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Treatment of xerostomia: a systematic review of therapeutic trials

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Xerostomia, the perception of dry mouth, may result from a range of etiologic factors. Although not always directly linked, xerostomia is commonly associated with salivary gland dysfunction [1]. It has been demonstrated that specific subjective complaints of oral dryness are related to a reduction in salivary flow [2], although in general xerostomia cannot be considered synonymous with salivary dysfunction. The lack of a strong association between the subjective perception of a dry mouth and decreased salivary flow is likely related to the finding that 50% of salivary function must be lost before subjective changes are recognized [3].

When xerostomia is related to salivary gland dysfunction, the cause will often fall into one of the following categories: medication side effects, autoimmune exocrinopathies (eg, Sjögren's syndrome), radiation-induced salivary gland dysfunction, dehydration, or salivary gland trauma. Other less common causes of salivary dysfunction include: salivary gland tumors, infectious processes (bacterial, viral), endocrine disease, dementia of the Alzheimer's type, cystic fibrosis, sarcoidosis, and amyloidosis [4]. Nonsalivary causes of xerostomia include cognitive or neurologic dysfunction, psychologic conditions, and idiopathic causes.

Over the years, a wide variety of agents and techniques have been used to manage patients with dry mouth complaints. In general, treatment is nonspecific, with the same therapeutic agents being applied in all cases. The range of systemic treatment options has been reviewed recently [5]. Although there are many published clinical trials and proposed therapies, the experimental quality varies considerably. The purpose of the present article is to systematically assess the level of evidence available in therapeutic

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clinical trials for the management of xerostomia. Specifically, we examine and rate the quality of randomized controlled trials in peer-reviewed journals, using established objective criteria. Our goal is to determine the strength of the clinical trial evidence for proposed xerostomia therapies.

Methods

Literature search

Articles were identified through the Pub Med search engine, http://www.ncbi.nlm.nih.gov/PubMed. The MESH terms "xerostomia" and "therapeutics" or "xerostomia" and "therapy" were used to identify published articles. Additionally, the following search limits were utilized: randomized controlled trial, human subjects, and the English language. We identified 52 articles classified as randomized controlled clinical trials for the treatment of xerostomia from 1966 to 2001 (Table 1). A wide variety of therapies assessed in randomized controlled trials were identified. Local therapies for xerostomia have ranged from saliva substitutes to electrostimulation, whereas systemic therapies have included agents from pilocarpine to acupuncture. Any therapy used for the treatment of dry mouth tested in a randomized clinical trial was included in the present article.

Quality assessment criteria

We utilized the criteria proposed by Hadorn to evaluate each clinical trial [6]. Assessment was completed for the following eight categories: selection of patients, allocation of patients to treatment groups, therapeutic regimen, study administration, patient withdrawals, patient blinding, blinding of outcome measures, and statistical analysis. Bias identified in each category was further classified into major and minor flaws. Examples of major flaws included: patients not randomly assigned, no placebo in the control group, and investigators not blinded to the patient treatment group. Minor flaws included items such as: nonideal randomization, imperfect blinding (eg, a patient could likely discern what was active treatment versus placebo), and withdrawals not handled appropriately in statistical analysis.

Two reviewers assessed each article. Discrepancies were resolved by a consensus meeting of reviewers. The sample size (number of subjects) was also recorded for each clinical trial.

Collectively, the major and minor flaws in the eight categories allow for clinical trials to be categorized into three levels: A, B, and C [6]. Level A, the highest quality evidence, requires a well-conducted clinical trial with no evidence of major flaws and less than three minor flaws. Level B includes more poorly controlled trials with one or more major or three or more minor flaws. Level C represents expert opinion derived from nonrandomized trials.

Table 1
Interventions assessed in clinical trials for xerostomia

Condition	Clinical trial intervention	References
Sjögren's syndrome	Pilocarpine	[10,20]
	Interferon alpha	[14,21,22]
	Longovital®	[23]
	Acupuncture	[24]
	Saliva substitutes	[25]
	Mucin-containing lozenges	[26]
	Mucin-containing gum vs. Carbamide-containing gum	[27]
	Electrostimulation	[18,28]
	Evening primrose oil	[29]
	N-Acetylcysteine	[30]
	Bromhexine	[17,31–33]
	Efamol	[16]
	Azathioprine	[34]
	Hydroxychloroquine	[35]
	Prednisone vs. Piroxicam	[36]
	Nandrolone decanoate	[37]
Radiotherapy damage	Pilocarpine	[8,9,38–43]
	Acupuncture	[44]
	Vegetable oil vs. Xerolube	[45]
	Linseed extract (Salinum®) vs. Methyl cellulose	[46]
	Saliva substitute	[38,47]
	Coumarin/troxerutine (Venalot®)	[48]
	Amifostine	[12,15]
	Oral balance gel and Biotene®	[49]
Radioiodine treatment	Amifostine	[50]
Xerostomia[a]	Anethole Trithione	[51]
	Lemon lozenge	[52]
	Saliva substitute	[19,52–54]
	Pilocarpine	[7,11,54]
	Oral lubricants	[55]
	Yohimbine vs. Anetholtrithione	[56]
	Acupuncture	[57]
	Chewing gum	[52,53,58]
	Anhydrous crystalline maltose	[13]

[a] Xerostomia trials represent inclusion of patients with dry mouth complaints from a wide variety of etiologies.

