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Practice Guideline Report 5-5 EDUCATION AND INFORMATION 2013

A Quality Initiative of the Program in Evidence-based Care (PEBC), Cancer Care Ontario

Symptomatic Treatment of Radiation-Induced Xerostomia in Head and Neck Cancer Patients

Report Date: March 2004

An assessment conducted in December 2012 put Practice Guideline (PG) 5-5 in the Education and Information section. This means that the recommendations will no longer be maintained but may still be useful for academic or other information purposes. The PEBC has a formal and standardized process to ensure the currency of each document (PEBC Assessment & Review Protocol).

PG 5-5 consists of a Summary and a Full Report and is available on the CCO website (http://www.cancercare.on.ca) PEBC Head and Neck Cancer Disease Site Group page at: https://www.cancercare.on.ca/toolbox/qualityguidelines/diseasesite/head-neck-ebs/

For information about the PEBC and the most current version of all reports, please visit the CCO website at http://www.cancercare.on.ca/ or contact the PEBC office at:
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Symptomatic Treatment of Radiation-Induced Xerostomia in Head and Neck Cancer Patients

Practice Guideline Report # 5-5

ORIGINAL GUIDELINE: October 15, 1998
MOST RECENT LITERATURE SEARCH: March 2004
NEW EVIDENCE ADDED TO GUIDELINE REPORT: March 2004

New evidence found by update searches since completion of the original guideline is consistent with the original recommendations.

SUMMARY

Guideline Question
Are there effective interventions for symptomatic xerostomia following conventionally fractionated radical radiotherapy for head and neck cancer?

Target Population
These recommendations apply to adult head and neck cancer patients with symptomatic xerostomia following radiation therapy.

Recommendations
- For head and neck cancer patients with symptomatic xerostomia following radiation therapy using conventional fractionation schedules, pilocarpine at 5 mg three times per day is recommended.
- Patients must have evidence of pre-existing salivary function and no medical contraindications to pilocarpine therapy.
- The ideal duration of treatment with pilocarpine is undefined. The decision to extend treatment beyond three months can be based only on clinical judgement and not on evidence.
- It is reasonable to use pilocarpine for patients with symptomatic xerostomia following hyperfractionated or accelerated fractionation radiotherapy.

Methods
Entries to MEDLINE (1980 through March 2004), CANCERLIT (1980 through September 2002), EMBASE (through March 2004), and Cochrane Library (Issue 1, 2004) databases, the Physician Data Query database, the Canadian Medical Association Infobase, and the National Guideline Clearinghouse, as well as abstracts published in the proceedings of the meetings of the American Society of Clinical Oncology (1995-2003), the American Society for Therapeutic Radiology and Oncology (2000-2003), and the European Society for Medical Oncology were systematically searched for evidence relevant to this practice guideline report. Article bibliographies and personal files were also searched to March 2004.

Evidence was selected and reviewed by one member of the Practice Guidelines Initiative's Head and Neck Cancer Disease Site Group and methodologists. This practice guideline has been

reviewed and approved by the Head and Neck Cancer Disease Site Group, which comprises medical and radiation oncologists, surgeons, epidemiologists, and one community representative.

External review by Ontario practitioners was obtained through a mailed survey. Final approval of the original guideline report was obtained from the Practice Guidelines Coordinating Committee. The Practice Guidelines Initiative has a formal standardized process to ensure the currency of each guideline report. This process consists of the periodic review and evaluation of the scientific literature and, where appropriate, integration of this literature with the original guideline information.

