Neuroelectrostimulation in Treatment of Hyposalivation and Xerostomia in Sjögren’s Syndrome: A Salivary Pacemaker

Xerostomia is the symptom of oral dryness resulting most frequently, but not exclusively, from salivary gland hypofunction. Xerostomia is a common problem. Its prevalence in the general population has been estimated to be 10%–29%, women being more commonly affected than men. Although more likely in middle to late life (perhaps reflecting the anticholinergic action of many drugs), xerostomia can affect young adults, but rarely children. Xerostomia often arises as an adverse effect of drug therapy and can be a feature of psychological upset, cholinergic dysfunction, radiotherapy to the head and neck, or disease of the salivary glands. Patients with xerostomia are frequently seen by a rheumatologist because Sjögren’s syndrome (SS) is the most common cause of salivary gland disease to give rise to xerostomia and because of the psychological distress, polypharmacy, or aging that characterizes individuals with fibromyalgia or osteoarthritis. Saliva is essential for lubrication and innate and probably acquired immunity of the mouth; hence xerostomia has the potential to give rise to a spectrum of problems that include infections (e.g., caries, gingivitis, acute suppurative sialadenitis), dysarthria, dysphagia, oral malodor and dysgeusia, oral mucosal soreness, and suboptimal absorption of sublingual tablets, all of which can lead to a reduced quality of life, altered sleep patterns, and psychological and social disability. As xerostomia is so common, there exists a significant unmet treatment need.

Xerostomia secondary to longstanding salivary gland disease such as SS remains difficult to manage. While the infectious complications can be prevented or treated by conventional therapy, there remains no reliable means of enhancing the production of saliva. Treatment with lubricants or saliva substitutes, and stimulation of salivation by either gustatory, masticatory, or pharmacologic methods can provide some symptomatic and intermittent relief, but the symptoms tend to recur once the active treatment is interrupted, and not all patients report benefit from these agents. The cholinergic sialogogue pilocarpine hydrochloride, used widely by rheumatologists, may be contraindicated for several patient groups, and can give rise to adverse effects in about one-third of the patients. Cevimeline, the alternative parasympathomimetic drug, can also cause side effects and is not available in all countries of the world. Ideally, to ensure both short- and long-term relief any means of stimulating salivary function should be easy to administer, reliable, and free of adverse side effects. Indeed, individuals with xerostomia often wish for a functional and nonpharmacological (“natural”) cure. There thus remains a need for a treatment of xerostomia that is effective, convenient, and safe.

Neurological control of salivary secretion: the basis for a novel therapeutic approach. Salivary secretion is regulated by a reflex arch that consists of 3 major components: (1) afferent receptors and nerves carrying impulses induced by actions on sialogogic gustation and mastication; (2) a central connecting and processing center (salivation center); and (3) an efferent pathway consisting of parasympathetic and sympathetic autonomic nerve bundles that separately but in a coordinated manner innervate the blood vessels and acini of their target glands.

It is believed that afferent nerves carry impulses from the periphery to the salivary nuclei (salivation center) in the medulla oblongata, which in turn directs signals to the efferent part of the reflex arch leading to initiation of salivation. This has been well recognized in clinical practice, as pilocarpine and cevimeline are widely used by rheumatologists. Interestingly, in the autoimmune SS, muscarinic receptor-blocking autoantibodies have raised excitement for their potential pathogenic and diagnostic utility. This suggests that the sicca component of the SS is not caused by irreversible structural damage of the secretory acinar cells but rather by, to at least some extent, reversible (treatable) functional perturbation.

Electrostimulation of neural and muscular structures is of therapeutic potential in several areas of medicine (pacemakers, phrenic stimulators, etc.) and, given the autonomic control of salivary secretion, a similar approach could potentially be applied to the management of salivary gland hypofunction. Application of electric impulses to 1 or more of the 3 components of the salivary reflex arch should in theory improve salivary secretion and, indirectly, lessen the various longterm effects of hyposalivation. Animal studies have demonstrated that the application of electrical current upon this reflex arch can increase salivary production and relieve symptoms of xerostomia. Moreover, Schneyer and Hall showed that electric neurostimulation in the rat is a more adequate substitute than pilocarpine to evoke salivary secretion via reflex stimulation. Similarly, the application of an electrical current via the oral mucosa on afferent neuronal receptors and pathways (using the first-generation stimulator, discussed below) increased salivary production and less-
ened xerostomia in patients with salivary gland hypofunction. More recently, the use of extra-oral transcutaneous electric nerve stimulation (TENS) over the parotid gland was reported to increase saliva production in healthy individuals and patients with radiation-induced xerostomia, suggesting that TENS might directly stimulate the auriculotemporal nerve (afferent pathway) that supplies the secretomotor drive to the parotid gland.

As the effects of electrostimulation were sustained for 6 months beyond cessation of therapy in some patients, it was suggested that the stimulation of the autonomic nervous system may enhance the release of specific neuropeptides that have trophic effects to salivary gland parenchyma, leading to regeneration of functional tissue. This assumption is based upon studies that have demonstrated mitogenic responses in rat parotid and submandibular glands following electrical stimulation of their parasympathetic nerves. Moreover, in the past 5 years, significant advances have been made in the development of a new generation of intra-oral devices, which, if confirmed by further studies, may revolutionize the management of xerostomia.

