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CADTH RAPID RESPONSE REPORT:
SUMMARY WITH CRITICAL APPRAISAL

Pilocarpine for Sjögren's Syndrome-Induced Dry Mouth and Dry Eyes: A Review of Clinical Effectiveness, Cost-Effectiveness, and Guidelines

Service Line:	Rapid Response Service
Version:	1.0
Publication Date:	January 21, 2020
Report Length:	30 Pages

CADTH

Authors: Christopher Freige, Caitlyn Ford

Acknowledgement: Kendra Brett

Cite As: Pilocarpine for Dry Mouth and Dry Eyes in Sjögren's Syndrome: A Review of Clinical Effectiveness, Cost-Effectiveness, and Guidelines. Ottawa: CADTH; 2020 January. (CADTH rapid response report: summary with critical appraisal).

ISSN: 1922-8147 (online)

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Funding: CADTH receives funding from Canada's federal, provincial, and territorial governments, with the exception of Quebec.

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Abbreviations

ACR	American College of Rheumatology
ACR/EULAR	American College of Rheumatology/European League Against Rheumatism
AECG	American-European Consensus Group
AGREE II	Appraisal of Guidelines for Research & Evaluation II
AMSTAR 2	A Measurement Tool to Assess Systematic Reviews 2
BSR	British Society for Rheumatology
CRD	Centre for Reviews and Dissemination
EULAR	European League Against Rheumatism
MA	meta-analysis
MeSH	Medical Subject Headings
MEDLINE	Medical Literature Analysis and Retrieval System Online
NRS	non-randomized study
PubMed	Public MEDLINE
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
RCT	randomized controlled trial
SR	systematic review

Context and Policy Issues

Sjögren's syndrome is an autoimmune disease most frequently affecting women between 30 and 50 years of age.[1] Sjögren's syndrome is often under-diagnosed but may affect up to 430,000 Canadians.[1] The cause of Sjögren's syndrome is currently unknown, however, one prevalent theory is that certain genetic factors coupled with an environmental stimulus (i.e., a virus) triggers the disease.[1,2]

There are two main classifications of Sjögren's syndrome: primary and secondary.[2] Patients are classified as having primary Sjögren's syndrome when there is no other autoimmune disease present.[2] Patients are classified as having secondary Sjögren's syndrome when another autoimmune disorder, such as rheumatoid arthritis, systemic lupus erythematosus or systemic sclerosis, is also present.[2] Both types of Sjögren's syndrome are characterized by damage to exocrine glands such as the salivary, tear and mucous-secreting glands, which can result in dry eyes and dry mouth.[1,2] Dry eyes can cause discomfort via a scratchy and gritty sensation.[2] In rare, severe cases, vision impairment may occur due to damage to the corneal surface.[2] Dry mouth occurs secondary to a diminished saliva production and can cause difficulty chewing and swallowing, *Candida* infections, tooth decay and sialolithiasis.[2] Both dry eyes and dry mouth can be managed with a variety of non-pharmacological and non-prescription therapies.[1] Pharmacological therapy with muscarinic agonists (i.e., pilocarpine, cevimeline) which stimulate exocrine glands, can also be used to alleviate the symptoms of dry eyes and dry mouth.[3] Other symptoms of Sjögren's syndrome may include extraglandular manifestations such as lymphadenopathy, Raynaud phenomenon, and vasculitis.[2]

This report aims to summarize the evidence regarding the clinical effectiveness, cost-effectiveness and evidence-based guidelines' recommendations for the use of pilocarpine in the treatment of Sjögren's syndrome-induced dry eyes and dry mouth.

Research Questions

1. What is the clinical effectiveness of pilocarpine for the treatment of dry mouth in Sjögren's syndrome?
2. What is the cost-effectiveness of pilocarpine for the treatment of dry mouth in Sjögren's syndrome?
3. What is the clinical effectiveness of pilocarpine for the treatment of dry eyes in Sjögren's syndrome?
4. What is the cost-effectiveness of pilocarpine for the treatment of dry eyes in Sjögren's syndrome?
5. What are the evidence-based guidelines regarding pilocarpine for the treatment of dry mouth and dry eyes in Sjögren's syndrome?

Key Findings

Seven systematic reviews (three of which contained relevant primary studies) were identified regarding the clinical effectiveness of pilocarpine in the treatment of Sjögren's syndrome-induced dry mouth and/or dry eyes. In addition, two evidence-based guidelines were identified regarding pilocarpine for the treatment of dry mouth and dry eyes in Sjögren's syndrome. No evidence on the cost-effectiveness of pilocarpine for patients with Sjögren's syndrome experiencing either dry mouth or dry eyes was identified.

Three systematic reviews of critically low quality contained three relevant primary studies which provided a limited quantity of evidence applicable to this report. The three primary studies provided heterogenous evidence as they had different patient populations, comparators and outcomes. Overall, pilocarpine was effective in the treatment of Sjögren's syndrome-induced dry mouth and dry eyes but may not be as tolerable as cevimeline.

Both guidelines recommend the use of pilocarpine for the treatment of dry mouth. One guideline also recommends pilocarpine for the treatment of dry eyes whilst the second guideline states it may be considered for the treatment of dry eyes.

Overall, the findings of this report come with a degree of uncertainty as the identified evidence was of critically low quality and quantity.

Methods

Literature Search Methods

A limited literature search was conducted by an information specialist on key resources including PubMed, 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 Sjogren's syndrome and pilocarpine. No filters were applied to limit the retrieval by study type. Where possible, retrieval was limited to the human population. The search was also limited to English-language documents published between January 1, 2009 and December 4, 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

Populations	Q1, 2, 5: People with Sjögren's syndrome-induced dry mouth Q3-5: People with Sjögren's syndrome-induced dry eyes
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: Recommendations 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 published in language other than English, or were published prior to 2009. Primary studies were excluded if they were captured in an included systematic review (SR). 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[4] (AMSTAR 2) and guidelines were assessed with the Appraisal of Guidelines for Research & Evaluation II[5] (AGREE II) instrument. Summary scores were not calculated for the included studies; rather, a review of the strengths and limitations of each included study was described narratively.

Summary of Evidence

Quantity of Research Available

A total of 238 citations were identified in the literature search. Following screening of titles and abstracts, 220 citations were excluded and 18 potentially relevant reports from the electronic search were retrieved for full-text review. Two potentially relevant publications were retrieved from the grey literature search for full-text review. Of these potentially relevant articles, 11 were excluded for various reasons and nine publications met the

inclusion criteria and were included in this report. These comprised seven SRs[6-12] and two evidence-based guidelines.[3,13] Appendix 1 presents the PRISMA[14] flowchart of the study selection. Appendix 5 includes additional references that did not meet the inclusion criteria of this report but may be of interest.

Summary of Study Characteristics

Seven relevant SRs[6-12] and two relevant evidence-based guidelines[3,13] were identified and included in this report, and a summary of their characteristics is provided below. The seven included SRs[6-12] had inclusion criteria that were broader in scope than the criteria for this report. Specifically, all seven SRs[6-12] included interventions other than pilocarpine and included different comparators (e.g., placebo). Three of the SRs[8-10] also included patients experiencing dry mouth due to a variety of causes. Consequently, four of the SRs[8-11] met the inclusion criteria for this report but did not include any eligible primary studies. This report will focus on the subset of SRs which contained primary studies matching the selection criteria. Additional details regarding the characteristics of included publications are provided in Appendix 2.

