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SUMMARY WITH CRITICAL APPRAISAL

Pilocarpine for Radiotherapy-Induced Dry Mouth and Dry Eyes: A Review of Clinical Effectiveness, Cost-Effectiveness, and Guidelines

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Abbreviations

AGREE II	Appraisal of Guidelines for Research Evaluation 2
ALTENS	acupuncture-like transcutaneous electrical nerve stimulation
AMSTAR 2	A Measurement Tool to Assess Systematic Reviews 2
CENTRAL	Cochrane Central Register of Controlled Trials
CINAHL	Cumulative Index to Nursing and Allied Health Literature
CRD	University of York Centre for Reviews and Dissemination
CTFPHC	Canadian Task Force on Preventative Health Care
EMBASE	Excerpta Medica database
HNC	head and neck cancer
MA	meta-analysis
MEDLINE	Medical Literature Analysis and Retrieval System Online
MeSH	Medical subject headings
MHTAS	Malaysia Health Technology Assessment Section
NR	not reported
NRS	non-randomized study
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
PubMED	Public MEDLINE
RCT	randomized controlled trial
SR	systematic review
VAS	visual analogue scale

Context and Policy Issues

The jaw, larynx, nasopharynx, mouth, ears, and salivary glands are some of the most common areas affected when referring to head and neck cancers.[1] The yearly incidence of head and neck cancer in Canada is over 4,300.[2] A common side-effect of radiation therapy for head and neck cancer is damage to the salivary glands which results in dry mouth (xerostomia),[1,3,4] lasting weeks and in some cases, can be permanent.[1,4] This adversely impacts the patient's quality of life and can lead to further complications such as dental caries.[1,3] Similarly, radiation therapy for the head and neck can damage lacrimal glands which results in dry eyes, affecting quality of life and leading to visual compromise.[5]

The clinical management of dry mouth and dry eyes includes the use of lifestyle modifications (e.g., use of a room humidifier, eating moist foods),[3,4] saliva substitutes,[3,4] tear replacement drops,[6] nonpharmacological interventions,[3,4,6] and pharmacological interventions.[3,4,6] The later include a variety of sialagogues (agents that promote the secretion of saliva), such as pilocarpine,[3] which can also be used to promote lacrimal secretions.[7] However, it is important to note that the drug may only stimulate secretion if there remains viable gland function.[4]

In Canada, pilocarpine is currently marketed as a tablet and an ophthalmic solution.[8] Because of its cholinergic agonist mechanism of action, it may cause frequent side effects including sweating, flushing, increased bowel and bladder motility, tachycardia, and hypertension.[3,9] As such, pharmacological and nonpharmacological alternatives are often sought in an effort to expose patients to fewer side effects.

This report is part of a series on the use of pilocarpine for dry mouth and dry eyes.[10,11] One report was a summary with critical appraisal of evidence available in November 2019 on medication induced dry mouth and dry eyes,[10] While another summary with critical appraisal focused on dry mouth and dry eyes in patients with Sjögren's syndrome.[11]

The objective of this report is to summarize the evidence regarding the clinical effectiveness, cost-effectiveness, and evidence-based guidelines regarding the use of pilocarpine for the treatment of dry mouth and dry eyes caused by radiotherapy for cancer of the head or neck.

Research Questions

1. What is the clinical effectiveness of pilocarpine for the treatment of dry mouth caused by radiotherapy for cancer of the head or neck?
2. What is the cost-effectiveness of pilocarpine for the treatment of dry mouth caused by radiotherapy for cancer of the head or neck?
3. What is the clinical effectiveness of pilocarpine for the treatment of dry eyes caused by radiotherapy for cancer of the head or neck?
4. What is the cost-effectiveness of pilocarpine for the treatment of dry eyes caused by radiotherapy for cancer of the head or neck?
5. What are the evidence-based guidelines regarding pilocarpine for the treatment of dry mouth or dry eyes caused by radiotherapy for cancer of the head or neck?

Key Findings

Two systematic reviews (one with meta-analysis), were identified regarding the effectiveness of pilocarpine for the treatment of dry mouth caused by radiotherapy of the head or neck.

The identified literature was at high risk of bias and revealed conclusions that were based on studies of limited quality. One study found no difference between a pilocarpine mouthwash and saliva substitutes, while another study found more patients responded favourably to 5 mg pilocarpine lozenges over tablets, lozenges of a lower strength, and inactive lozenges.

One evidence-based guideline was identified regarding the use of pilocarpine for dry mouth caused by radiotherapy of the head or neck. It recommends that pilocarpine be offered, if available.

No evidence regarding the cost-effectiveness of pilocarpine for the treatment of dry mouth caused by radiotherapy of the head or neck was identified. Furthermore, no evidence regarding the clinical effectiveness and cost-effectiveness of pilocarpine for the treatment of dry eyes caused by radiotherapy of the head or neck was identified.

The limitations of the included studies, such as the high risk of bias of the primary studies included in the systematic review and the low-quality evidence upon which guideline recommendations were based, should be considered when interpreting the results.