Key Evidence

- Four randomized placebo-controlled trials involving a total of 401 patients with evidence of pre-existing salivary function treated with oral pilocarpine following radical radiotherapy were identified and included in the systematic review of the evidence.
- Pilocarpine at 5 mg to 10 mg orally three times per day produced subjective responses to treatment including improvements in overall xerostomia symptoms (Risk Ratio of improvement[1.83; 95% confidence interval, 1.34 to 2.49; p=0.00013), oral dryness (Risk Ratio, 1.60; 95% confidence intervalI, 1.17 to 2.19; p=0.0035), and the need for salivary substitutes (Risk Ratio, 2.51; 95% confidence interval, 1.51 to 4.15; p=0.00035).
- Adverse events were dose-related. Adverse parasympathetic events were reported by participants in randomized controlled trials, the most frequent and troublesome being increased sweating which occurred in about one-quarter of patients taking 5 mg three times per day and about one-half of patients taking 10 mg. Eighteen percent of patients discontinued treatment because of adverse effects during a 36-month maintenance study. None of the events reported in any of these studies were classified as severe or life threatening.
- Update searches found eleven new randomized trials. Evidence from four additional trials of pilocarpine is consistent with evidence used to inform the original guideline recommendations. Seven randomized trials of other treatments for radiation-induced xerostomia did not detect a meaningful difference between treatment and control.

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The Practice Guidelines Initiative is sponsored by: Cancer Care Ontario & the Ontario Ministry of Health and Long-term Care.

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PREAMBLE: About Our Practice Guideline Reports

The Practice Guidelines Initiative (PGI) is a project supported by Cancer Care Ontario (CCO) and the Ontario Ministry of Health and Long-Term Care, as part of the Program in Evidence-based Care. The purpose of the Program is to improve outcomes for cancer patients, to assist practitioners to apply the best available research evidence to clinical decisions, and to promote responsible use of health care resources. The core activity of the Program is the development of practice guidelines by multidisciplinary Disease Site Groups of the PGI using the methodology of the Practice Guidelines Development Cycle.[1] The resulting practice guideline reports are convenient and up-to-date sources of the best available evidence on clinical topics, developed through systematic reviews, evidence synthesis, and input from a broad community of practitioners. They are intended to promote evidence-based practice.

This practice guideline report has been formally approved by the Practice Guidelines Coordinating Committee, whose membership includes oncologists, other health providers, patient representatives, and CCO executives. Formal approval of a practice guideline by the Coordinating Committee does not necessarily mean that the practice guideline has been adopted as a practice policy of CCO. The decision to adopt a practice guideline as a practice policy rests with each regional cancer network that is expected to consult with relevant stakeholders, including CCO.

Reference:
[1] Browman GP, Levine MN, Mohide EA, Hayward RSA, Pritchard KI, Gafni A, et al. The practice guidelines development cycle: a conceptual tool for practice guidelines development and implementation. J Clin Oncol 1995;13(2):502-12.

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FULL REPORT

I. QUESTION

Are there effective interventions for symptomatic xerostomia following conventionally fractionated radical radiotherapy for head and neck cancer?

II. CHOICE OF TOPIC AND RATIONALE

Xerostomia is a common sequelae for patients treated with radical doses of radiation to salivary glandular tissue. This causes not only troublesome oral symptomatology but also a predisposition to the acceleration of dental caries and associated problems. Current management is unsatisfactory and is usually limited to support and generally ineffective salivary substitutes.

Post-radiation xerostomia was thought to be relevant to general practice patterns and a condition for which there would likely be changes to practice in response to practice guidelines. The Head and Neck Cancer Disease Site Group (DSG) was aware that several randomized controlled trials (RCTs) had been reported and recognized the need for a synthesis of the evidence.

III. METHODS

Guideline Development

This practice guideline report was developed by the Practice Guidelines Initiative (PGI), of Cancer Care Ontario's Program in Evidence-based Care (PEBC), using the methods of the Practice Guidelines Development Cycle (1u). Evidence was selected and reviewed by two members of the PGI's Head and Neck Cancer DSG and methodologists. Members of the Head and Neck DSG disclosed potential conflict of interest information.

The guideline is a convenient and up-to-date source of the best available evidence on the symptomatic treatment of radiation-induced xerostomia in head and neck cancer patients, developed through systematic reviews, evidence synthesis and input from practitioners in Ontario. The body of evidence in this report is primarily comprised of mature randomized controlled trial data; therefore, recommendations by the DSG are offered. The report is intended to enable evidence-based practice. The Practice Guidelines Initiative is editorially independent of Cancer Care Ontario and the Ontario Ministry of Health and Long-term Care.