Study Design

Three relevant SRs containing eligible primary studies were identified regarding the clinical effectiveness of pilocarpine for the treatment of dry mouth or dry eyes in Sjögren's syndrome. One SR,[6] published in 2019, searched multiple databases for randomized controlled trials from an unspecified date to February 2018. The review[6] contained one randomized controlled trial (RCT) (assessed by the authors to have a low risk of bias) relevant to this report which was published in 2018. Another SR,[7] also published in 2019, searched multiple databases for meta-analyses, randomized controlled trials, cohort studies, case-control studies and case-series studies. MEDLINE was searched from January 1986 to December 2017; the date ranges for the other databases were not included.[7] The review[7] contained one non-randomized study (NRS) (not assessed for quality by the authors) relevant to this report which was published in 2014. A third SR,[12] published in 2017, searched one database for RCTs from an unspecified date to April 18, 2017. The review[12] contained one RCT (not assessed for quality by the authors) relevant to this report which was published in 2003. The remaining four SRs, published in 2016,[10] 2013,[8] 2011[9] and 2010,[11] met the inclusion criteria for this report but did not include any eligible primary studies. There was no overlap in relevant primary studies between the included SRs.

Two relevant guidelines were identified regarding pilocarpine for the treatment of dry mouth and dry eyes in Sjögren's syndrome. One guideline,[13] published in 2019, was developed by the European League Against Rheumatism (EULAR) and was informed by a SR[7] of the literature (which was also included in this report). The EULAR guideline[13] used the Oxford Centre for Evidence-Based Medicine standards and a web-based Delphi consensus procedure to evaluate the level of evidence (highest being 1a and lowest being 5) and grade of the recommendations (highest being A and lowest being D). The second guideline,[3] published in 2017, was developed by the British Society for Rheumatology (BSR) and was informed by a systematic review of the literature in multiple databases from 1990 to January 2016. The BSR guideline[3] used grading criteria endorsed by the EULAR Standing Committee and a Delphi consensus process to evaluate the level of evidence (highest being Ia and lowest being IV) and to provide the determination of recommendation strength (highest being A and lowest being D). Additional details regarding the level of evidence and grade or strength of recommendations are provided in Appendix 2

Country of Origin

The authors of the SRs were based in Canada,[8] the United Kingdom,[6,9] Spain[7,10,11] and Hong Kong.[12] It was not reported where the relevant primary studies were conducted.

The EULAR guideline[13] was developed for European nations whilst the BSR guideline[3] was developed for the United Kingdom.

Patient Population

One SR[6] included studies with patient populations consisting of adults with Sjögren's syndrome-induced dry mouth and salivary gland hypofunction. In the SR,[6] the characteristics of the patient population in the relevant RCT's (N = 72) were not described. The second SR[7] included studies with patient populations consisting of adults with primary Sjögren's syndrome as classified by the 2002 American-European Consensus Group (AECG) or the 2016 American College of Rheumatology (ACR)/EULAR criteria. The relevant NRS (N = 118) in this SR[7] included patients with primary Sjögren's syndrome as classified by the 2002 AECG criteria. The third SR[12] included studies with patients who have primary Sjögren's syndrome-induced dry eyes. In the SR,[12] the relevant RCT's (N = 85) patient population was solely described as being all female.

The EULAR guideline's[13] target population is patients with primary Sjögren's syndrome as classified by the 2002 AECG or the 2016 ACR/EULAR criteria. The guideline's[13] intended users are healthcare professionals, doctors in specialist training, medical students, the pharmaceutical industry and drug regulatory organizations. The BSR guideline's[3] target population is patients with with primary Sjögren's syndrome as classified by the AECG or the ACR/EULAR criteria. This guideline's[3] intended users are rheumatologists, general physicians, general practitioners, specialist nurses, other specialists (e.g., ophthalmologists, dental practitioners, ear-nose-throat specialists), specialist registrars and specialist nurses in training.

Interventions and Comparators

The relevant RCT included in the first SR[6] compared 10 drops (5 mg) of pilocarpine three times a day to 10 drops of an unspecified artificial saliva substitute (dosing regimen not provided). The relevant NRS included in the second SR[7] compared pilocarpine to cevimeline, however, the dose and dosing regimen of the drugs were not described. The relevant RCT included in the third SR[12] compared pilocarpine 5 mg 2 times daily to two other intervention arms: an unspecified artificial tear (dose and dosing regimen not specified) or an inferior lacrimal puncta occlusion. The intervention of interest in both guidelines[3,13] is pilocarpine.

Outcomes

The relevant RCT included in one of the SRs[6] reported unstimulated salivary flow rate at 12 weeks via the oral Schirmer test. The relevant NRS included in the second SR[7] reported therapy failure rate amongst first time users or all users (definitions not provided), and rates of adverse events. Another relevant RCT included in a third SR[12] reported dry eye symptoms via a visual analogue scale, Rose Bengal stain test results and Schirmer 1 test results. The outcomes of the two tests were not described in the SR, but the Rose Bengal stain is a quantitative score of conjunctival staining in which a higher score is suggestive of a diagnosis of Sjögren's syndrome whereas the Schirmer 1 test is often used to determine unstimulated tear production.[15,16]

Each guideline[3,13] included two recommendations relevant to this report. The EULAR guideline[13] considered improvement in visual analogue scale for dry mouth, salivary flow rate, tolerance and safety profiles (i.e., drug therapy failure rates and incidences of adverse events), subjective oral outcomes (not described) and subjective ocular outcomes (not described) in formulating their recommendations. The BSR guideline[3] considered symptomatic improvement of dry mouth, salivary flow rate, levels of *Candida* colonization, safety profiles (i.e. incidences of adverse events), and subjective and objective ocular outcomes (not described).

Summary of Critical Appraisal

Additional details regarding the strength and limitations of included publications are provided in Appendix 3.

Systematic Reviews

The three SRs[6,7,12] that contained primary studies relevant to this report were appraised to be of critically low quality using the AMSTAR 2[4] tool. In terms of strengths, the three SRs[6,7,12] included clearly stated objectives, populations, interventions, comparators and outcomes. One SR[7] had clearly defined inclusion and exclusion criteria (e.g., the diagnostic criteria and study designs) whereas the two other SRs[6,12] did not which decreased the generalizability of the results. Two SRs[6,7] performed comprehensive literature searches of multiple database but none of the three SRs[6,7,12] performed a grey literature search and only two SRs[6,12] conducted study selection with two or more people. Furthermore, none of the SRs[6,7,12] included a list of excluded studies nor the reasons for exclusion. This decreased the confidence in the reviews as it was unclear which publications were omitted. None of the SRs[6,7,12] reported performing data extraction from included studies in duplicate. Two SRs[7,12] had poorly-described study characteristics, and it was unclear if this was due to poor reporting by the authors of the primary studies or by the authors of the SR. The authors of one SR[6] considered the risk of bias in individual studies when interpreting and discussing results, whereas the authors of the other two SRs[7,12] did not. This lead to a lack of context for the evidence when interpreting the results of the included studies. Lastly, the authors of two SRs[7,12] disclosed potential conflicts of interest and funding sources for their reviews but did not include the funding sources of the included studies, whereas the third SR[6] did not disclose the authors' conflicts of interest, or the funding sources of the review or the included studies. This leads to uncertainty regarding the potential impact of funding organizations in the work.