Methods

Literature Search Methods

A limited literature search was conducted by an information specialist on key resources including Medline, Embase, the Cochrane Library, the University of York Centre for Reviews and Dissemination (CRD) databases, the websites of Canadian and major international health technology agencies, as well as a focused Internet search. The search strategy was comprised of both controlled vocabulary, such as the National Library of Medicine's MeSH (Medical Subject Headings), and keywords. The main search concepts were pilocarpine and dry eye or dry mouth, and radiation exposure. No filters were applied to limit the retrieval by study type. A secondary search was conducted on dry eye or dry mouth and radiation exposure. For the secondary search, search filters were applied to limit retrieval to guidelines. Where possible, retrieval was limited to the human population. The search was also limited to English language documents published between January 1, 2009 and November 27, 2019.

Selection Criteria and Methods

One reviewer screened citations and selected studies. In the first level of screening, titles and abstracts were reviewed and potentially relevant articles were retrieved and assessed for inclusion. The final selection of full-text articles was based on the inclusion criteria presented in Table 1.

Table 1: Selection Criteria

Population	Q1,2,5: People with dry mouth caused by radiotherapy for cancer of the head or neck Q3-5: People with dry eyes caused by radiotherapy for cancer of the head or neck
Intervention	Pilocarpine, all formulations
Comparators	Q1-4: Sialagogues (e.g., anethole trithione, cevimeline); Q1,2: Nonpharmacological therapy (e.g., dental care, salivary flow stimulation [e.g., sugarless gum, lozenges], water consumption); artificial saliva, saliva substitutes, oral lubricants Q3,4: Non-prescription artificial tears, ocular lubricants, or viscosity agents (e.g., carboxymethyl cellulose, polyethylene glycol, sodium hyaluronate, petrolatum, carbomer) Q5: not applicable
Outcomes	Q1: Clinical effectiveness (e.g., oral mucosa health, dental health, salivary flow rate, comfort, quality of life, dysphagia, dysgeusia, side effects) Q2,4: Cost-effectiveness (e.g., cost per quality adjusted life year, cost per clinical outcome) Q3: Clinical effectiveness (e.g., ocular surface health, lacrimal flow rate, ocular comfort, quality of life, side effects) Q5: Evidence based guidelines on appropriate use and place in therapy
Study Designs	Health technology assessments, systematic reviews, randomized controlled trials, non-randomized studies, economic evaluations, evidence-based guidelines

Exclusion Criteria

Articles were excluded if they did not meet the selection criteria outlined in Table 1, they were duplicate publications, or were published prior to 2009. Systematic reviews (SRs) that had broader inclusion criteria than the present review were examined in detail to ascertain whether data could be extracted from a relevant sub-set of included studies, rather than excluding the SR entirely. Guidelines with unclear methodology were also excluded.

Critical Appraisal of Individual Studies

The included SRs were critically appraised by one reviewer using A Measurement Tool to Assess Systematic Reviews 2 (AMSTAR 2),[12] and the guidelines were assessed with the Appraisal of Guidelines for Research Evaluation II (AGREE II) instrument.[13] Summary scores were not calculated for the included studies; rather, a review of the strengths and limitations of each included study were described narratively.

Summary of Evidence

Quantity of Research Available

A total of 156 citations were identified in the literature search. Following screening of titles and abstracts, 126 citations were excluded and 30 potentially relevant reports from the electronic search were retrieved for full-text review. Four potentially relevant publications were retrieved from the grey literature search for full text review. Of these potentially relevant articles, 31 publications were excluded for various reasons, and three publications met the inclusion criteria and were included in this report. Appendix 1 presents the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA)[14] flowchart of the study selection. Note that because the included SRs had broader inclusion criteria than the present review (i.e., were wider in scope), only subsets of primary studies that met the selection criteria for the present review are described.

Appendix 6 includes 12 additional references that did not meet the inclusion criteria of this report but may be of interest.

Summary of Study Characteristics

Two SRs[15,16] (one with MA),[15] and one evidence-based guideline[17] were identified and included in this review. One SR[16] met the inclusion criteria for this report; however, none of its primary studies met the eligibility criteria for this report; therefore, no summary can be provided. No relevant health technology assessment, randomized controlled trial (RCT), non randomized study (NRS), or economic evaluation were identified. Detailed characteristics are available in Appendix 2 Table 2, and Table 3.

Study Design

One SR, published in 2017, sought out relevant RCTs published up to July 2016.[15] There were three relevant primary studies retained from this SR with MA; however, none of the relevant publications were included in the MA.[15] The second SR, published in 2016, reviewed relevant clinical trials published between 2006 and March 2015, and contained no relevant primary studies.[16] Appendix 5 Table 8 highlights the absence of overlap in primary studies between the SRs.