Results

For randomized controlled trials, the maximum number of major flaws using Hadorn criteria is 18, whereas the maximum number of minor flaws is 20. In the 52 articles reviewed, the mean $\pm$ SD number of major flaws was 2.2 ± 1.7 (range = 0–5), of minor flaws 4.3 ± 1.6 (range = 1–7). Of the 52

clinical trials assessed, only 4 could be classified as A-level evidence (ie, no major flaws and <3 minor flaws) [7–10]. Each of A level trials assessed pilocarpine treatment of xerostomia. The remaining 48 trials were classified as B level evidence. Because our search strategy selected only randomized controlled trials, no C level (expert opinion) studies were present.

A further analysis of individual major and minor flaws demonstrated common biases in the xerostomia literature (Table 2). The most frequent major flaws included the lack of a placebo control and inappropriate or absent measurement of baseline confounders or prognostic factors. A failure to ensure investigator blinding to treatment group was also a common major flaw. The most common minor flaw was a lack of details on treatment compliance (such as a pill count), which was found in 71% of clinical trials. Additional minor flaws found in the majority of the xerostomic literature included an inadequate explanation of admission and exclusion criteria as well as an incomplete explanation of the randomization method.

Wide variations in sample size were found (range; 10–373). Many studies were small; 16 (31%) had a sample size ≤25. Eight studies had a sample size >100 [8–15]. Three studies judged to be A level evidence had a sample size >100 [8–10], whereas the other A level study had a sample size of 39 [7].

Based on this review, pilocarpine is the only therapeutic agent that has a strong evidence base supporting its use for treatment of xerostomia. There are well-controlled clinical trials demonstrating efficacy of pilocarpine in at least two xerostomic conditions: Sjögren's syndrome (SS) and postradiation

Table 2
Common major and minor flaws in the xerostomia literature

	% (n) of trails
Major flaw	
Placebo not used for control group	35% (n = 18)
Prognostic factors or confounders not measured at baseline	35% (n = 18)
Investigator not blinded to patient treatment group	31% (n = 16)
Study population was not representative of majority of patients with condition under investigation[a]	25% (n = 13)
Analytical techniques described are incorrect	21% (n = 11)
Patients withdrew with reasons not listed	17% (n = 9)
Patients not randomly assigned	13% (n = 7)
Minor flaw	
Actual dose taken by patients was not recorded (e.g. pill count)	71% (n = 37)
Criteria for admission to and exclusion not adequately described	65% (n = 34)
Method of randomization inadequately described or not truly randomized	58% (n = 30)
Diagnostic criteria inadequately described	50% (n = 26)
Excessive withdrawal[b]	40% (n = 21)
Withdrawals not handled appropriate in statistical analysis	35% (n = 18)

[a] Sample size of <10/treatment group was placed in this category.

[b] >10% withdrawal for study duration ≤3 months and >15% withdrawal for study duration >3 months.

salivary dysfunction [7–10]. Other interventions appear promising (see below) but presently lack a strong evidence base in the published literature. Further well-designed and carefully conducted studies will be necessary to establish the efficacy of these interventions.

Discussion

A wide range of interventions for the management of xerostomia has been studied (see Table 1). Evidence in the form of randomized clinical trials to support the efficacy of most of these interventions is limited or of less than optimal quality. Only four randomized clinical trials in the xerostomia literature met an A level of evidence. All four of these studies, discussed below, assessed the efficacy of pilocarpine in the treatment of xerostomia.

In the SS literature, two studies met the highest level of evidence. In the first study, Vivino et al compared the efficacy of 2.5 mg pilocarpine, 5.0 mg pilocarpine, and placebo given 4× daily for 12 weeks in a multi-center trial of 373 patients. Results demonstrated that patients in the 5.0 mg pilocarpine group had greater global improvement of dry mouth and dry eyes symptoms compared with placebo. Additionally, salivary flow was significantly higher in the 5.0 mg pilocarpine group compared with the placebo group [10].

The second study was by Fox et al [7]. This clinical trial examined the safety and efficacy of 5.0 mg pilocarpine given for a range of xerostomia etiologies: 18 primary SS, 3 secondary SS, 12 cancer radiotherapy, and 6 idiopathic. Results demonstrated a significant increase in both parotid and submandibular flow rates in the pilocarpine compared with the placebo group. Subjective improvements in oral dryness, speaking, chewing, and swallowing were reported as well [7].