Four of the seven included SRs[8-11] did not contain any primary studies relevant to this report and, as such, several of the items in the AMSTAR 2[4] checklist were not applicable. The four SRs[8-11] included clearly stated objectives, and three of the SRs[8,9,11] included clearly described populations, interventions, comparators and outcomes. Two SRs[8,9] had clearly defined their inclusion and exclusion criteria, whereas the other two SRs[10,11] did not define which diagnostic criteria were used for Sjögren syndrome or dry mouth and therefore it is uncertain which publications were omitted based on the diagnostic criteria. One SR[9], a Cochrane review, had an a priori published protocol. Three of the SRs[8,9,11] performed comprehensive literature searches of two or more databases, and all four of the SRs[8-11] conducted study selection with two or more people, but only one SR[9] performed grey literature search and provided a list of excluded studies with reasons for exclusion. Furthermore, none of the SRs provided a reason for excluding certain study designs, and relevant publications may have been omitted. The authors of two of the SRs[9,11] reported no conflicts of interest and the funding sources of the review. The authors of the other two

SRs[8,10] reported no conflicts of interest but did not disclose the funding sources of the review, thus the potential impact of funding organizations was unclear.

Evidence-Based Guidelines

The two evidence-based guidelines[3,13] were appraised to be of high quality as they only had minor limitations. The objectives and populations to whom both guidelines[3,13] are meant to apply were clearly stated. Neither guideline described the health questions they planned to address specifically, however, their intents were easily perceived.[3,13] Both guidelines[3,13] took appropriate steps to ensure stakeholder involvement as they included relevant professionals and patient representatives in their development groups and their target users were clearly defined. The development of the guidelines[3,13] included systematic searches of the literature and clearly specified criteria for selecting the evidence. Nevertheless, the EULAR guideline[13] poorly-described the selection and data extraction processes, and it was unclear whether relevant publications may have been omitted (the supporting SR[7] is critically appraised above). The guidelines[3,13] utilized appropriate methods to assign the levels of evidence and grades to the recommendations, and the overall strengths and limitations of the body of evidence were well described. The link between the supporting evidence and the recommendations was clear and both guidelines[3,13] weighed the risks and benefits of therapies when formulating the recommendations. The EULAR guideline[13] was reviewed by a separate group within the same organization (EULAR Executive Committee) whereas the BSR guideline[3] was not externally reviewed. In terms of editorial independence, both guidelines[3,13] were self-funded by their respective organizations and the guideline development group members declared competing interests transparently, but these interests were not addressed. Thus, the potential impact of funding organizations was unclear.

Summary of Findings

The overall findings of the included studies are highlighted below, and Appendix 4 presents tables with a summary of findings and recommendations.

Clinical Effectiveness of Pilocarpine for the Treatment of Sjögren's Syndrome-Induced Dry Mouth

Unstimulated Salivary Flow Rate (via oral Schirmer test)

One RCT included in a SR[6] found that there was a statistically significant improvement in unstimulated salivary flow rate at 12 weeks with pilocarpine compared to an unspecified artificial saliva in patients with Sjögren's syndrome-induced dry mouth and salivary gland hypofunction. Although a statistically significant difference was reported, the authors stated the clinical significance was unclear.[6]

Drug Therapy Failure Rates

One NRS included in a SR[7] found that there were significantly higher drug therapy failure rates amongst both first-time users ($P = 0.02$) and all users ($P < 0.001$) with pilocarpine compared to cevimeline in patients with primary Sjögren's syndrome as classified by the 2002 AECG criteria.

Discontinuation of First Line Therapy

One NRS included in a SR[7] found that discontinuation of first line therapy due to an adverse event was numerically higher with pilocarpine compared to cevimeline (statistical comparisons not provided) in patients with primary Sjögren's syndrome as classified by the

2002 AECG criteria. The discontinuation of first line therapy due to lack of efficacy was also numerically higher with pilocarpine compared to patients cevimeline (statistical comparisons not provided) in patients with primary Sjögren's syndrome as classified by the 2002 AECG criteria.[7]

Discontinuation of Second Line Therapy

One NRS included in a SR[7] found that discontinuation of second line therapy due to an adverse event was numerically higher with pilocarpine compared to cevimeline (statistical comparisons not provided) in patients with primary Sjögren's syndrome as classified by the 2002 AECG criteria. The discontinuation of second line therapy due to lack of efficacy was also numerically higher with pilocarpine compared to cevimeline (statistical comparisons not provided) in patients with primary Sjögren's syndrome as classified by the 2002 AECG criteria.[7]

Incidence of Severe Sweating

One NRS included in a SR[7] found that there was a significantly higher incidence of severe sweating (P = 0.02) with pilocarpine compared to cevimeline in patients with primary Sjögren's syndrome as classified by the 2002 AECG criteria .

Clinical Effectiveness of Pilocarpine for the Treatment of Primary Sjögren's Syndrome-Induced Dry Eyes

Improvement in Symptoms of Dry Eyes (via visual analogue scale)

One RCT included in a SR[12] found that there was a statistically significant improvement in symptoms at 12 weeks with pilocarpine compared to artificial tears (unspecified type or dose) or inferior lacrimal puncta occlusion in female patients with primary Sjögren's syndrome, however numerical data were not provided.

Improvement in Rose Bengal Stain Test (quantitative score of conjunctival staining[15])

One RCT included in a SR[12] found that there was a statistically significant improvement in the Rose Bengal stain test at 12 weeks with pilocarpine compared to artificial tears (unspecified type or dose) or inferior lacrimal puncta occlusion in female patients with primary Sjögren's syndrome. Neither the outcome of measure nor the numerical data were provided.

Cost-Effectiveness of Pilocarpine for Dry Mouth

No relevant cost-effectiveness studies regarding the use of pilocarpine for the treatment of dry mouth in Sjögren's syndrome were identified; therefore, no summary can be provided.

Cost-Effectiveness of Pilocarpine for Dry Eyes

No relevant cost-effectiveness studies regarding the use of pilocarpine for the treatment of dry eyes in Sjögren's syndrome were identified; therefore, no summary can be provided.

Guidelines

Oral Dryness

Both guidelines[3,13] recommend the trial use of pilocarpine for the treatment of oral dryness in patients with primary Sjögren's syndrome. However, the guidelines[3,13] differ in the strength of their evidence/recommendations and pilocarpine's place in therapy. The EULAR guideline[13] recommends the use of pilocarpine for the treatment of patients with moderate

glandular dysfunction or mild glandular dysfunction refractory to non-pharmacological treatment (Level of evidence, 1b [evidence from RCTs]; Grade of recommendation, B [extrapolations from level 1 studies]) whereas the BSR guideline[3] recommends pilocarpine's use in patients with significant sicca symptoms (criteria for "significant" sicca symptoms not provided) (Level of evidence, IIb [evidence from quasi-experimental studies]; Strength of recommendation, B [category 2 evidence]).