One guideline was identified regarding radiotherapy for head and neck cancer (HNC) that contained recommendations on the use of pilocarpine for dry mouth or dry eyes.[17] Published in 2016,[17] by the Malaysia Health Technology Assessment Section (MHTAS) of the Ministry of Health, the guideline bases its recommendation on a SR of the literature.[17] The quality of the evidence was assessed by the authors using the ranking of the Canadian Task Force on Preventative Health Care (CTFPHC) prior to consensus discussion with members of the review committee.[17]

Country of Origin

The SRs were authored in the United Kingdom[15] and Spain.[16]

The guideline was developed in Malaysia.[17]

Patient Population

One SR included adults with a diagnosis of radiotherapy-induced xerostomia.[15] The primary studies included within the SR had sample sizes of 33,[18] 20,[19] and 146[20] participants. While the other SR explored an elderly population with dry mouth as a result of medication, Sjögren's syndrome or other systemic disease, or who received radiation for HNC.[16]

The MHTAS guideline target patients with nasopharyngeal carcinoma, and the intended users are health care professionals involved in their care.[17]

Interventions and Comparators

One SR compared various techniques designed to replace or stimulate saliva production with various comparators (e.g., placebo, no intervention, active intervention).[15] The second SR compared pharmacological treatments (e.g., pilocarpine, cevimeline), with non-pharmacological saliva products, and with alternative treatments.[16]

The guideline considers a broader scope of treatments for the management of cancer treatment side effects. Interventions relevant to dry mouth include: non-pharmacological interventions, and pharmacotherapy (e.g., pilocarpine).[17]

Outcomes

The SRs considered outcomes relating to xerostomia symptoms,[15,16] quality of life,[15] and salivary flow.[15,16]

The outcomes of interest in the guideline are broad and included physical and psychosocial effects of cancer treatment. Outcomes relevant to dry mouth include oral complications.[17]

Summary of Critical Appraisal

Additional details regarding the strengths and limitations of the included publications are provided in Appendix 3, Table 4, and Table 5.

Systematic Reviews

The strengths and limitations of the SRs[15,16] were assessed using the relevant components of AMSTAR 2;[12] however, for the second SR[16] none of the primary studies included were relevant to this report, resulting in a number of checklist items being not applicable.

In both SRs,[15,16] the research questions and the inclusion criteria were well described, the study selection was completed in duplicate, and although the included studies were partially described, greater detail regarding the population characteristics (such as age, gender, dose of radiation received) and study designs were not provided. Neither SR[15,16] reported whether data extraction was conducted in duplicate, nor provided a justification of their choice of included study designs, nor provided a list of excluded studies. It is possible this may have resulted in missed studies. Although both SR[15,16] indicated having an *a priori* protocol, details were lacking on the risk of bias assessment,[15,16] components of the review question,[15,16] or whether there were any significant deviations from the protocol.[15,16] As such, reporting bias cannot be assessed. Authors of one SR did not extend their search

beyond one database (i.e., PubMED),[16] and neither SRs report having searched the grey literature;[15,16] as such, it is possible these may have resulted in missed studies.

Evidence-Based Guidelines

In the guideline,[17] the scope and purpose are well described, and recommendations are clearly presented. While none are developed in Canada, authors sought the views and preferences of the target population, employed systematic methods to search for evidence, and clearly described the methods for formulating the recommendations. Furthermore, resources to support guideline implementation are provided, and a procedures is provided for future updates to the recommendations.[17] Lastly, the views of the funding body do not appear to have influenced the content of the guidelines.[17]

Summary of Findings

A detailed summary of findings and guideline recommendations is provided in Appendix 4, Table 6, and Table 7. One SR,[16] met the inclusion criteria for this report; however, none of its primary studies met the eligibility criteria. As such, no summary can be provided for this SR.

Clinical Effectiveness of Pilocarpine for the Treatment of Dry Mouth Caused by Radiotherapy for Cancer of the Head or Neck

Xerostomia Symptoms

Information regarding the effect of pilocarpine on dry mouth of HNC patients who are post-radiotherapy, was available from two unique primary studies[18,19] included in one SR.[15]

A study of 33 participants[18] compared the effect of systemic pilocarpine (i.e., oral tablet, dose not reported), versus a 3 mg pilocarpine lozenges, versus a 5 mg pilocarpine lozenge, versus an inactive lozenge.[15] After 180 minutes, more participants in the 5 mg pilocarpine lozenge group reported a reduction in xerostomia sensation compared to other groups.[15] (no effect estimates or statistics provided). A second study, with 20 participants,[19] compared a pilocarpine mouthwash versus saliva substitutes. After 12 weeks of use, there was no between-group statistically significant difference (as reported by the SR authors, *P*-value not reported) in changes of xerostomia symptoms on a visual analogue scale (VAS).[15]

Salivary Function

Information regarding the effect of pilocarpine on salivary function of HNC patients who are post-radiotherapy, was available from two unique primary studies[18,20] included in one SR.[15]

A study of 33 participants[18] compared the effect of systemic pilocarpine (i.e., oral tablet, dose not reported), versus a 3 mg pilocarpine lozenges, versus a 5 mg pilocarpine lozenge, versus a placebo lozenge.[15] After 180 minutes, the unstimulated whole salivary flow was significantly higher (no effect estimates or statistics provided) in all groups of participants on pilocarpine compared to the inactive lozenge group.[15] A second study, with 146 participants,[20] compared systemic pilocarpine with acupuncture-like transcutaneous electrical nerve stimulation (ALTENS). After nine months of use, the was no statistically significant difference (as reported by the SR authors, *P*-value not reported) in unstimulated and stimulated whole salivary flow change between groups.[15]

Quality of Life

Information regarding the effect of pilocarpine on quality of life of HNC patients who are post-radiotherapy, was available from one unique primary study[20] included in one SR.[15]

The study, with 146 participants,[20] compared systemic pilocarpine with acupuncture-like transcutaneous electrical nerve stimulation (ALTENS). After nine months of use, the was no statistically significant difference (as reported by the SR authors, *P*-value not reported) in Xerostomia-Related Quality of Life Scale (XeQOLS) score change between groups.[15]

Cost-Effectiveness of Pilocarpine for the Treatment of Dry Mouth Caused by Radiotherapy for Cancer of the Head or Neck

No relevant evidence regarding the comparative cost-effectiveness of pilocarpine versus nonpharmacological therapy or saliva substitutes for people with dry mouth caused by radiotherapy for HNC was identified; therefore, no summary can be provided.

