



MASCC/ISOO Clinical Practice Statement: Management of salivary gland hypofunction and xerostomia in cancer patients

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Abstract

Purpose A MASCC/ISOO Clinical Practice Statement (CPS) is aimed at generating a concise tool for clinicians that concentrates practical information needed for the management of oral complications of cancer patients. This CPS is focused on the management of salivary gland hypofunction and xerostomia in cancer patients.

Methods This CPS was developed based on critical evaluation of the literature followed by a structured discussion of a group of leading experts, members of the Oral Care Study Group of MASCC/ISOO. The information is presented in the form of succinct bullets and tables to generate a short manual about the best standard of care.

Results Salivary gland hypofunction and xerostomia in cancer patients are managed by (i) stimulating saliva production of salivary glands with residual secretory capacity or (ii) artificial wetting of the oral and lip surfaces which can be achieved by pharmacological or non-pharmacological interventions. Pharmacological interventions encompass the use of sialagogues and sialolytics, while non-pharmacological interventions involve the use of moistening agents, mechanical, gustatory, or electrostimulation of the salivary glands. Additional treatment modalities may be incorporated in practice based on local availability and the clinician's experience.

Conclusion The information presented in this CPS offers clinicians convenient access to the dosages and regimens of different interventions for managing salivary gland hypofunction or xerostomia to facilitate clinical efficiency and conserve valuable time for clinicians.

Keywords Cancer · Dry mouth · Oral manifestations · Salivary gland hypofunction · Xerostomia

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Introduction

Dry mouth is a common and distressing symptom among patients undergoing cancer therapy and cancer survivors. Often in head and neck cancer patients, dry mouth is lifelong. Dry mouth is a layperson term used when patients experience either salivary gland hypofunction, xerostomia, or both. Among healthcare professionals, the terms salivary gland hypofunction and xerostomia are used to describe objectively low saliva secretion and the subjective sensation of oral dryness, respectively.

Saliva plays a crucial role in daily functions such as taste perception as well as facilitating chewing, swallowing, and speech [1]. It is also essential in maintaining tooth and mucosal integrity, including protecting mucosal surfaces against trauma and opportunistic infections. The Oral Care Study Group (OCSG) of the Multinational Association of Supportive Care in Cancer (MASCC) and the International Society of Oral Oncology (ISOO) have previously published several systematic reviews on the management of salivary gland hypofunction and xerostomia in cancer patients [2, 3]. However, these reviews described interventions that have been evaluated in clinical trials but did not include many non-invasive interventions accepted by expert opinion to be beneficial for patients suffering from salivary gland hypofunction and/or xerostomia. The published MASCC/ISOO reviews also do not provide details as to how these interventions are prescribed. Therefore, a working group of the OCSG of MASCC/ISOO was established to formulate an expert-opinion Clinical Practice Statement (CPS) to provide a concise summary for clinicians to reference when prescribing these interventions.

Objective

This CPS provides information on the dose and regimen of common interventions used for salivary gland hypofunction and xerostomia, as well as specific considerations for their use in cancer patients.

Methods

As outlined in the MASCC/ISOO guidelines policy, this CPS was developed based on a critical literature evaluation by domain experts and discussion by an international working group of the OCSG of MASCC/ISOO. During the development of the manuscript, point questions that deemed a closer look were generated, and a literature search was done to ensure accuracy of information. The CPS was

further reviewed and approved by two independent boards: the ISOO Advisory Board and the MASCC Guidelines Committee.

Management

- Currently, the treatment goals of managing salivary gland hypofunction and xerostomia in cancer patients are to relieve symptoms by the following:

- i) Stimulating saliva production of salivary glands with residual secretory capacity
- ii) Artificial wetting of the oral and lip surfaces

Whenever possible, stimulating saliva production should be considered the primary approach because it helps to preserve salivary gland function. Aside from alleviating xerostomia, saliva provides additional benefits such as anti-microbial properties, whereas wetting agents only serve to artificially lubricate the affected surfaces.