Ocular Dryness

The BSR guideline[3] recommends the trial use of pilocarpine for the treatment of ocular dryness in patients with primary Sjögren's syndrome who are experiencing significant symptoms (i.e., moderate or severe dry eye) (Level of evidence, IIb [evidence from quasi-experimental studies]; Strength of recommendation, B [category 2 evidence]). The EULAR guideline[13] does not provide a recommendation specific to pilocarpine's use in the treatment of ocular dryness, but states that pilocarpine can be considered as a rescue therapy for the treatment of patients with refractory or severe ocular dryness (strength of evidence and recommendation not reported).

Limitations

There were numerous limitations to this report, one of which was the small amount of relevant literature identified. Studies not meeting the inclusion criteria of this report often compared pilocarpine to placebo rather than another active ingredient or a non-pharmacological treatment. Although seven SRs[6-12] that met the inclusion criteria were identified, only three SRs[6,7,12] contained primary studies relevant to this report. This demonstrates a lack of studies comparing pilocarpine to other active interventions and suggests further research on the topic is required. Pilocarpine was compared to an unspecified artificial saliva[6] and cevimeline[7] for the treatment of dry mouth and to an unspecified artificial tear[12] for the treatment of dry eye in the identified relevant primary studies; no information for the other comparators of interest was identified. Because cevimeline is a drug which is not currently available in Canada[17] and it is unknown whether the artificial saliva or artificial tears are available in Canada, these findings are not generalizable to the Canadian setting. Furthermore, this report was limited by the uncertainty regarding the diagnosis of Sjögren's syndrome. Five different diagnostic criteria of Sjögren's syndrome have been used since 1986[11] and it can take up to 9 years for patients to be diagnosed even when the relevant symptoms are present.[1] The difficulty in diagnosing Sjögren's syndrome may have led to patients being labelled by their symptoms rather than the disease state and may explain why many large trials contain an assortment of causes for patients' dry mouth or dry eyes symptoms. Lastly, there was no evidence on the cost-effectiveness of pilocarpine for patients with Sjögren's syndrome experiencing either dry mouth or dry eyes. This again suggests that additional research is required.

Conclusions and Implications for Decision or Policy Making

Seven SRs[6-12] (three[6,7,12] of which contained relevant primary studies) were identified regarding the clinical effectiveness of pilocarpine in the treatment of patients with dry mouth and/or dry eyes secondary to Sjögren's syndrome. The three SRs[6,7,12], assessed to be of critically low quality, contained two relevant primary studies which addressed the clinical effectiveness of pilocarpine in the treatment Sjögren's syndrome-induced dry mouth and one relevant primary study which addressed the clinical effectiveness of pilocarpine in the treatment Sjögren's syndrome-induced dry eyes. In addition, two evidence-based

guidelines[3,13] were identified regarding pilocarpine for the treatment of dry mouth and dry eyes in patients with Sjögren's syndrome.

One SR[6] contained a relevant RCT (assessed by the authors of the SR to have a low risk of bias) which found pilocarpine significantly increased unstimulated salivary flow rate compared to an unspecified artificial saliva in patients with Sjögren's syndrome-induced dry mouth. The clinical significance of the results was unclear.[6] Another SR[7] contained a relevant NRS (not assessed for bias by the authors of the SR) which found pilocarpine had a significantly higher failure rate amongst first-time and all users and a higher incidence of severe sweating compared to cevimeline in patients with Sjögren's syndrome-induced dry mouth.[7] The third SR[12] contained a relevant RCT (not assessed for bias by the authors of the SR) which found pilocarpine significantly improved symptoms of dry eyes and Rose Bengal stain test results compared to an unspecified artificial tear or inferior lacrimal puncta occlusions. Of note is that the availability of the unspecified artificial saliva and the unspecified artificial tears in Canada are unknown and that cevimeline is not currently available in Canada.[17] Given the small quantity of heterogenous evidence, the possible lack of availability of the comparators in Canada, and the limitations identified in this report, there was insufficient evidence for the clinical effectiveness of pilocarpine in the treatment of Sjögren's syndrome patients experiencing dry mouth or dry eyes.

The two guidelines[3,13] both recommend the use of pilocarpine for the treatment dry mouth secondary to Sjögren's syndrome. The EULAR guideline[13] recommends the use of pilocarpine for the treatment of mild or moderate dry mouth whereas the BSR guideline[3] recommends the use of pilocarpine for the treatment of significant sicca symptoms. With respect to the treatment of dry eyes secondary to Sjögren's syndrome, the EULAR guideline[13] states pilocarpine may be considered as a rescue therapy for the treatment of subjective ocular dryness whereas the BSR guideline[3] recommends the use of pilocarpine for patients experiencing severe/refractory dry eyes.

Overall, the findings of this report come with a degree of uncertainty and the limitations discussed should be considered when interpreting the results within the Canadian context. The lack of evidence in terms of both quantity and quality suggests the need for well designed RCTs to investigate the clinical effectiveness and cost-effectiveness of pilocarpine for the treatment of dry mouth and dry eyes in patients with Sjögren's syndrome.

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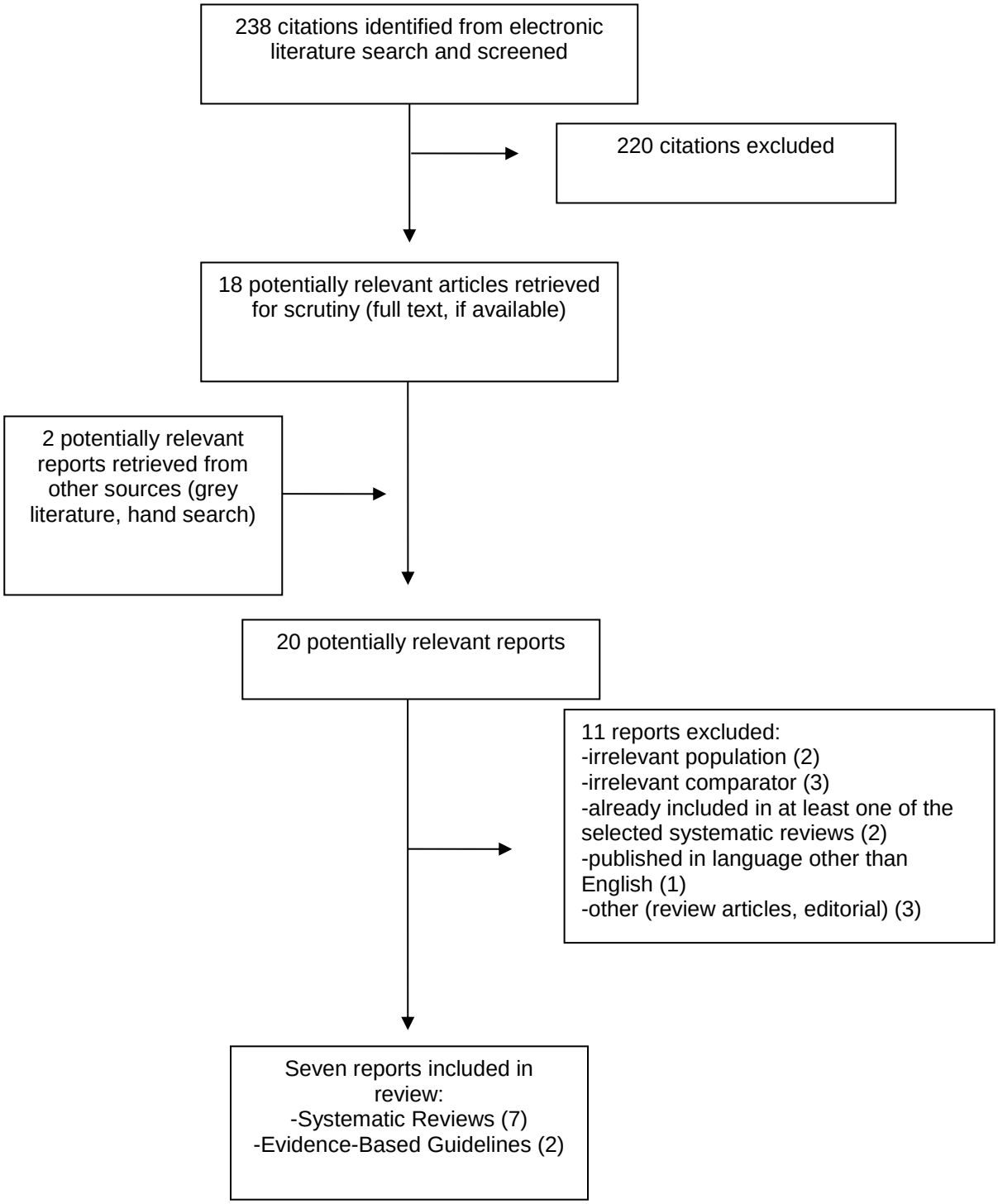
Appendix 1: Selection of Included Studies