Clinical Effectiveness of Pilocarpine for the Treatment of Dry Eyes Caused by Radiotherapy for Cancer of the Head or Neck

No relevant evidence regarding the clinical effectiveness of pilocarpine versus non-prescription artificial tears, ocular lubricants, or viscosity agents for people with dry eyes caused by radiotherapy for HNC was identified; therefore, no summary can be provided.

Cost-Effectiveness of Pilocarpine for the Treatment of Dry Eyes Caused by Radiotherapy for Cancer of the Head or Neck

No relevant evidence regarding the cost-effectiveness of pilocarpine versus non-prescription artificial tears, ocular lubricants, or viscosity agents for people with dry eyes caused by radiotherapy for HNC was identified; therefore, no summary can be provided.

Evidence-Based Guidelines of Pilocarpine for the Treatment of Dry Mouth or Dry Eyes Caused by Radiotherapy for Cancer of the Head or Neck

One guideline[17] was identified regarding recommendations on the use of pilocarpine for the treatment of dry mouth or dry eyes of HNC patients who are post-radiotherapy.

The MHTAS guideline recommend, based on evidence obtained from at least one RCT (strength of recommendation not reported), that pilocarpine be offered if it is available.[17]

Limitations

A number of limitations were identified in the critical appraisal as shown in Appendix 3, Table 4, and Table 5; however, additional limitations exist. The main limitations of this review relate to the scarcity of high-quality comparative evidence identified and the generalisability of the findings.

Authors of the SR[15] assessed the relevant primary studies[18-20] as having a high risk of bias, introducing uncertainty in their results. Additionally, the SR[15] reported results without providing statistical data or effect size (as appropriate), which may have introduced an outcomes reporting bias, also limiting the overall reliability of the results.

The sample size of two primary studies[18,19] may have been too small to examine uncommon clinical events, and these may have been underpowered to detect differences between groups. Except for the primary study that measured outcomes shortly after the

administration of the intervention,[18] participant's adherence with treatment was not reported in the SR, which introduces uncertainty with regards to the magnitude of effects.

Another limitation that should be considered when interpreting these results is that studies in the SR[15] were open-label,[18-20] where participants or outcome assessors were not blinded to the treatment. Thus, consideration should be given to the reliability of subjective or self-reported outcomes (e.g., xerostomia sensation), since these findings may be at risk of bias (in either direction) depending on the perceptions and expectations of participants and clinicians involved.

Moreover, the treatment formulations that were studied (i.e., pilocarpine lozenges and pilocarpine mouthwash) are currently not available as a marketed product in Canada and would necessitate compounding by a licensed pharmacist.

The primary studies included in the SR[15] were conducted between 1994[19] and 2015.[19] During this time, HNC treatment modalities have advanced and participants of the most recent studies likely received lower radiation doses to, or better protection of, salivary glands.

It is important to note that patients with HNC often have multiple chronic conditions. Due to inadequate reporting in the SR,[15] a thorough assessment of populations in the primary studies[18-20] could not be completed. Consequently, caution should be exercised when generalising the results from included studies, in which selection criteria may have excluded patients with multiple chronic conditions.

The applicability of the evidence to the Canadian setting is unclear since the country of origin of the primary studies[18-20] was not reported and the evidence-based guidelines[17] were not developed in Canada.

Guideline recommendations are based on current evidence in the literature; however, the evidence was not sufficient to warrant a strong recommendation.[17]

Although data were identified regarding pilocarpine's use, there was no clear evidence that emerged from the literature on the optimal dose, formulation, or route of administration, suggesting that additional research in this area is required.

No relevant studies reported on harm outcomes (e.g., side effects, morbidity, mortality); consequently, the comparative safety of pilocarpine with various nonpharmacological therapy or saliva substitutes is largely unknown.

No relevant studies reported on the effectiveness of pilocarpine for dry eyes, and no cost-effectiveness studies were identified, suggesting that additional research in these areas is required.

Conclusions and Implications for Decision or Policy Making

This report identified clinical evidence and evidence-based guidelines regarding the use of pilocarpine for the treatment of dry mouth caused by radiotherapy for cancer of the head or neck. Two SRs[15,16] (one with MA),[15] and one evidence-based guideline[17] were identified and included in this review. One SR[16] met the inclusion criteria for this report; however, none of its primary studies met the eligibility criteria; therefore, no summary can be provided.

The identified literature was at high risk of bias and revealed mixed conclusions regarding clinical evidence of pilocarpine on dry mouth of HNC patients who are post-radiotherapy. No clear direction emerged from the SR regarding relief of xerostomia symptoms, with one study finding no difference between a pilocarpine mouthwash and saliva substitutes,[18] while another study found more patients responded favourably to 5 mg pilocarpine lozenges over tablets, lozenges of lower strength, and inactive lozenges.[19] In the presence of this ambivalent body of evidence, it is therefore difficult to close the gap on whether pilocarpine is effective for this application.

