fibrosis". We identified 30 relevant randomised controlled trials (RCTs), adding 28 new trials to the previous review. The primary objective for the review was to evaluate patient-reported outcomes (PROs), specifically resumption of normal eating, chewing, and speech, as these indicators hold the greatest importance to patients. However, we found that PROs were only assessed in only four studies and were reported dichotomously as presence/absences of patients experiencing difficulties or not.

The outcomes most frequently measured were inter-incisal distance (the distance between the upper and lower central incisors) and intensity of burning sensation (measured through a visual analogue scale ranging from 0 -100 mm). Adverse effects and adverse events caused by treatments were reported in 50% of studies, although the extent of detail provided varied. No studies measured any health economic outcomes.

We grouped interventions into six broad subgroups based on our judgement about the likely primary mechanism of action:

- Any Intervention vs Placebo
- Different surgical techniques
- Surgery alone compared with surgery plus adjunctive treatments
- Physiotherapy alone compared with physiotherapy plus ultrasound
- Physiotherapy compared with medications
- Surgery combined with different physiotherapy techniques

Whilst we accept that these groupings are arbitrary, they serve to help structure the data and make sense of the wide variety of evaluations within included studies.

Habit cessation advice and patient education are widely recognised as the primary and essential components of the standard care for OSMF (Rai[4] et al., 2021). This was reported in most of the included studies, and we therefore assumed this was a feature of normal clinical care that could be considered redundant in our evaluation. Several studies also included physiotherapy exercises in both study arms, which makes evaluation of specific physiotherapy/jaw exercise interventions challenging as the true effect of such interventions may be underestimated. In the absence of a standard of care among the interventions we evaluated (excluding habit cessation), we deemed any intervention compared to non-active control as our primary outcome with the rationale that it is essential to establish the fundamental effectiveness of interventions before conducting head-to-head comparisons. The aetiopathogenesis of OSMF is complex and incompletely understood. The uncertainty regarding OSMF causation is reflected in management protocols, which largely remain empirical, and lack clear proposed modes of action. Proposed medical mechanisms, which could improve OSMF symptoms include: promotion of non-fibrotic tissue regeneration; enzymatic breakdown of fibrotic tissue; reduction of pro-fibrotic inflammation via immune responses; promotion of blood flow to ischaemic tissues, and correcting nutritional deficiencies. The clinical trial participants underwent various treatments for oral submucous fibrosis, including steroids (alone or combined with other agents), vasoactive substances like pentoxifylline, and antioxidants or plant-based derivatives such as aloe vera or spirulina. Many of the studies included within the systematic review provided no clear clinical justification for the interventions. Moreover, in multiple studies included in this review, combined interventions addressed overlapping putative mechanisms, which makes reliable assessment of the effectiveness of individual treatments difficult. We therefore suggest that

128 further detailed understanding of aetiopathogenesis of OSMF is needed for stronger
129 biological rationale in selecting management strategies.

130 ## Key findings

131 We found moderate-certainty evidence from three studies (620 participants) that
132 antioxidants improved mouth opening (interincisal distance) by 8.83 mm compared to
133 placebo after three to six months. However, the studies had an unclear risk of bias, and no
134 benefit was seen beyond six months, based on a single study of 90 participants. No other
135 treatment consistently improved mouth opening compared to non-active controls.
136 Similarly, moderate-certainty evidence from two studies (500 participants) showed that
137 antioxidants reduced burning sensation on a visual analogue scale (VAS) by 70.82 mm after
138 three to six months. This effect was present at three months and beyond, but with reduced
139 magnitude. Very low-certainty evidence indicated that dexamethasone (one study, 25
140 participants) reduced burning sensation by 46 mm, and vasodilators (two studies, 85
141 participants) improved VAS scores by 51.02 mm, though all these studies had unclear or high
142 risk of bias.

143

144 Substantial heterogeneity was observed among the interventions evaluated. Out of the 30
145 studies included, only 13 compared an active treatment against a non-active or placebo
146 control. Additionally, there was a lack of standardisation in intervention protocols. Trials
147 utilising similar medical agents exhibited a wide range of treatment durations and doses, with
148 the authors failing to provide a clear rationale for the varying treatment regimens.
149 Furthermore, few studies evaluated participants for more than 6 months and the longest
150 identified follow-up period with usable data was only nine months. While shorter follow up is
151 frequently a limitation of interventional research due to cost and logistical issues, OSMF is a

chronic, lifelong condition, therefore longer term follow up is important to ensure that interventions provide meaningful benefits to patients.