External review by Ontario practitioners was obtained through a mailed survey consisting of items that address the quality of the draft practice guideline report and recommendations, and whether the recommendations should serve as a practice guideline. Final approval of the original guideline report was obtained from the Practice Guidelines Coordinating Committee (PGCC).

The PGI has a formal standardized process to ensure the currency of each guideline report. This process consists of the periodic review and evaluation of the scientific literature and, where appropriate, the integration of this literature with the original guideline information.

Guideline History

This practice guideline report was originally completed on October 15, 1998 and published in Current Oncology 1999;6(3):155-60. The guideline was reviewed monthly from November 1998 to December 1999, in April 2000, July 2000, April 2002, October 2002 and most recently in March 2004.

Literature Search Strategy

MEDLINE and CANCERLIT searches were performed for the period 1980 to October 1998. Search terms included "radiation", "treatment", "xerostomia", "prevention", "management", "clinical trial", "meta-analysis" and "practice guideline(s)". To locate recent articles that had not yet been indexed in MEDLINE, PREMEDLINE was searched up to October 1998, using the textwords "xerostomia" and "radiation." Ongoing trials (actively recruiting or recently closed) were identified from the Physician Data Query (PDQ) database. Articles identified by the search or cited in relevant papers or reviews were retrieved and reviewed.

Update

The original literature search has been updated using MEDLINE (through March 2004), EMBASE (through March 2004), the Cochrane Library (Issue 1, 2004), the Physician Data Query database, the Canadian Medical Association Infobase, and the National Guideline Clearinghouse, as well as abstracts published in the proceedings of the meetings of the American Society of Clinical Oncology (1995-2003), the American Society for Therapeutic Radiology and Oncology (2000-2003) and the European Society for Medical Oncology (1998, 2000,2002). Article bibliographies and personal files were also searched to March 2004 for evidence relevant to this practice guideline report.

Inclusion Criteria

Articles were included in the systematic review of the evidence if they met the following criteria:

- Randomized controlled trials (RCTs) that measured symptomatic relief of radiation-induced xerostomia in head and neck cancer
- English language publications

Synthesizing the Evidence

To obtain a more precise overall estimate of the effects of treatment, results were pooled across trials where possible and appropriate using *Metaanalyst*[0.988] software provided by Dr. Joseph Lau (Boston, MA). Pooled results are expressed as risk ratios (RR, the proportion of patients in the treated group reporting improvement over the proportion in the placebo group) with 95% confidence intervals (CI). In this case, risk ratios greater than 1.0 favour the active treatment group. Data were analysed using the more conservative random-effects model (1). All significance tests are two-sided.

IV. RESULTS

Literature Search Results

Of 65 articles identified by the searches, 11 were deemed appropriate for in-depth review. Five of these were general management overviews (2-6). No published guidelines or meta-analyses were found. Five randomized trials (four placebo-controlled trials of oral pilocarpine (7-10) and one trial comparing artificial saliva with a mouthwash containing pilocarpine (11) met the inclusion criteria. There was also one cohort study which addressed some of the DSG member's concerns about long-term treatment (12). The four placebo-controlled trials of oral pilocarpine included in this practice guideline report are presented in Table 1.

Table 1. Description of placebo-controlled trials of pilocarpine included in this practice guideline report.

Study (Reference)	Number of Patients (Number Analysed)	Total Dose of Radiation Received	Treatment Groups (n)	Dose of Pilocarpine	Duration of Treatment
Greenspan & Daniels, 1987 (7)	12 (12)	5500-8000 rad	Pilocarpine Placebo (Cross-over)	5.0 - 7.5 mg tablets 3 - 4 X daily	3 months
Schuller et al, 1989 (8)	20 (14)	50-60 Gy	Pilocarpine (5) Placebo (9)	3 mg, 2% solution, rinse and swallow t.i.d.	3 months
LeVeque et al, 1993 (9)	162 (156)	40->70 Gy	Pilocarpine (74) Placebo (82)	2.5 mg tablets t.i.d. x 4 weeks with titration to 5 mg t.i.d. x 4 weeks and 10 mg t.i.d. x 4 weeks	4 months
Johnson et al, 1993 (10)	207 (191)	40-75 Gy	Pilocarpine: 5 mg (71) 10 mg (56) Placebo (64)	 5 mg tablets t.i.d. 10 mg tablets t.i.d.	4 months

Update

An update of the literature identified one systematic review (2u), a paper integrating results of two previously identified trials (3u), ten fully published new randomized trials (4u-13u) and one new trial published as an abstract (14u). The new randomized trials identified by the literature search are presented in Table 1u.