Appendix 2: Characteristics of Included Publications

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

First Author, Publication Year, Country, Funding	Study Design, Search Strategy, Numbers of Studies Included, Quality Assessment Tool, and Objective	Population Characteristics	Intervention and Comparators	Clinical Outcomes
Al Hamad, 2019[6] **Country: United Kingdom** **Funding:** Not disclosed	**Study design:** SR with MA of RCTs. **Literature search strategy:** Authors performed literature searches in MEDLINE, EMBASE and The Cochrane Central Register of Controlled Trials from an unspecified date to February 26, 2018. A supplemental search of reference lists of retrieved articles and textbooks was also completed. **Number of studies included:** 36 studies were included in the SR; one of these was relevant to this report (One RCT which was not included in the MA). **Quality assessment tool:** Conducted using the Cochrane Collaboration tool for assessing risk of bias. **Objective:** To review the clinical effectiveness of available treatment options for dry mouth, hyposalivation and quality of life in Sjögren's syndrome patients.	Adults with Sjögren's syndrome-induced dry mouth and salivary gland hypofunction. The relevant RCT included 72 patients. No other information regarding the patient population was provided.	**Interventions:** Saliva stimulants or treatments to reduce symptoms of dry mouth. **Comparators:** No treatment, placebo, another therapeutic intervention, or a combination of both placebo and another therapeutic intervention. The relevant RCT compared pilocarpine 10 drops (5 mg) three times a day to 10 drops of an unspecified artificial saliva substitute for a duration of 12 weeks. No dosing regimen for the artificial saliva was provided.	**Relevant Outcome:** - Unstimulated salivary flow rate (via oral Schirmer test)

First Author, Publication Year, Country, Funding	Study Design, Search Strategy, Numbers of Studies Included, Quality Assessment Tool, and Objective	Population Characteristics	Intervention and Comparators	Clinical Outcomes
Brito-Zerón, 2019[7] **Country: Spain** **Funding:** European League Against Rheumatism	**Study design:** SR of MAs, RCTs, cohort studies, case-control studies and case series. **Literature search strategy:** Authors performed literature searches in MEDLINE (January 1, 1986 to December 31, 2017), EMBASE and the Cochrane Central Library. The search was restricted to English language articles and adults. **Number of studies included:** 37 studies were included in the SR; one of these was relevant to this report (One NRS which was not included in the MA). **Quality assessment tool:** Conducted using the Cochrane Collaboration tool for assessing risk of bias for RCTs and the Strengthening the Reporting of Observational Studies in Epidemiology checklist for uncontrolled studies. **Objective:** To review the clinical effectiveness of topical and systemic therapies used in Sjögren's syndrome as well as inform EULAR recommendations.	Adults with primary Sjögren's syndrome as classified by the 2002 AECG or the 2016 ACR/EULAR criteria. The relevant NRS included patients with primary Sjögren's syndrome as classified by the 2002 AECG criteria (N= 118).	**Interventions:** Topical or systemic medications. **Comparators:** Placebo or another therapeutic intervention. The relevant NRS compared pilocarpine to cevimeline. No dose or dosing regimen were provided. The study was conducted over 2.8 years.	**Relevant Outcomes:** - Therapy failure rate amongst first time users - Therapy failure rate amongst all users - Rate of adverse events

First Author, Publication Year, Country, Funding	Study Design, Search Strategy, Numbers of Studies Included, Quality Assessment Tool, and Objective	Population Characteristics	Intervention and Comparators	Clinical Outcomes
Shih, 2017[12] **Country: Hong Kong** **Funding:** No funding was acquired	**Study design:** SR RCTs. **Literature search strategy:** Authors performed a literature search in Entrez PubMed database and went back in time 15 years from April 18, 2017. References of included studies were also checked for relevant studies. The search was restricted to English language articles. **Number of studies included:** 20 studies were included in the SR; one of these was relevant to this report (One RCT) **Quality assessment tool:** NR **Objective:** To assess the effectiveness of topical and systemic therapies in the treatment of Sjögren's syndrome-induced dry eyes.	Patients with primary Sjögren's syndrome. The relevant RCT included 85 female patients. No other information regarding the patient population was provided.	**Interventions:** Topical or systemic medications. **Comparators:** Placebo or standard therapy (not defined). The relevant RCT compared pilocarpine 5 mg 2 times daily to unspecified artificial tears in one comparator arm and an inferior lacrimal puncta occlusion in a second comparator arm. The study was conducted over 12 weeks. No dose or dosing regimen for the unspecified artificial tears was provided.	- Dry eye symptoms via visual analogue scale - Rose Bengal stain test (quantitative score of conjunctival staining in which a higher score is suggestive of a diagnosis of Sjögren's syndrome[15]) - Schirmer 1 test (generally used to determine unstimulated tear production[16])
Gil-Montoya, 2016[10] **Country: Spain** **Funding:** Not disclosed	**Study design:** SR of clinical trials. **Literature search strategy:** Authors performed a literature search in PubMed from 2006 to March 2015. The search was restricted to the English language.	Older adults experiencing drug-induced dry mouth, dry mouth secondary to Sjögren's syndrome or another systemic disease and dry mouth secondary to radiation treatment for head and neck cancer.	**Interventions:** Pharmacological therapies (i.e., pilocarpine or cevimeline), non-pharmacological therapies, artificial saliva substitutes, alternative treatments (i.e., acupuncture, electro-stimulation). **Comparators:** NR	- Decrease in symptoms of dry mouth - Increase in salivary flow