Two clinical trials of pilocarpine for treatment of radiotherapy-induced xerostomia also met the highest level of evidence. In the first study by Johnson et al, 207 patients with previous radiotherapy $\geq$4000 cGy were randomized to 5 mg pilocarpine, 10 mg pilocarpine, or placebo tid for 12 weeks [8]. Both pilocarpine groups had a significant improvement in symptoms of oral dryness, as well as improved mouth comfort. Although a significant increase in whole saliva was noted for the pilocarpine compared with the placebo group, this was not consistent for all individual study visits [8].

The other A level study in the radiation-induced xerostomia literature by LeVeque et al was a multicenter study of 162 patients that had received $\geq$4000 cGy for head and neck cancer [9]. In this dose-escalation trial, patients were randomized to receive active treatment with 2.5 mg pilocarpine tablets tid, titrated first to 5.0 mg and then to 10 mg or a placebo, over a 12-week period. A significant improvement in the overall global assessment of xerostomia was demonstrated in patients receiving the 5 mg and 10 mg pilocarpine doses. A significant increase in whole saliva production for pilocarpine compared with placebo was found at each study visit [9].

Although the remainder of clinical trials met the B level of evidence, five were close to the highest level of evidence, having no major flaws and only 3 or 4 minor flaws [14,16–19]. These trials looked at a variety of interventions for xerostomia. Four were SS studies, and the fifth enrolled hospice patients with a complaint of dry mouth. The first study examined the efficacy of very low-dose interferon-alpha, 150 or 450 IU once a day or three times a day, compared to placebo, given orally for 12 weeks in 109 patients with primary SS. Although no changes were demonstrated in the primary endpoints of symptomatic oral dryness and unstimulated whole saliva, a secondary analysis did show a significant benefit of 150 IU interferon-alpha tid over placebo, with increased stimulated whole salivary flow rates at 12 weeks [14].

The next study in the higher range of B level evidence examined the effect of an electrical simulation device on whole salivary flow rates in SS patients [18]. Results demonstrated a small yet significant increase in flow rates in patients utilizing the electrical stimulation device compared with a nonactive placebo device. It was noted, however, that significant differences could be attributed to the responses of only 3 of 14 subjects assigned to the active device [18].

Another study in the Sjögren's literature with higher B level evidence examined the efficacy of Efamol® (evening primrose oil) in a randomized, double-blind, cross-over study [16]. Results demonstrated no significant differences in xerostomia outcome measures with active drug compared with a placebo [16].

The final Sjögren's study with higher B level evidence and xerostomia outcome measures assessed bromhexine in a randomized placebo-controlled study [17]. Although an improvement in ocular measures was demonstrated, the bromhexine group had no improvement in mouth dryness [17].

The fifth study compared the effects of a mucin-based saliva substitute to a mucin-free placebo saliva substitute in patients with advanced malignant disease with dry mouth complaints [19]. No differences between the two saliva substitutes were found [19].

One of the most frequent major flaws in the xerostomia literature was a failure to use a placebo control. Although ethical concerns may preclude the use of a placebo control in some conditions (eg, cancer therapy), few arguments can be made to exclude a placebo in xerostomia clinical trials. As with the use of a placebo control, the other common major and minor flaws identified can be eliminated with appropriate clinical trial design and data collection.

The very frequently found minor flaw of excessive withdrawal of patients is likely related to the inherent logistic difficulties of clinical trials: the severity of side effects with some treatment regimens or the frustration of patients with no apparent treatment response. This often unavoidable loss of patients during a clinical trial is evidenced by the finding that all four A level studies in the xerostomia literature demonstrated this minor flaw.

One notable therapy not included in the present systematic review was cevimeline, a muscarinic agonist with a spectrum of activity similar to

pilocarpine. Although this drug is United States Food and Drug Administration approved for the treatment of xerostomia in Sjögren's syndrome, and phase 3 clinical trials have been conducted, no studies had been published in a peer-reviewed journal at the time this article was written.

Summary

The results of the present systematic review of randomized controlled trials published in peer-reviewed journals demonstrate the presence of a wide variety of biases and the weakness of the existing literature of xerostomia treatment. The report of statistically significant efficacy on an outcome measure is only meaningful in the setting of a well-controlled, appropriately designed clinical trial. This points to the importance of evaluating the quality of the clinical trial closely when deciding if study results are applicable to a specific patient population.

Future studies in the management of xerostsomia will require an increased effort on the part of investigators to eliminate easily recognized flaws during the planning stages of a clinical trial. Minimizing bias in clinical studies will allow for easier interpretation and comparisons of different studies. Better clinical trial design is vital to provide maximal confidence in the efficacy of xerostomia interventions.

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