Table 1u. Description of new randomized trials identified in the update of the literature, published after completion of the original practice guideline.

Author, Year, (Reference)	Total Number of Patients	Comparisons
Frydrych, 2002 (4u)	23 total	Pilocarpine added to artificial saliva spray Artificial saliva spray
Hamlar, 1996 (5u)	40 total	Pilocarpine pastille (dose escalation) Placebo pastille
Davies, 1998 (6u)	NR	Pilocarpine tablet -> artificial saliva spray Artificial saliva spray -> pilocarpine tablet
Gorsky, 2004 (7u)	42 total	Pilocarpine -> bethanechol Bethanechol -> pilocarpine
Jellema, 2001 (8u)	30 total	Xialine -> placebo Placebo -> xialine
Davies, 2000 (9u)	NR	Artificial saliva-> Chewing Gum Chewing gum -> Artificial saliva
Criswell, 2001 (10u)	NR	Humidifier -> supersaturated humidification Supersaturated humidification -> humidifier
Stewart, 1998 (11u)	NR	Chewing Gum Lozenges Saliva Substitute Spray
Epstein, 1999 (12u)	19 total	Oral gel + toothpaste -> placebo Placebo -> oral gel + toothpaste
Blom, 1996 (13u)	38 total	Classical Acupuncture Superficial placebo acupuncture
Wong, 2001 (14u) [abstract]	32 total	Acupuncture simulator site 1 Acupuncture simulator site 2 Acupuncture simulator site 3

NR, not reported

The guideline authors have reviewed the new evidence from four trials of pilocarpine (4u-7u) and have concluded that it is consistent with evidence used to inform the original guideline recommendations. No changes to the recommendations are warranted at this time. The remaining randomized trials of novel agents or aids have failed to demonstrate a meaningful difference between treatment and control arms (8u-14u). Again no changes to the recommendations are warranted at this time.

Outcomes

Four randomized placebo-controlled trials of oral pilocarpine in patients with xerostomia after treatment with radiation for head and neck cancer are summarized in Tables 1 and 2.

Greenspan & Daniels (7) conducted a cross-over study of pilocarpine in which 12 patients with severe xerostomia participated six months after radiation therapy for head and neck cancer. Seventy-five percent reported symptomatic improvement after treatment with 15 to 30 mg

pilocarpine daily for three months, compared with 17% of patients at the end of the placebo period (p<0.001).

Schuller at al (8) conducted a study of only 14 patients and failed to detect any improvement in dry mouth, taste or swallowing with an oral solution containing 3 mg of pilocarpine compared with placebo (8). Patients in this study had been treated with surgery and postoperative radiation an average of 21 months before randomization.

Two larger studies had identical eligibility criteria and outcome measures (9,10). To be eligible for these studies, patients had to be symptomatic for more than four months after radiation therapy, and have evidence of pre-existing salivary function and no contraindications to pilocarpine therapy. LeVeque et al (9) described a randomized, placebo-controlled dose-escalation study with 162 patients. After four weeks of treatment with 2.5 mg three times per day (t.i.d.), patients in the pilocarpine arm could have the dose increased to 5 mg t.i.d. The dose was increased further to 10 mg t.i.d. at week eight if necessary. Johnson et al (10) reported on a three-arm trial in which 207 patients were randomized to either placebo, pilocarpine at 5 mg t.i.d. or pilocarpine at 10 mg t.i.d. In both studies, visual analog scales of symptom severity were used to assess response (9,10).