First Author, Publication Year, Country, Funding	Study Design, Search Strategy, Numbers of Studies Included, Quality Assessment Tool, and Objective	Population Characteristics	Intervention and Comparators	Clinical Outcomes
	Number of studies included: No relevant primary studies; 26 studies were included in the SR. **Quality assessment tool:** Conducted using the Oxford Quality Scale for assessing risk of bias. **Objective:** To review the evidence for the treatment of dry mouth secondary to any cause.			
Daniels, 2013[8] **Country: Canada** **Funding:** Not disclosed	**Study design:** SR with MA of RCTs, quasi-randomized controlled trials and NRSs with blinded outcome assessments. **Literature search strategy:** Authors performed literature searches in the Cochrane Library (Issue 7, 2009), PubMed (1950- July 2009), EMBASE (1980-July 2009), and CINAHL (1982-February 2010). An updated search for systematic reviews was conducted up to June 2012 in the Cochrane Library and PubMed. **Number of studies included:** No relevant primary studies; eight studies were included in the SR.	Adults over 60 years of age experiencing drug-induced dry mouth, dry mouth secondary to Sjögren's syndrome and dry mouth secondary to radiation treatment for head and neck cancer. Dry mouth defined as a subjective perception of dry mouth with or without clinically measured hyposalivation using a visual analog scale and a resting whole saliva flow rate < 0.1-0.2 mL/min or a stimulated whole saliva flow rate < 0.7 mL/min using sialometry.	**Interventions:** Saliva substitutes, saliva stimulants, and topical fluoride treatment. **Comparators:** Placebo, no treatment or an alternative treatment	- Reduction in patient's perceived dry mouth using visual analog scale - Change in unstimulated salivary flow rate from baseline - Change in taste and ability to swallow - Reduction in root caries

First Author, Publication Year, Country, Funding	Study Design, Search Strategy, Numbers of Studies Included, Quality Assessment Tool, and Objective	Population Characteristics	Intervention and Comparators	Clinical Outcomes
	Quality assessment tool: Conducted using the Cochrane Collaboration tool for assessing risk of bias. **Objective:** To assess the effectiveness of saliva substitutes, saliva stimulants and topical fluoride in managing drug-induced dry mouth, dry mouth secondary to Sjögren's syndrome and dry mouth secondary to radiation treatment for head and neck cancer.			
Furness, 2011[9] **Country: United Kingdom** **Funding:** Department of Health United Kingdom and the British Orthodontic Society	**Study design:** SR with MA of RCTs and randomized crossover studies. **Literature search strategy:** Authors performed literature searches in The Cochrane Oral Health Group Trials Register (28 October 2011), The Cochrane Central Register of Controlled Trials (*The Cochrane Library*, Issue 4 2011), MEDLINE (1950 to 28 October 2011), EMBASE (1980 to 28 October 2011), CINAHL (1980 to 28 October 2011) AMED (1985 to 28 October 2011), CANCERLIT (1950 to 28 October 2011). A supplemental search of the reference lists of review articles and all articles	Patients experiencing dry mouth due to any cause. This included patients with autoimmune conditions, hormonal disorders, immune disorders as well as patients undergoing hemodialysis, with dry mouth secondary to medications and patients with salivary gland hypofunction secondary to prior radiotherapy. Trials of healthy volunteers were excluded.	**Interventions:** Any topical treatment including saliva substitutes and saliva stimulants. **Comparators:** Placebo, no treatment or another active topical treatment	- Dry mouth (via visual analogue scale, dry mouth questionnaire, dichotomous outcome [either improved or not compared to baseline] or dry mouth score) - Salivary flow rate - Quality of life (via health-related quality of life questionnaire or another specific instrument) - Oral health assessment (via plaque or gingival indices, oral

First Author, Publication Year, Country, Funding	Study Design, Search Strategy, Numbers of Studies Included, Quality Assessment Tool, and Objective	Population Characteristics	Intervention and Comparators	Clinical Outcomes
	obtained as well as a search of the controlled trials database was completed. **Number of studies included:** No relevant primary studies; 36 studies were included in the SR. **Quality assessment tool:** Conducted using the recommended approach for Cochrane reviews. **Objective:** To determine which topical therapies are effective at relieving the symptom of dry mouth.			mucositis scales, number of oral infections or tooth loss)
Ramos-Casals 2010[11] **Country: Spain** **Funding:** La Marató de TV3 and Fondo de Investigaciones Sanitarias	**Study design:** SR of randomized controlled trials and prospective cohort studies. **Literature search strategy:** Authors performed literature searches in MEDLINE and EMBASE from January 1, 1986 to April 30, 2010. A search of reference lists from relevant articles was also completed. The search was restricted to English language articles and adults. **Number of studies included:** No relevant primary studies; 56 studies were included in the SR.	Adult patients with primary Sjögren syndrome.	**Interventions:** Any drug therapy. **Comparators:** Placebo or standard therapy (not described).	- Effect of the drug on clinical outcomes (not specified) - Rate of adverse events

First Author, Publication Year, Country, Funding	Study Design, Search Strategy, Numbers of Studies Included, Quality Assessment Tool, and Objective	Population Characteristics	Intervention and Comparators	Clinical Outcomes
	Quality assessment tool: Conducted using the Cochrane Collaboration tool for assessing risk of bias. **Objective:** To summarize the evidence on drug therapies used to treat sicca and extraglandular symptoms of primary Sjögren syndrome.			

ACR/EULAR = American College of Rheumatology/ European League Against Rheumatism; AMED = Allied and Complementary Medicine Database; CINAHL = Cumulative Index to Nursing and Allied Health Literature; EMBASE = Excerpta Medica database; EULAR = European League Against Rheumatism; MA = meta-analysis; MEDLINE = Medical Literature Analysis and Retrieval System Online; mg = milligram; mL/min = milliliter/minute; NR = not reported; NRS = non-randomized study; PubMed = Public Medline; RCT = randomized controlled trial; SR = systematic review.

Table 3: Characteristics of Included Guidelines

Intended Users, Target Population, Relevant Interventions	Evidence Collection, Selection, and Synthesis	Evidence Quality Assessment	Recommendations Development and Evaluation	Guideline Validation
Ramos-Casals, 2019[13]				
Intended users: Healthcare professionals, doctors in specialist training, medical students, pharmaceutical industry, regulatory bodies. **Target population:** Individuals with primary Sjögren syndrome according to the 2002 AECG or 2016 EULAR criteria.	One author conducted a systematic review of the literature in MEDLINE, EMBASE and the Cochrane Central Library from January 1986 to December 2017. MAs, RCTs, cohort studies case-control studies, and case series	According to the Oxford Centre for Evidence-Based Medicine- **Level of Evidence:** • **1a:** SR of RCTs • **1b:** RCT • **2a:** SR of cohort studies • **2b:** Cohort study or low quality RCT • **3a:** SR of case-control studies • **3b:** Case-control study • **4:** Case-series, retrospective study, low quality cohort study, low quality case-control study • **5:** Expert opinion **Grade of Recommendation:** • **A:** Level 1 studies	A task force of 77 physicians with various specialties, general practitioners, nurses, epidemiologists, statisticians, and patient representatives divided into nine groups which reviewed the evidence for a question and formulated recommendations. Consensus via Delphi procedure for recommendations to be accepted into final document.	External peer review by the EULAR Executive Committee.