The Malaysia evidence-based guideline recommends (based on evidence from at least one RCT) that pilocarpine be offered;[17] however, this recommendation should be interpreted cautiously as it comes with a high level of uncertainty, based on appraisal and limitations.

No relevant literature or evidence-based guidelines were identified regarding dry eyes caused by HNC radiotherapy. Likewise, no clinical or cost-effectiveness evidence was identified regarding dry mouth or dry eyes caused by HNC radiotherapy.

The limitations of the included studies should be considered when interpreting the results. The findings highlight a lack of high-quality comparative studies regarding the effectiveness of pilocarpine compared with nonpharmacological measures and saliva substitutes. Further research, especially by way of methodologically-sound RCTs, would help reduce this uncertainty.

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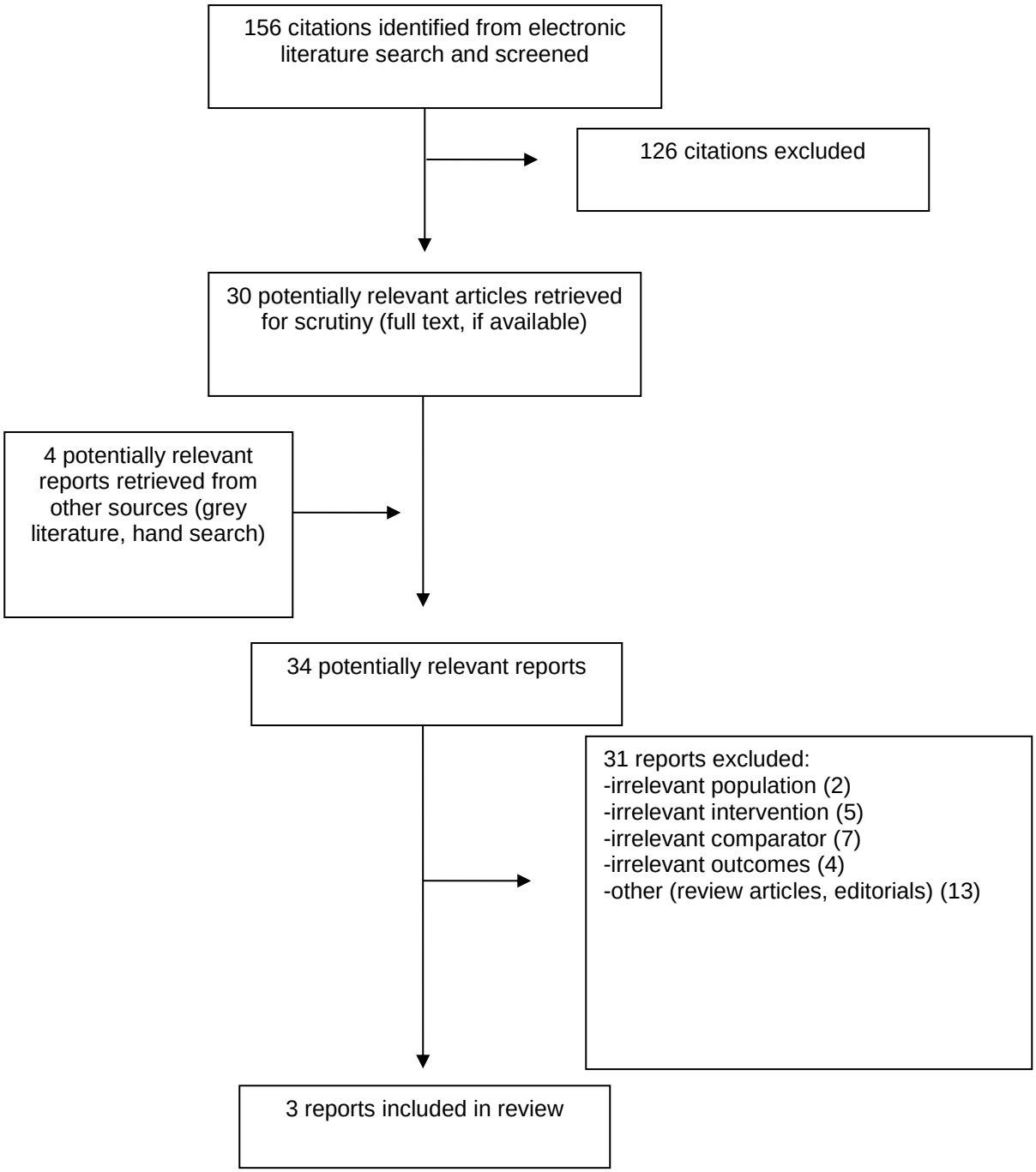
Appendix 1: Selection of Included Studies