At the end of three months of treatment in the dose-titration study (9), 13% of patients allocated to pilocarpine were taking 2.5 mg, 27% were taking 5 mg and 60% were taking 10 mg t.i.d.. Significantly more patients in the pilocarpine group reported improvement in the overall condition of xerostomia compared with placebo in both studies (9,10). LeVeque et al (9) found a 49% improvement in overall condition of xerostomia for pilocarpine versus 28% for placebo (p=0.015). Similarly, Johnson et al (10) documented an improvement of 53% in the 5 mg group and 43% in the 10 mg group versus 25% with placebo (p=0.010). Statistically significant improvements with pilocarpine were also observed in the need for oral comfort agents in the study by LeVeque et al, and for the symptomatic relief of oral dryness in the study by Johnson et al (Table 2). Improvement in symptoms was similar with 5 and 10 mg of pilocarpine.

Table 2. Results of randomized placebo-controlled trials of pilocarpine.

Study	Treatment Group (n)	Improvement in Symptoms (% of patients)					
		Overall Xerostomia	Oral Dryness	Mouth & Tongue Comfort	Speaking Without Requiring Liquids	Less Need for Oral Comfort Agents	Swallowing
Greenspan & Daniels, 1987 (7)	Pilocarpine Placebo (Cross-over)	75% 17% (p<0.001)	NR NR	NR NR	NR NR	NR NR	NR NR
Schuller, 1989 (8)	Pilocarpine (5) Placebo (9)	NR NR	40% 78%	NR NR	NR NR	NR NR	60% 33%
LeVeque, 1993 (9)	Pilocarpine (74) Placebo (82)	49% 28% (p=0.015)	43% 29%	23% 21%	36% 29%	30% 12% (p=0.02)	NR NR
Johnson, 1993 (10)	Pilocarpine: 5 mg (71) 10 mg (56) Placebo (64)	53% 43% 25% (p=0.010)	44% 46% 25% (p=0.037)	31% 37% 9% (p=0.001)	33% 35% 17%	25% 32% 11%	NR NR

The results of our pooled analysis based on the three studies with parallel group designs (8-10) are presented in Table 3. Data are reported for five variables for two of these studies (8,9), but only oral dryness was measured in the third study (10). Results from the study by Greenspan & Daniels could not be included because they were not provided separately by group for either period of the

crossover (7). The 5 mg and 10 mg groups in the Johnson et al study were combined for this analysis after establishing that results were consistent across these two treatment groups. When data from the Johnson et al and LeVeque et al studies were pooled, there were statistically significant improvements in favour of pilocarpine in overall xerostomia (RR of improvement, 1.83; 95% CI, 1.34 to 2.49; p=0.00013) and the need for salivary substitutes (RR of improvement, 2.51; 95% CI, 1.51 to 4.15; p=0.00035). Repeating these meta-analyses using odds ratios and risk differences gave similar results but with somewhat smaller p values. Pooling data for oral dryness from the two trials of pilocarpine tablets (9,10) yielded a risk ratio of 1.60 (95% CI, 1.17 to 2.19; p=0.0035). Schuller et al measured subjective improvement in dry mouth during treatment with pilocarpine administered as a solution at a dose of 3 mg (8). Adding this study to the meta-analysis results in a risk ratio for improvement in oral dryness of 1.37 (95% CI, 0.86 to 2.19; p=0.18).

Table 3. Meta-analysis of randomized placebo-controlled trials of pilocarpine (random effects model).

Outcome	Number of Trials	Number of Patients	Risk Ratio*	95% Confidence Interval		P Value
				Low	High	
Improvement in overall condition of xerostomia	2	346	1.83	1.34	2.49	0.00013
Improvement oral dryness	3**	361	1.37	0.86	2.19	0.18
Improved comfort of mouth & tongue	2	346	1.62	0.37	7.11	0.52
Improvement in speaking without requiring liquids	2	347	1.48	0.98	2.25	0.064
Less need for oral comfort agents	2	347	2.51	1.51	4.15	0.00035

* Estimates >1.0 favour pilocarpine for all outcome variables.
** Includes trial by Schuller et al (8)