Intended Users, Target Population, Relevant Interventions	Evidence Collection, Selection, and Synthesis	Evidence Quality Assessment	Recommendations Development and Evaluation	Guideline Validation
Relevant interventions: Pilocarpine, cevimeline, non-pharmacological saliva stimulants (i.e., sugar-free acidic candies, lozenges, xylitol, sugar-free chewing gum), saliva substitutes (gels, rinses, sprays), ocular gels with polymeric base, methylcellulose or hyaluronate, topical ocular non-steroidal anti-inflammatory drugs or corticosteroids, topical cyclosporine, serum tear drops, ocular plug insertions.	were included. (SR[7] also discussed in this report)	• **B:** Level 2 or 3 studies, extrapolations from level 1 studies • **C:** Consistent level 4 studies, extrapolations from level 2 or 3 studies • **D:** Level 5 evidence, inconsistent or inconclusive studies of any level		
Elizabeth, 2017[3]				
Intended users: Rheumatologists, general physicians, general practitioners, specialist nurses, other specialists, specialist registrars and in-training specialist nurses. **Target population:** Individuals with primary Sjögren syndrome according to the AECG or ACR/EULAR criteria. **Relevant interventions:** Pilocarpine, cevimeline, oral lozenges, sprays, mouth rinses, gels oils, chewing gym and toothpastes, xylitol, anhydrous	Authors conducted a systematic review of the literature in the Cochrane Library, MEDLINE and EMBASE from 1990 to February 2015 with updates in September 2015 and January 2016.	**Level of Evidence:** • **Ia:** MA of RCTs • **Ib:** RCTs • **IIa:** Non-randomized controlled studies • **IIb:** Quasi-experimental studies • **III:** Comparative studies, correlation studies of case-control studies • **IV:** Expert opinion or clinical experience of respected authorities **Determination of Recommendation Strength:** • **A:** Category 1 evidence • **B:** Category 2 evidence, extrapolations from category 1 evidence • **C:** Category 3 evidence or extrapolations from category 1 or 2 evidence • **D:** Category 4 evidence or extrapolations from category 2 or 3 evidence	A multidisciplinary team reviewed the evidence and formulated recommendations. Consensus via Delphi process for final recommendations.	NR

Intended Users, Target Population, Relevant Interventions	Evidence Collection, Selection, and Synthesis	Evidence Quality Assessment	Recommendations Development and Evaluation	Guideline Validation
crystalline maltose, topical ocular therapies (containing hypromellose, polyvinyl alcohol, carbomers, carmellose, guar gums, sodium hyaluronates, paraffin/white petroleum, liposomes, soy bean/ mineral oil, mucolytics, anti-inflammatories, immune regulators, disaccharides), serum tear drops, ocular plug insertions, periorbital botulinum toxin.				

ACR/EULAR = American College of Rheumatology/European League Against Rheumatism; AECG = American-European Consensus Group; EMBASE = Excerpta Medica database; EULAR = European League Against Rheumatism; MA = meta-analysis; MEDLINE = Medical Literature Analysis and Retrieval System Online; NR = not reported; 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[4]

Strengths	Limitations
Al Hamad et al., 2019[6]	
• The objective of the review was clearly stated • The eligible population, interventions, comparators, and outcomes of the review were well defined • A comprehensive literature search of multiple databases, reference lists and textbooks was performed without language restrictions • Study selection was completed in duplicate and described in detail • A list of included studies was provided and the studies' characteristics were well described • Authors considered risk of bias in individual studies when interpreting and discussing results • Authors described heterogeneity across studies and the reason for not including some studies in the meta-analysis	• An *a priori* protocol was not reported for the review • The inclusion and exclusion criteria were poorly defined • A search of the grey literature was not preformed • Reasoning for excluding certain study designs was not provided • Data extraction from included studies was not reported to be done in duplicate • Neither a list of excluded studies nor the reasons for exclusion were provided • No declaration of authors' conflicts of interest was reported • Funding sources of included study was not provided • Funding sources of the review was not disclosed
Brito-Zerón et al., 2019[7]	
• The objective of the review was clearly stated • The eligible population, interventions, comparators, and outcomes of the review were well defined • The inclusion and exclusion criteria were well defined • A comprehensive literature search of multiple databases was performed without language restrictions • Study design eligibility described in detail • A list of included studies was provided • Authors described heterogeneity across studies and the reason for not conducting a meta-analysis of results • Authors disclosed potential conflicts of interest • Funding sources of the review were disclosed	• An *a priori* protocol was not reported for the review • A search of the grey literature was not preformed • Study selection not performed in duplicate • Data extraction methods not reported • Neither a list of excluded studies nor the reasons for exclusion were provided • The included studies' characteristics were poorly described • Assessment of risk of bias was not reported for non-randomized studies • Authors did not consider risk of bias in individual studies when interpreting and discussing results • Funding sources of included study not provided
Shih et al., 2017[12]	
• The objective of the review was clearly stated • The eligible population, interventions, comparators, and outcomes of the review were well defined • A list of included studies was provided • Study selection was performed in triplicate • Authors disclosed potential conflicts of interest • Funding sources of the review were disclosed	• An *a priori* protocol was not reported for the review • The inclusion and exclusion criteria were poorly defined • Neither a comprehensive literature search nor a search of the grey literature was conducted • Data extraction methods not reported • Reasoning for excluding certain study designs was not provided • A list of excluded studies was not provided • The included studies' characteristics were poorly described

Strengths	Limitations
	• Assessment of risk of bias poorly described and performed • Authors did not consider risk of bias in individual studies when interpreting and discussing results • Funding sources of included study not provided
Gil-Montoya et al., 2016[10]	
• The objective of the review was clearly stated • The eligible populations and interventions of the review were well defined • Study selection was completed in duplicate • A list of included studies was provided • Authors reported no conflicts of interest	• An *a priori* protocol was not reported for the review • The eligible comparators and outcomes of the review were not described • The inclusion and exclusion criteria were poorly defined • Neither a comprehensive literature search nor a search of the grey literature was conducted • Reasoning for excluding certain study designs was not provided • A list of excluded studies was not provided • Funding sources of the review were not disclosed
Daniels et al., 2013[8]	
• The objective of the review was clearly stated • The eligible populations, interventions, comparators and outcomes of the review were well defined • The inclusion and exclusion criteria were well defined • A comprehensive literature search of multiple databases was performed • Thorough search strategies of the databases were used and described in detail • Study selection was completed in duplicate and described in detail • A list of included studies was provided • Authors reported no conflicts of interest	• An *a priori* protocol was not reported for the review • A search of the grey literature was not preformed • Reasoning for language restrictions of literature search was not provided • Reasoning for excluding certain study designs was not provided • A list of excluded studies was not provided • Funding sources of the review were not disclosed
Furness et al., 2011[9]	
• The objective of the review was clearly stated • The eligible populations, interventions, comparators and outcomes of the review were well defined • The inclusion and exclusion criteria were well defined • An *a priori* protocol was reported for the review • A comprehensive literature search of multiple databases and the grey literature was performed with no restrictions • Thorough search strategies of the databases were used and described in detail • Study selection was completed in duplicate and described in detail • A list of included studies was provided • A list of excluded studies and the reasons for exclusion was provided • Authors reported no conflicts of interest • Funding sources of the review were disclosed	• Reasoning for excluding certain study designs was not provided
Ramos-Casals et al., 2010[11]	

Strengths	Limitations
• The objective of the review was clearly stated • The eligible population, interventions, comparators and outcomes of the review were well defined • A comprehensive literature search of two databases and reference lists of relevant articles was performed • Study selection was completed in triplicate and described in detail • A list of included studies was provided • Authors reported no conflicts of interest • Authors reported the funding sources of the review	• The inclusion criteria were poorly defined • An *a priori* protocol was not reported for the review • Reasoning for date and language restrictions of literature search were not provided • A search of the grey literature was not preformed • Reasoning for excluding certain study designs was not provided • A list of excluded studies was not provided