There is no established minimum clinically important difference (MCID) for change in burning sensation in the OSMF population. A systematic review of MCIDs in chronic pain conditions by Olsen[5] (2018) has suggested a MCID of 32% relative reduction in VAS scores. We found a similar effect size only for intralesional dexamethasone compared to placebo, with benefits sustained up to six months, though further validation is needed.

For mouth opening, a report of the minimum clinically important difference (MCID) in an OSMF population was suggested to be 10 mm by Kaur[6] (2022), however none of the interventions we reviewed reached this level at any time point.

## Methodological limitations

Most of the studies evaluated appeared to be open label trials, where allocation concealment and blinding were either not performed or not described, leading to them being judged to be at unclear or high risk of bias in one or more domains. In 9 studies, a placebo control was used to blind participants. To be an effective control, a placebo must be indistinguishable from the active comparator in terms of appearance, taste, dosing schedule and any other characteristics. However, Piyush[7] (2018) included a placebo capsule in their three-arm trial, which acted as an effective placebo control for lycopene capsules, but not curcumin tablets. A more extreme example is the three-arm trial undertaken by Kumar[8] (2007), which compared lycopene with lycopene plus intralesional betamethasone. Here, placebo capsules were provided to a control group, but no placebo intralesional injections were given, meaning only one comparator arm was effectively blinded.

Only 3 studies undertook power calculations to inform study sample sizes. There was a wide range (8-400, median 50) in the number of participants included within studies.

Reporting adverse events is fundamental to detecting and managing safety issues arising from medical or surgical intervention trials. Of the trials we reviewed, only half published information relating to adverse events. Of the 15 trials that did make adverse event information available, none of this data was presented in a format suitable for quantitative analysis and so we were unable to make an informed judgement about potential adverse effects of any of the treatments assessed.

The goal of a randomised controlled trial is to compare groups that only differ by the treatment the participants have received. For this reason, it is important that the characteristics of participants in the intervention and control groups are comparable. Evaluating and reporting participant demographics at baseline allows us to determine that groups are comparable, and that randomisation has been effective. Providing participant demographic information also allows readers to consider the external validity of findings and assess whether the results apply to the patient groups they wish to treat. Of the trials reviewed less than half (11) reported baseline demographic information and several reported only participant age ranges. Age and gender were the most consistently reported demographics, but other factors such as ethnicity, clinical or histological staging of disease, or habit information such as nature and duration of areca nut use were infrequently reported. Future trials should ensure that all relevant covariates and potential confounders are reported adequately.

The systematic review included only four studies which reported surgical interventions for OSMF. Careful consideration should be given to proposing surgical management of OSMF due to the high potential for complications relative to the low quality of evidence to support surgical interventions.

Further analysis of both included and excluded surgical studies revealed inconsistencies in the reporting of adverse events/effects (AEs). Half (11) of the 22 studies evaluated did not report AEs. Out of the studies that reported adverse events (AEs), only one study indicated that no AEs were encountered. One study (Kania[9] et al., 2022) reported 4 adverse events that we judged to be serious/severe (total graft necrosis in 3 of 30 patients and one case of commissure tear). The remaining studies reported AEs that while not severe, caused morbidity and distress to patients, including perforation of the soft palate, TMJ subluxation, infection, and partial graft necrosis. The frequency of AEs reported in all surgical studies assessed ranged from 10-60 %. However, given the overall poor reporting of AEs, it is likely that this is an underestimate of the true rate.

## Conclusion

The findings of this systematic review highlight the need for more comprehensive research on the management of OSMF, conducted with greater methodological rigour. Priority should be given to identifying biologically plausible interventions with adequately characterised mechanisms of action through basic preclinical research before embarking on clinical trials. Once candidate interventions have been established, clinical trials should compare such interventions to non-active controls, and interventions that carry the lowest risk of adverse sequelae should be favoured. Trial methodologies should be standardised in terms of participant inclusion criteria, diagnostic criteria, and intervention follow-up protocols. Patient-reported outcomes should be included alongside objective outcomes such as inter-incisal distance. Additionally, priority should be given to gaining an understanding of the pathogenesis of OSMF and optimising behaviour change interventions at both population and individual level to prevent the disease through education and promoting a shift in cultural and behavioural attitudes towards areca nut consumption.

## Conflict of Interest

No

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## Ethics statement/confirmation of patient permission

Not required

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