Comparison of Pilocarpine and Artificial Saliva

In a randomized crossover study of pilocarpine mouthwash versus artificial saliva by Davies & Singer (11), 17 patients reported on symptoms of xerostomia, dysphagia and dysgeusia after treatment with a mouthwash containing 5 mg of pilocarpine three times a day for three months. Responses were compared with symptom scores after these patients used a mucin-based artificial saliva, administered as a spray, for three months. There was a one-week washout between treatment periods. Changes on the visual analogue scales for all three symptoms favoured pilocarpine mouthwash over artificial saliva, but only the difference in scores for dysgeusia reached statistical significance (mean change from baseline = 18.4% for pilocarpine versus 1.0% for artificial saliva, p=0.04). The mean change in xerostomia score over three months was 22.5% for pilocarpine mouthwash and 15.2% for artificial saliva.

Long-term Efficacy

Patients in the trials described above were treated and followed for up to three months. In a single arm cohort study, Jacobs & van der Pas followed 265 patients who were started on 5 mg t.i.d. of oral pilocarpine after participating in controlled trials or dose-ranging studies (12). After 36 months of follow-up, 136 patients (51%) were still on pilocarpine therapy. Thirty-four patients (13%) cited lack of efficacy as the reason for discontinuing treatment. Forty-four percent of patients continued treatment at 5 mg; 3% had the dose reduced to 2.5 mg, 25% increased to 7.5 mg, and 28% increased to 10 mg. The average rating of xerostomia at the last study visit compared with baseline on a visual analogue scale (where 0 represented worse and 100 represented better) was 56.1 for 224 patients. Dryness of the mouth and tongue, oral comfort, ability to sleep, ease of speaking, and ability to eat, measured using visual analogue scales at each visit for 236 patients, were improved from baseline at the last evaluable visit. For example, the average score for dryness (on a scale

from 0 = very dry to 100 = not dry) improved from 23.9 (standard error of the mean (SEM)=1.4) at baseline to 42.0 (SEM=1.8) at the last visit. However, the average time from baseline to the last evaluable visit was not stated.

Adverse Effects

There were no serious adverse effects related to treatment with pilocarpine for four to 12 weeks in the RCTs reported above.

Sweating was reported by 9% of patients while on 2.5 mg of pilocarpine, by 21% on 5 mg and by 52% on 10 mg, compared with 9% of the placebo group in the dose-escalation study by LeVeque et al (9). Ten percent of the placebo group and 15% of the pilocarpine group withdrew from the study because of adverse effects.

Five percent of patients randomized to 5 mg and 29% of those randomized to 10 mg withdrew from the study by Johnson et al because of adverse effects, which included sweating, chills, nausea, dizziness, rhinitis and asthenia (10). Sweating was the most frequently experienced adverse effect, reported by 27% of patients in the 5 mg group, 55% in the 10 mg group and 5% in the placebo group ($p<0.001$).

Half of the patients in the cross-over study by Greenspan & Daniels complained of mild sweating during treatment with pilocarpine tablets (5 to 7.5 mg) while none of the patients reported sweating during the placebo period (7). However, all patients continued on medication until the end of the study.

Twenty percent of patients reported nausea and 15% reported sweating during treatment with pilocarpine mouthwash, compared with 5% and 10% respectively with artificial saliva (11).

Fox et al reported on a single cohort study of 31 patients with xerostomia who were given pilocarpine, 5 mg t.i.d. for five months. Only 12 of the 31 patients had received radiation treatment (3). No adverse effects were noted in blood laboratory values, blood pressure, heart rate, or electrocardiographic PR intervals during the observation period.

Jacobs & van der Pas followed a single cohort of 265 patients with post-radiation xerostomia and some residual salivary gland function who were treated with 2.5 to 10 mg of pilocarpine two or three times a day for 36 months (12). Patients kept a diary of adverse experiences and had a physical examination, complete blood count, chemistry panel and urinalysis every three to six months; an ECG after nine months of treatment and an ophthalmologic examination at the end of the study were also required. No significant toxicity was found. As with the randomized trials, the most common adverse event was sweating, experienced by 55% of patients. Eighteen percent of patients discontinued treatment because of adverse effects.