- This is commonly achieved by pharmacological (Table 1) or non-pharmacological interventions (Table 2). The interventions in Tables 1 and 2 are not an exhaustive list of those being used in clinical practice.
- Other than traditional Chinese herbal remedies that have been studied in cancer patients, there are topical agents that have been investigated in non-cancer patients (e.g., pilocarpine, anticholinesterase physostigmine, 1% malic acid, oxygenated glycerol triester spray, mucoadhesive lipid-based bioerodable tablet containing lubricating agents) that may provide symptomatic relief to cancer patients with salivary gland hypofunction or xerostomia. Clinicians should periodically review the literature for updated information.
- If appropriate, a review and adjustment of the patient's concomitant medications (i.e., number, dosage, formulation) to alleviate salivary gland hypofunction or xerostomia may be explored [4]. For cancer patients, opioids and anti-cholinergic agents are common culprits for causing dry mouth.
- Post-head and neck radiation patients and those with oral chronic graft-versus-host disease may suffer from mucosal sensitivity. The symptoms may be aggravated in individuals with salivary gland hypofunction due to lack of lubrication and excessive friction during oral physiologic function. Thus, alcohol-free oral agents with neutral pH and bland or non-mint taste are preferred.
- Dry, cracked, and painful lips often accompany signs and symptoms in cancer patients with salivary gland hypo-

Table 1 Pharmacological Interventions^{a, b}

Agent	Formulation	Dose and regimen	Contraindication ^c
SIALAGOGUES – suitable for patients with residual salivary gland function			
Pilocarpine - systemic	Tablet	<ul style="list-style-type: none"> • 5 mg, 7.5 mg, 10 mg; X3–4/day • Max. dose: 30 mg/day • Response may take 12 weeks • To avoid dehydration, take with plenty of water unless contraindicated • 4% pilocarpine: 3 (≈6 mg) – 5 (≈10 mg) drops; X3/day • 2% pilocarpine: 5 (≈5 mg) – 10 (≈10 mg) drops; X3/day • 1% pilocarpine: 10 (≈5 mg) – 20 (≈10 mg) drops; X3/day • Max. dose: 30 mg/day • To avoid dehydration, take with plenty of water unless contraindicated • 0.01–2%, swish for 1 minute and spit; X2–3/day • Consider adding sweetener for better compliance • 30 mg X3/day • Max. dose: 90 mg/day • 10–25 mg X3/day 	Acute or uncontrolled asthma, acute iritis, narrow angle glaucoma
Pilocarpine – topical	Ophthalmic drop		
Mouthrinse	Mouthrinse		
Cevimeline	Capsule		Acute or uncontrolled asthma, acute iritis, narrow angle glaucoma
Bethanechol	Tablet		Bladder neck obstruction, bladder surgery, recent gastrointestinal surgery (recent), gastrointestinal disturbance (spastic), gastrointestinal lesion (acute inflammatory), peptic ulcer disease, peritonitis, vasomotor instability, coronary artery disease, severe hypotension, severe bradycardia, hyperthyroidism, asthma, seizure disorder, Parkinson disease
Anethole trithione	Tablet	<ul style="list-style-type: none"> • 25 mg X3/day 	No contraindications reported; however, caution should be practiced as it may have some muscarinic agonist effect.
SIALOLYTICS – suitable for patients with thick, ropery and/or viscous saliva			
N-acetylcysteine	Granules for oral solution	<ul style="list-style-type: none"> • Dissolve in a glass of water • Adult and child >6 years: 200 mg X2–3/day • Dissolve in ½ glass of water • Adult: 600 mg X1–2/day 	Mention of ‘caution’ level only
Guafenesin	Short-acting formulation Long-acting/ extended-release formulation	<ul style="list-style-type: none"> • Adult: 200 – 400 mg up to X6/day • Drink plenty of water; do not eat/crush/chew progress upwards • Adults: 600–1200 mg X2/day; start with 600 mg X2/day and progress upwards • Max. dose: 2400 mg/day 	Mention of ‘caution’ level only

^aStandard protocols are available on Epocrates (<https://online.epocrates.com/>). Clinicians are advised to check drug information against formal resources as drug specifications (e.g., contraindications and precautions, permitted dose) may vary between medical resources and change over time

^bThere may be geographic variation in the drug availability, formulation or tablet dosage and prescription regulations

^cContraindications for each of the agents - hypersensitivity to drug or ingredient; additional relative contraindications exist on Epocrates website at a level of “caution”