Appendix 2: Characteristics of Included Publications

Table 2: Characteristics of Included Systematic Reviews and Meta-Analyses

First Author, Publication Year, Country	Study Designs and Numbers of Primary Studies Included	Population Characteristics	Intervention and Comparator(s)	Clinical Outcomes
Mercadante, 2017[15] **United Kingdom** Relevant publications: • Taweechaisupapong, 2006[18] • Davies, 1994[19] • Wong, 2015[20]	**Study design**: SR of relevant RCTs, with a MA (none of the relevant publications were included in the MA) **Literature search strategy**: Authors performed literature searches in several databases (e.g., MEDLINE, EMBASE, CENTRAL, CINAHL).up to July 2016 **Number of studies included**: In total, 20 studies were included, with three relevant for this review **Quality assessment tool**: The Cochrane Risk of Bias assessment tool **Objective**: To examine the effectiveness of available treatments for the management of radiotherapy-induced hyposalivation and xerostomia	Adults with a diagnosis of radiotherapy-induced xerostomia The studies relevant to this report has sample sizes of 33,[18] 20,[19] and 146[20] participants	**Intervention**: various techniques designed to stimulate saliva production or to replace saliva **Comparator**: placebo, no intervention, another active intervention, or a combination of these Studies relevant to the present report compared: • Pilocarpine tablet versus pilocarpine lozenges (3 and 5 mg) versus placebo lozenges[18] • Pilocarpine mouthwash versus saliva substitutes[19] • Pilocarpine versus ALTENS[20]	**Outcomes**: • Xerostomia symptoms • Quality of life • Salivary flow
Gil-Montoya, 2016[16] **Spain** Relevant publications: • None	**Study design**: SR of relevant clinical trials **Literature search strategy**: Authors performed a literature search in PubMED from 2006 to March 2015	Elderly participants with dry mouth as a result of medication, Sjögren's syndrome or other systemic disease, or who have received radiation for HNC	**Intervention**: • pharmacological treatments (e.g., pilocarpine, cevimeline) • nonpharmacological or artificial saliva products	**Outcomes**: • Xerostomia symptoms • Salivary flow

First Author, Publication Year, Country	Study Designs and Numbers of Primary Studies Included	Population Characteristics	Intervention and Comparator(s)	Clinical Outcomes
	Number of studies included: In total, 26 were relevant to other questions in the review. No primary studies were relevant to this report **Quality assessment tool**: The Oxford Quality Scale **Objective**: To review the evidence regarding treatments of dry mouth, regardless of etiology		• alternative treatments (e.g., acupuncture or electro-stimulation) **Comparator**: to each other	

ALTENS = acupuncture-like transcutaneous electrical nerve stimulation; CENTRAL = Cochrane Central Register of Controlled Trials; CINAHL = Cumulative Index to Nursing and Allied Health Literature; EMBASE = Excerpta Medica database; HNC = head and neck cancer; MA = meta-analysis; MEDLINE = Medical Literature Analysis and Retrieval System Online; NR = not reported; PubMED = Public MEDLINE; RCT = randomized controlled trial; SR = systematic review.

Table 3: Characteristics of Included Guidelines

Intended Users, Target Population	Intervention and Practice Considered	Major Outcomes Considered	Evidence Collection, Selection, and Synthesis	Evidence Quality Assessment	Recommendations Development and Evaluation	Guideline Validation
Malaysia Health Technology Assessment Section (MHTAS), 2016[17] Malaysia						
Intended users: Those involved in the management of nasopharyngeal carcinoma (e.g., medical and dental officers, allied health professionals, medical students, patients) **Target population:** All patients with	Various interventions pertaining to the diagnosis and treatment of nasopharyngeal cancer Relevant interventions include: pilocarpine, non-pharmacological measures, gargles	Various outcomes pertaining to the follow-up of nasopharyngeal cancer Relevant outcomes include: Oral complications	Authors conducted a SR using MEDLINE, Cochrane Database of SRs, Guidelines International Network, retaining literature published in the 20 years prior to August 2016	Quality of evidence assessed using the ranking of the CTFPHC: • I: at least one proper RCT • II-1: well designed trial without randomizatio n • II-2: well designed cohort or case-control study	Members of the guideline development group discussed findings and agreed upon recommendations via consensus with members of the review committee	The draft guidelines were sent for external review and public stakeholder feedback

Intended Users, Target Population	Intervention and Practice Considered	Major Outcomes Considered	Evidence Collection, Selection, and Synthesis	Evidence Quality Assessment	Recommendations Development and Evaluation	Guideline Validation
nasopharyngeal carcinoma				• II-3: comparisons between times or places with or without the intervention • III: expert opinions		

CTFPHC = Canadian Task Force on Preventive Health Care; MEDLINE = Medical Literature Analysis and Retrieval System Online; MHTAS = Malaysia Health Technology Assessment Section; RCT = randomized controlled trial; SR = systematic review.