Objective Response

Objective measurement of saliva production is technically difficult. Briefly, unstimulated salivary flow was collected from parotid glands by placing a Carlson-Crittenden cup over the parotid papillae and collecting saliva for one minute (9,10) or from the submandibular/sublingual glands using a micropipet apparatus (3). Stimulation of the tongue on the dorsolateral surface may be applied using a 2% citrate solution (10). Although data were reported for whole and parotid salivary flow in all of the placebo-controlled trials described above, these measurements did not correlate with patients' symptomatic responses.

V. INTERPRETIVE SUMMARY

Although there are published results from phase II studies of the prophylactic use of pilocarpine during radiation therapy (13), evidence from Phase III studies is restricted to the treatment of post-radiation xerostomia. Three randomized placebo-controlled trials demonstrate that oral pilocarpine at doses of 5 to 10 mg t.i.d. improves the symptoms of xerostomia in patients with evidence of salivary function (7,9,10). Pooling results from 347 patients in two large parallel design trials (9,10) yields a risk ratio for improvement of xerostomia symptoms of 1.83 (95% CI, 1.34 to 2.49; p=0.00013) for

improvement in overall xerostomia. Toxicity profiles suggest that 5 mg t.i.d. is more acceptable than 10 mg.

However, pilocarpine has limitations in its usefulness. Patients must have remaining salivary function and an intact neural network. In general, patients not responding to gustatory stimulation with citric acid will not respond to pilocarpine. As a parasympathomimetic agent, pilocarpine has potential cardiovascular and respiratory effects. Although no significant effects were noted on heart rate, blood pressure or cardiac conductivity in one study (3), patients with possible complicating medical conditions, such as asthma or use of beta-blockers, were excluded.

The most frequently reported adverse experience was sweating, reported by 27% of patients on 5 mg t.i.d. and 55% of those on 10 mg t.i.d. in the RCT by Johnson et al (10). The proportion of patients discontinuing treatment with pilocarpine because of adverse experiences during the studies described above varied from 0 to 29%, with the highest rate among those on 10 mg t.i.d.

There are no data from randomized trials on the optimum duration of treatment or on the magnitude of symptomatic relief at various follow-up times after starting treatment. However, the cohort study by Jacobs & van der Pas suggests that pilocarpine is safe and moderately effective for up to 36 months (12).

All trials cited here used conventional fractionation radiotherapy with total radiation doses of 40 to 75 Gy. The DSG members considered whether the end results could be generalized in practice to patients with symptomatic xerostomia receiving alternative radiation fractionation schedules.

VI. ONGOING TRIALS

- A randomized trial of Glandosane spray versus sodium bicarbonate 1% versus artificial saliva pump action spray (15u)
- DAIICHI-2011A. A randomized trial of 280 patients comparing Cevimeline versus placebo (16u).

VII. DISEASE SITE GROUP CONSENSUS PROCESS

The practice guideline was initially prepared by two members of the Hamilton Regional Cancer Centre Head and Neck Cancer DSG. The report was discussed by the Provincial Head and Neck Cancer DSG, and the amended report circulated for critique and comment.

Issues discussed by the Provincial Head and Neck Cancer DSG included the ideal time to start treatment with pilocarpine, the duration of treatment, the duration of benefit, toxicity, availability and cost, and the target patient population. The DSG members agreed that the ideal time to start treatment with pilocarpine and the duration of treatment remain undefined.

VIII. EXTERNAL REVIEW OF THE PRACTICE GUIDELINE REPORT

This section describes the external review activities undertaken for the original guideline report.

Draft Practice Guideline

Based on the evidence contained under the Original subtitles throughout this report, the Head and Neck Cancer DSG drafted the following recommendations:

- Pilocarpine, at 5 mg t.i.d., is recommended for head and neck cancer patients with symptomatic xerostomia post-radiation therapy.
- Patients must have evidence of pre-existing salivary function and no medical contraindications to pilocarpine therapy.
- The ideal duration of treatment with pilocarpine is undefined. The decision to extend treatment beyond three months can be based only on clinical judgement and not on evidence.