Table 2 Non-Pharmacological Interventions

Interventions	Common active ingredients/mechanism of action	Considerations
<p>Main action: Artificial surface lubrication</p> <p>Saliva substitutes and mucosal moistening agents [7]</p>	<p>Some of the agents may have more than one property.</p> <ul style="list-style-type: none"> • Adhesive properties: Natural polysaccharides (e.g., guar gum), semi-synthetic polymers (e.g., carboxymethylcellulose), synthetic polymers (e.g., polyethylene glycol/ polyethylene oxide), thiolated polymers • Lubricating properties: Mucin, glycerin, synthetic polymers, cellulose-based polymers, hydrocolloids/water soluble polymers (e.g., carrageenan) • Moisturizing properties: Glycerin, hydrocolloids/water soluble polymers • Thickening properties: Hydrocolloids/water soluble polymers • Optional ingredients: Neutralizer, anti-cariogenic agents (e.g., fluorides), sweetener, cooling sensation agent, surfactant • Oral hydration devices (e.g., device that pumps small amounts of liquid into the oral cavity at patient-set intervals with an indwelling oral canula attached to an external water pump) • Use of room humidifier 	<ul style="list-style-type: none"> • Mucin-containing saliva substitutes are generally preferred over carboxymethylcellulose containing ones. • Combination therapy may be helpful • Consistency of product catered to the symptom severity and daytime versus night-time use (e.g., use of higher viscosity products during the night) • Consider different delivery methods (e.g., sprays versus rinse) • Disadvantages <ul style="list-style-type: none"> - short duration - minimal benefit for individuals with mild symptoms - some patients may dislike taste and consistency or complain of nausea with use • Cost and availability
<p>Mucosal hydration devices</p>	<p>Oral hydration devices (e.g., device that pumps small amounts of liquid into the oral cavity at patient-set intervals with an indwelling oral canula attached to an external water pump)</p> <ul style="list-style-type: none"> • Use of room humidifier 	<ul style="list-style-type: none"> • Erosive and cariogenic effect on teeth <p>Some patients may not tolerate agents with strong flavors or taste (e.g., menthol, acidic pH)</p> <ul style="list-style-type: none"> • Cost and availability
<p>Main action: Stimulate saliva production</p> <p>Gustatory stimulants</p>	<p>Stimulate saliva production by sucking or chewing on sugar-free gum, sugarless hard candy, salivary stimulating lozenge</p>	<ul style="list-style-type: none"> • Erosive and cariogenic effect on teeth <p>Some patients may not tolerate agents with strong flavors or taste (e.g., menthol, acidic pH)</p> <ul style="list-style-type: none"> • Cost and availability
<p>Electro-stimulation devices</p>	<p>Increase salivary flow rate by stimulating the neurons of the salivary reflex arch or lingual nerve</p> <ul style="list-style-type: none"> • Extraoral (e.g., transcutaneous electrical nerve stimulation) • Intraoral (e.g., a patient-operated, hand-held oral device delivering low intensity electrostimulation to the lingual nerves near the mandibular third molars) 	<ul style="list-style-type: none"> • Patient tolerance and compliance
<p>Mechanical stimulation of salivary gland</p>	<p>Stimulate saliva production by massaging the parotid or submandibular gland to stimulate mechanoreceptors and subsequent drainage of saliva into the mouth</p>	<ul style="list-style-type: none"> • Patient tolerance and compliance
<p>Others</p>	<p>There are a few randomized controlled trials evaluating the use of acupuncture [2, 8], photobiomodulation [9], salivary gland ductal irrigation/dilation [10] in alleviating salivary gland hypofunction and/or xerostomia. However, the recommendation for their routine use in the clinical setting is premature mainly because of conflicting evidence and the heterogeneities in treatment protocols.</p>	

function. Application of lanolin-based or wax-based lip lubricant may help relieve this complaint.

- Patients with salivary gland hypofunction are at risk for opportunistic oral candidiasis. Antifungal therapy should be initiated when there are clinical signs of oral candidiasis, and considered when there are non-specific symptoms suggesting subclinical infection.
- Patients with salivary gland hypofunction are at increased risk for dental caries. As such, all patients should have regular professional dental care two to four times a year. They should also incorporate high-concentration, pH-neutral fluoride products into their daily oral hygiene routine and avoid highly cariogenic and acidic foods in their diet.
- Patients may benefit from avoidance of oral care products with sodium lauryl sulfate and intense flavors as well as acidic or spicy foods as they may aggravate the discomfort associated with salivary gland hypofunction or xerostomia.
- There is emerging literature to suggest that head and neck cancer patients are at a higher risk for sleep apnea [5]. Salivary gland hypofunction or xerostomia may compromise the treatment of sleep apnea. Clinicians can consider the use of nocturnal mouth moistening strategies for such patients.
- Advanced radiation techniques such as intensity-modulated radiation therapy, radioprotectors (e.g., amifostine [6]), pilocarpine or bethanechol administration before and during radiation therapy, surgical transfer of submandibular gland and acupuncture have shown mixed findings or weak evidence for the prevention of salivary gland hypofunction [3].

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Data availability No datasets were generated or analysed during the current study.

Declarations

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Disclaimer The MASCC/ISOO OCSG statements have been developed to facilitate expert-opinion-based management of oral complications of cancer itself and cancer therapy, where high-quality evidence is lacking. Clinicians should use their judgment when making treatment decisions for individual patients. Statement authors and the MASCC/ISOO do not guarantee or take responsibility for the clinical outcomes in individual patients.

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