Appendix 3: Critical Appraisal of Included Publications

Table 4: Strengths and Limitations of Systematic Reviews and Meta-Analyses using AMSTAR 2[12]

Strengths	Limitations
Mercadante, 2017[15] United Kingdom	
• The objectives and inclusion/exclusion criteria were clearly stated and included components of the population, intervention, comparator, and outcomes • Study selection was completed in duplicate • Bias was assessed using the Cochrane Risk of Bias tool • Authors used an appropriate method for statistical combination of the results, they justified combining the data and used an appropriate weighted technique to combine study results (i.e., fixed effect model) • Only randomized control trials with low risk of bias were included in the meta-analysis • Authors provided a discussion of the likely impact of risk of bias of individuals studies on the results of the review • Sources of funding were disclosed (no direct funding) • Authors provided a statement on conflicts of interest (none known)	• Included studies were inadequately described, (e.g., the number of participants was the only population descriptor) • Although a protocol was established prior to the conduct of the review, it did not include components of the review questions or details of the risk of bias assessment. Furthermore, the report did not discuss whether there were any significant deviations from the protocol • The choice of included study designs was not justified • Although authors searched at least two databases, they did not provide key words or search strategy, nor did they justify their publication restrictions. Furthermore, grey literature searching was not reported • Data extraction was not reported as being done in duplicate • A list of excluded studies was not provided • Review authors did not report on source of funding for the included studies • Publication bias was not investigated and the impact on results of the review not discussed
Gil-Montoya, 2016[16] Spain	
• The research question included a description of the population, intervention, comparator, and outcomes • Study selection was completed in duplicate • Although, authors applied the Oxford Quality Scale and only retained articles with a score of four or five, they did not discuss risk of bias for individual articles • Authors provided a statement on conflicts of interest (none known)	• Included studies were inadequately described, (e.g., the research design was not mentioned) • Although authors indicate that a protocol was established prior to the conduct of the review, no details were given on its content and the report does not discuss whether there were any significant deviations from the protocol • The choice of included study designs was not justified • Only one database was searched, and publication restrictions were not justified • Data extraction was not reported as being done in duplicate • A list of excluded studies was not provided • Review authors did not report on source of funding for the included studies • Publication bias was not investigated and the impact on results of the review not discussed • Authors did no discuss any heterogeneity observed in the results of the review.

Table 5: Strengths and Limitations of Guidelines using AGREE II[13]

Item	Guideline
	MHTAS, 2016[17] Malaysia
Domain 1: Scope and Purpose	
1. The overall objective(s) of the guideline is (are) specifically described.	Yes
2. The health question(s) covered by the guideline is (are) specifically described.	Yes
3. The population (patients, public, etc.) to whom the guideline is meant to apply is specifically described.	Yes
Domain 2: Stakeholder Involvement	
4. The guideline development group includes individuals from all relevant professional groups.	Yes
5. The views and preferences of the target population (patients, public, etc.) have been sought.	Yes
6. The target users of the guideline are clearly defined.	Yes
Domain 3: Rigour of Development	
7. Systematic methods were used to search for evidence.	Yes
8. The criteria for selecting the evidence are clearly described.	Yes
9. The strengths and limitations of the body of evidence are clearly described.	Yes
10. The methods for formulating the recommendations are clearly described.	Yes
11. The health benefits, side effects, and risks have been considered in formulating the recommendations.	Yes
12. There is an explicit link between the recommendations and the supporting evidence.	Yes
13. The guideline has been externally reviewed by experts prior to its publication.	Yes
14. A procedure for updating the guideline is provided.	Yes
Domain 4: Clarity of Presentation	
15. The recommendations are specific and unambiguous.	Yes
16. The different options for management of the condition or health issue are clearly presented.	Yes
17. Key recommendations are easily identifiable.	Yes
Domain 5: Applicability	
18. The guideline describes facilitators and barriers to its application.	Yes
19. The guideline provides advice and/or tools on how the recommendations can be put into practice.	Yes
20. The potential resource implications of applying the recommendations have been considered.	Yes
21. The guideline presents monitoring and/or auditing criteria.	Yes
Domain 6: Editorial Independence	
22. The views of the funding body have not influenced the content of the guideline.	Yes
23. Competing interests of guideline development group members have been recorded and addressed.	Yes

Appendix 4: Main Study Findings and Authors' Conclusions

Table 6: Summary of Findings Included Systematic Reviews and Meta-Analyses

Main Study Findings	Authors' Conclusion
Mercadante, 2017[15] United Kingdom	
Primary study citation: • Taweechaisupapong, 2006[18] • Davies, 1994[19] • Wong, 2015[20] **Xerostomia symptoms** • Pilocarpine tablet vs pilocarpine lozenges (3 and 5 mg) vs placebo lozenges[18] ○ After 180 minutes of use, more participants in the 5 mg lozenge group reported a reduction in xerostomia sensation compared to other groups.[18] (no effect estimates, or statistics provided) • Pilocarpine mouthwash vs saliva substitutes[19] ○ No statistically significant difference (*P*-value not reported) in changes on VAS between groups after 12 weeks of use. **Salivary function** • Systemic pilocarpine (oral tablet) vs pilocarpine lozenges (3 and 5 mg) vs placebo lozenges[18] ○ After 180 minutes of use, the unstimulated whole salivary flow was significantly higher (no effect estimates, or statistics provided) in all groups of participants on pilocarpine compared to the placebo lozenge group. • Pilocarpine vs ALTENS[20] ○ After nine months of use, the was no statistically significant difference (*P*-value not reported) in unstimulated and stimulated whole salivary flow change between groups. **Quality of Life** • Systemic pilocarpine vs ALTENS[20] ○ After nine months of use, the was no statistically significant difference (*P*-value not reported) in XeQOLS score changes between groups.	"Pilocarpine and cevimeline should represent the first line of therapy in HNC survivors with radiotherapy-induced xerostomia and hyposalivation. There is very weak evidence that salivary substitutes can provide some, if any, benefit of small magnitude and unclear clinical significance. The use of other treatment modalities cannot be supported on the basis of current evidence."[15] (*p*73)
Gil-Montoya, 2016[16] Spain	
No relevant primary studies were identified therefore no summary can be provided.	