Practitioner Feedback

Based on the evidence contained under the Original subtitles in this report and the draft recommendations presented above, feedback was sought from Ontario clinicians.

Methods

Practitioner feedback was obtained through a mailed survey of 41 practitioners in Ontario (17 radiation oncologists, seven medical oncologists, nine surgeons, and eight otolaryngologists). The survey consisted of items evaluating the methods, results and interpretive summary used to inform the draft recommendations and whether the draft recommendations above should be approved as a practice guideline. Written comments were invited. Follow-up reminders were sent at two weeks (post card) and four weeks (complete package mailed again). The results of the survey were reviewed by the Head and Neck Cancer DSG.

Results

Key results of the practitioner feedback survey of the original draft guideline report are summarized in Table 4. Twenty-four (59%) surveys were returned. Twenty-one (88%) respondents indicated that the practice-guideline-in-progress report was relevant to their clinical practice and they completed the survey. Seven (33%) respondents provided written comments.

Table 4. Practitioner responses to the practitioner feedback survey.

Item	Number (%)*		
	Strongly agree or agree	**Neither agree nor disagree**	**Strongly disagree or disagree**
The rationale for developing a clinical practice guideline, as stated in the "*Choice of Topic*" section of the report, is clear.	18 (86%)	2 (10%)	1 (5%)
A practice guideline on this topic will be useful to clinicians.	18 (86%)	2 (10%)	1 (5%)
The literature search is relevant and complete.	17 (81%)	3 (14%)	1 (5%)
The summary of the evidence is acceptable to me.	20 (95%)	1 (5%)	0
I agree with the draft recommendations as stated.	18 (86%)	3 (14%)	0
This report should serve as a practice guideline.	15 (71%)	6 (29%)	0
If this report were to become a practice guideline, would you use it in your own practice?	**Yes**	**Unsure**	**No**
	18 (86%)	1 (5%)	1 (5%)

* Percentages may not total 100% due to missing data.

Summary of Main Findings

Eighty-six per cent of practitioners agreed with the draft recommendations, and 71% agreed that the report should be approved as a practice guideline. A few practitioners requested more information on the tests used to measure salivary function, the use of pilocarpine during radiation therapy, and a more detailed explanation of medical contraindications. These requests, however, were beyond the scope of this report.

Modifications/Actions

No changes were made to the draft recommendations in response to the practitioner feedback. Discussion among DSG members, however, led to a change in wording to clarify the patient population. Additional points were also included to expand the use of pilocarpine for patients following hyperfractionated or accelerated fractionation radiotherapy, and to briefly describe the methods used to measure salivary flow.

IX. PRACTICE GUIDELINE

This practice guideline reflects the most current information integrating the new evidence with evidence from the original guideline report.

Target Population
These recommendations apply to adult head and neck cancer patients with symptomatic xerostomia following radiation therapy.

Recommendations
- For head and neck cancer patients with symptomatic xerostomia following radiation therapy using conventional fractionation schedules, pilocarpine at 5 mg three times per day is recommended.
- Patients must have evidence of pre-existing salivary function and no medical contraindications to pilocarpine therapy.
- The ideal duration of treatment with pilocarpine is undefined. The decision to extend treatment beyond three months can be based only on clinical judgement and not on evidence.
- It is reasonable to use pilocarpine for patients with symptomatic xerostomia following hyperfractionated or accelerated fractionation radiotherapy.

X. JOURNAL REFERENCE
Hodson DI, Haines T, Berry M, Johnston M, and the Provincial Head and Neck Cancer Disease Site Group. Symptomatic treatment of radiation-induced xerostomia in head and neck cancer patients. *Curr Oncol* 1999;6(3):155-60.

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For a complete list of the Head and Neck Disease Site Group members and the Practice Guidelines Coordinating Committee members, please visit the PEBC section of the Cancer Care Ontario Web site at: http://www.cancercare.on.ca/access_PEBC.htm.

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