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

Item	Guideline	
	Ramos-Casals, 2019[13]	Elizabeth, 2017[3]
Domain 1: Scope and Purpose		
1. The overall objective(s) of the guideline is (are) specifically described.	Yes	Yes
2. The health question(s) covered by the guideline is (are) specifically described.	No	No
3. The population (patients, public, etc.) to whom the guideline is meant to apply is specifically described.	Yes	Yes
Domain 2: Stakeholder Involvement		
4. The guideline development group includes individuals from all relevant professional groups.	Yes	Yes
5. The views and preferences of the target population (patients, public, etc.) have been sought.	Yes	Yes
6. The target users of the guideline are clearly defined.	Yes	Yes
Domain 3: Rigour of Development		
7. Systematic methods were used to search for evidence.	Yes	Yes
8. The criteria for selecting the evidence are clearly described.	Yes	Yes
9. The strengths and limitations of the body of evidence are clearly described.	Yes	Yes
10. The methods for formulating the recommendations are clearly described.	Yes	Yes
11. The health benefits, side effects, and risks have been considered in formulating the recommendations.	Yes	Yes
12. There is an explicit link between the recommendations and the supporting evidence.	Yes	Yes
13. The guideline has been externally reviewed by experts prior to its publication.	Yes	No

Item	Guideline	
	Ramos-Casals, 2019[13]	Elizabeth, 2017[3]
14. A procedure for updating the guideline is provided.	No	No
Domain 4: Clarity of Presentation		
15. The recommendations are specific and unambiguous.	Yes	Yes
16. The different options for management of the condition or health issue are clearly presented.	Yes	Yes
17. Key recommendations are easily identifiable.	Yes	No
Domain 5: Applicability		
18. The guideline describes facilitators and barriers to its application.	No	No
19. The guideline provides advice and/or tools on how the recommendations can be put into practice.	No	No
20. The potential resource implications of applying the recommendations have been considered.	No	Partially (brief mention)
21. The guideline presents monitoring and/or auditing criteria.	No	Yes
Domain 6: Editorial Independence		
22. The views of the funding body have not influenced the content of the guideline.	Yes	Yes
23. Competing interests of guideline development group members have been recorded and addressed.	Yes	Yes

Appendix 4: Main Study Findings and Authors' Conclusions

Table 6: Summary of Findings Included Systematic Reviews

Main Study Findings	Authors' Conclusion
Al Hamad et al., 2019[6]	
Unstimulated salivary flow rate at 12 weeks (via oral Schirmer test): Pilocarpine (0.924 cm/min) vs. artificial saliva (0.297 cm/min), *P* < 0.05	*"There is moderate quality evidence that pilocarpine can lead to a large effect size of short-term increase in unstimulated salivary flow, which is however of unclear clinical significance."* (p.1,044)
Brito-Zerón et al., 2019[7]	
Failure rates among first time users: Cevimeline (27%) vs. pilocarpine (47%), *P* = 0.02 **Failure rates among all users:** Cevimeline (32%) vs. pilocarpine (61%), *P* < 0.001 **Discontinuation of first line therapy due to adverse event (statistical comparison not provided):** Pilocarpine: 28 of 59 patients (47%) Cevimeline: 16 of 59 patients (27%) **Discontinuation of first line therapy due to lack of efficacy (statistical comparison not provided):** Pilocarpine: 11 of 59 patients (19%) Cevimeline: 6 of 59 patients (10%) **Discontinuation of second line therapy due to adverse event (statistical comparison not provided):** Pilocarpine: 3 of 13 patients (23%) Cevimeline: 7 of 32 patients (22%) **Discontinuation of second line therapy due to lack of efficacy (statistical comparison not provided):** Pilocarpine: 2 of 13 patients Cevimeline: 0 of 32 patients **Incidence of severe sweating:** Cevimeline (11%) vs. pilocarpine (25%), *P* = 0.02	*"There is very limited evidence to support the use of these drugs* [pilocarpine, cevimeline] *in the treatment of oral dryness in primary-2002* patients. It would seem appropriate to offer patients a trial of the drug* [pilocarpine] *assuming there are no contraindications to the use of the drug."* (p.18) *"Additional studies are required to clarify the role of muscarinic agonists in the treatment of xerostomia in primary SjS patients."* (p.18) *Note: "primary-2002 patients" refers to adult primary Sjögren's syndrome patients meeting the 2002 American-European Consensus Group diagnostic criteria
Shih et al., 2017[12]	
Dry eye symptoms (no numerical data provided): Improved symptoms of dry eyes with pilocarpine compared to artificial tears or inferior lacrimal puncta occlusion, *P* < 0.05 **Rose Bengal stain (no numerical data provided):** Improved quantitative score of conjunctival staining with pilocarpine compared to artificial tears or inferior lacrimal puncta occlusion, *P* < 0.05	*"…oral pilocarpine, cevimeline, lactoferrin, a traditional Chinese medicine (TCM) herb and linoleic acid/ gamma linoleic acid (5/13 systemic modalities) were found to be more effective than placebo or artificial tear in the treatment of dry eye."* (p.7)

cm/min = centimeter/minute; SjS = Sjögren's syndrome; SS = Sjögren's syndrome.

Table 7: Summary of Recommendations in Included Guidelines

Recommendations	Strength of Evidence and Recommendations
Ramos-Casals, 2019[13]	
Oral Dryness 1. *"…we recommend offering a trial of muscarinic agonists [pilocarpine or cevimeline] to patients with moderate glandular dysfunction (or in those with mild dysfunction who are refractory or who do not wish to use non-pharmacological stimulation)."* p.8 **Refractory/ Severe Ocular Dryness** 2. *"With respect to systemic therapies, oral muscarinic agonists [pilocarpine or cevimeline] may be considered on the basis of the improvement of subjective (not objective) ocular outcomes."* p.10	1. Level of Evidence: 1b Grade of Recommendation: B 2. NR
Elizabeth, 2017[3]	
Oral Dryness 1. *"A trial of pilocarpine 5 mg once daily increasing stepwise to 5 mg qds is recommended for patients with significant sicca symptoms and no contraindications to its use."* p.33 **Ocular Dryness** 2. *"A trial of pilocarpine 5 mg once daily increasing stepwise to 5 mg qds is recommended for patients with significant sicca symptoms and no contraindications to its use."* p.30	1. Level of Evidence: IIb Determination of Recommendation Strength: B 2. Level of Evidence: IIb Determination of Recommendation Strength: B

mg = milligram; qds = quater die sumendum (to be taken four times daily).

Appendix 5: Additional References of Potential Interest

Non-Randomized Study - Mixed Population

Farag AM, Holliday C, Cimmino J, Roomian T, Papas A. Comparing the effectiveness and adverse effects of pilocarpine and cevimeline in patients with hyposalivation. *Oral Dis*. 2019 Sep 14.
PubMed: PM31520497

Non-Randomized Study - Different Comparator

Hsu CY, Hung KC, Lin MS, et al. The effect of pilocarpine on dental caries in patients with primary Sjogren's syndrome: a database prospective cohort study. *Arthrit Res Ther*. 2019 Nov 27;21(1):251.
PubMed: PM31775834