ALTENS = acupuncture-like transcutaneous electrical nerve stimulation; HNC = head and neck cancer; VAS = visual analogue scale; XeQOLS = Xerostomia-Related Quality of Life Scale.

Table 7: Summary of Recommendations in Included Guidelines

Recommendations	Strength of Evidence and Recommendations
Malaysia Health Technology Assessment Section (MHTAS), 2016[17] Malaysia	
1. "Pilocarpine may be offered for treatment of post-radiotherapy xerostomia in NPC patients, if it is available."[17] (*p*17) (Strength of recommendation NR)	Quality of the evidence was judged using CTFPHC ranking. 1. (I) Evidence obtained from at least one properly randomized controlled trial

CTFPHC = Canadian Task Force on Preventive Health Care; MHTAS = Malaysia Health Technology Assessment Section; NPC = nasopharyngeal carcinoma.

Appendix 5: Overlap between Included Systematic Reviews

Table 8: Relevant Primary Study Overlap between Included Systematic Reviews

Relevant Primary Study Citation	Systematic Review Citation	
	Mercadante, 2017[15] United Kingdom	Gil-Montoya, 2016[16] Spain
Taweechaisupapong, 2006[18]	X	
Davies, 1994[19]	X	
Wong, 2015[20]	X	

Appendix 6: Additional References of Potential Interest

Systematic Review

Alternative Population – Not Specific to Head or Neck Cancer

Jensen SB, Pedersen AML, Vissink A, et al. A systematic review of salivary gland hypofunction and xerostomia induced by cancer therapies: Management strategies and economic impact. *Support Care Cancer*. 2010 August;18(8):1061-1079.
PubMed: PM50846741

Randomized Controlled Trial

Alternative Indication – Prophylaxis

Haghighatafshar M, Ghaedian M, Etemadi Z, Entezarmahdi SM, Ghaedian T. Pilocarpine effect on dose rate of salivary gland in differentiated thyroid carcinoma patients treated with radioiodine. *Nucl Med Commun*. 2018 May;39(5):430-434.
PubMed: PM29517578

Pimentel MJ, Filho MM, Araujo M, Gomes DQ, LJ DAC. Evaluation of radioprotective effect of pilocarpine ingestion on salivary glands. *Anticancer Res*. 2014 Apr;34(4):1993-1999.
PubMed: PM24692737

Alternative Comparator – Salivary Gland Transfer

Jha N, Seikaly H, Harris J, et al. Phase III randomized study: oral pilocarpine versus submandibular salivary gland transfer protocol for the management of radiation-induced xerostomia. *Head Neck*. 2009 Feb;31(2):234-243.
PubMed: PM19107948

Clinical Practice Guidelines

Alternative Outcome – Pilocarpine not Explicitly Part of Recommendations

Cohen EE, LaMonte SJ, Erb NL, et al. American Cancer Society Head and Neck Cancer Survivorship Care Guideline. CA Cancer J Clin. 2016 May;66(3):203-39. doi: 10.3322/caac.21343. Epub 2016 Mar 22.
https://onlinelibrary.wiley.com/doi/epdf/10.3322/caac.21343

Peterson DE, Boers-Doets CB, Bensadoun RJ, Herrstedt J. Management of oral and gastrointestinal mucosal injury: ESMO Clinical Practice Guidelines for diagnosis, treatment, and follow-up. *Ann Oncol.* 2015;26(Supplement 5):v139-v151.
http://dx.doi.org/10.1093/annonc/mdv202

Glenny AM, Gibson F, Auld E, et al. The development of evidence-based guidelines on mouth care for children, teenagers and young adults treated for cancer. *Eur J Cancer.* 2010;46(8):1399-1412.
https://dx.doi.org/10.1016/j.ejca.2010.01.023

Unspecified Methodology

White JM, Panchal NH, Wehler CJ, et al. Department of Veterans Affairs Consensus: Preradiation dental treatment guidelines for patients with head and neck cancer. *Head Neck*. 2019 May;41(5):1153-1160.
PubMed: PM30620438

Mehanna H, Kong A, Ahmed SK. Recurrent head and neck cancer: United Kingdom National Multidisciplinary Guidelines. *J Laryngol Otol*. 2016 May;130(S2):S181-S190.
PubMed: PM27841130

Sood S, McGurk M, Vaz F. Management of Salivary Gland Tumours: United Kingdom National Multidisciplinary Guidelines. *J Laryngol Otol*. 2016 May;130(S2):S142-S149.
PubMed: PM27841127

Kumar N, Brooke A, Burke M, John R, O'Donnell A, Soldani F. The Oral Management of Oncology Patients Requiring Radiotherapy, Chemotherapy and / or Bone Marrow Transplantation: Clinical Guidelines. London, UK: The Royal College of Surgeons of England and the British Society for Disability and Oral Health; 2012: http://www.bsdh.org/documents/pBSDH_RCS_Oncol_Radio_BMT_update_2012.pdf. Accessed 16-Dec-2019.