Previous first-generation and novel electrostimulating devices. The first attempt to exploit neuro-electrostimulation to increase salivary secretion led to production of a device that was marketed in the USA (Salitron; Biosonics, Fort Washington, PA, USA). The probe was applied to the intraoral mucosal surfaces by the user (between the dorsum of the tongue and palate) for a few minutes each day and delivered a stimulating signal to sensitive neurons of the mouth to induce salivation. Using this somewhat clumsy apparatus, it was found that such neuro-electrostimulation, when delivered repeatedly, led to both an immediate (direct) response (increase of salivation as a result of the stimulation) and a cumulative long-term (indirect) response (sustained increase of basal salivary flow rate) as well as subjective improvement in symptomatic xerostomia.

As the device gave promising results in proof-of-principle clinical studies and did not give rise to any concomitant local or systemic adverse effects, it was approved by the US Food and Drug Administration in 1988 (PMA No. P860067). However, its wider use was hampered by its large size, high price, and lack of user-friendliness. To circumvent some of the limitations of this first-generation device, a European Commission-funded research consortium developed novel miniature intra-oral neuro-electrostimulators to enhance salivary flow. Two devices were produced, one designed to be part of a removable intra-oral splint appliance (second-generation device), the other to be fixed to an osteointegrated dental implant (third-generation device).

Removable intra-oral dental splint-embedded second-generation device. The second-generation salivary neuro-electrostimulator (GenNarino) is a removable intraoral appliance produced for individual patients by using their teeth pattern molds. It is similar to a mouth guard used to treat temporomandibular joint disorders and bruxism (involuntary tooth grinding performed usually while sleeping, a common cause of temporomandibular pain, and often generating diagnostic problems in rheumatology practice). It has a horseshoe-like shape and fits on the lower dentition. It is designed so that it is easy to insert and remove by the patient him- or herself. The electronic components are embedded within the appliance to allow safe and contamination-free intra-oral application. A remote control permits the patient to communicate with the device and modify its functions.

Figure 1. First-generation neuroelectrostimulation device consisted of a hand-held probe, tipped with stainless steel electrodes, and a console that housed a battery and the electronic signal-generating power source, the size and shape of which were similar to a video or CD player.
The short-term effectiveness of the second-generation device in the management of xerostomia was suggested in a double-blind, crossover, sham-controlled randomized multi-center trial of patients with dry mouth due to different causes (Table 1). The 2 primary and interrelated outcomes of this study were (1) decrease of oral dryness (as objectively verified and measured by a built-in wetness sensor) and (2) improvement of xerostomia-related symptoms (a patient-centered outcome measure). The results of the study demonstrated that the device was relatively well tolerated by all patients and did not, with the exclusion criteria applied, give rise to any local or systemic adverse effect. Significant moistening of the oral mucosal membranes was recorded objectively (p < 0.0001) and diminished xerostomia was reported subjectively (p < 0.005). The device was effective in reducing dryness of the mouth during application and up to 10 min after its removal. To verify these clinical observations, a multinational study to investigate the effect of the device during a 12-month period is under way (ClinicalTrials.gov identifier: NCT00509808).
this study is to determine if repeated short-time neuro-electrostimulations of salivary glands lead to improved salivary gland performance in the long term (as suggested in previous studies).

**Dental implant-based third-generation intra-oral device.** Some patients may require frequent and/or constant stimulation of salivary glands. Therefore, a miniature neuro-electrostimulating device to be permanently implanted into the oral cavity was developed (the Salwell Crown; Figure 3). Use of this dental implant-based neuro-electrostimulator avoids the inconvenience associated with the repeated application and removal of a splint-based stimulator. The components of the second-generation device were miniaturized and packaged into a device that has the dimensions and shape of a molar tooth. This device can be mounted on a commercially available osteointegrated implant. A wetness sensor has been embedded into the device to detect changes in wetness/dryness.

This third-generation implantable device has been developed (1) to generate continuous or frequent stimuli, (2) to be applied into the oral cavity without interfering with regular oral functions, and (3) to sense the wetness/dryness status of salivary glands.

![Figure 2.](image_url) **Figure 2.** Second-generation removable device consists of 3 components: a miniaturized electronic stimulator that has a signal generator, power source, and conducting circuitry; an intra-oral removable appliance; an infrared remote control. The miniaturized electronic stimulator is mounted in a removable intraoral appliance (A), which is under remote control that activates the stimulator (B). This device is applied into the mouth in a noninvasive manner (C).

![Figure 3.](image_url) **Figure 3.** Third-generation implant-supported neuro-electrostimulating device can be permanently applied into the oral cavity as it can be screwed onto an osteo-integrated dental implant inserted in the third molar area. Figure shows the implantation procedure and application of the device. Transmucosal exposure of mandibular bone (A) is followed by preparation of the implant bed in mandibular bone (B) and insertion of the dental root implant (C). The neuro-electrostimulating device is shown in its applicator (D) and mounted onto the root implant (E). A radiograph of the implant-supported device is shown (F).
the oral cavity and automatically increase/decrease the stimulus within a preset range (autoregulatory mode), but (4) to be controlled by the patient via a remote control. Some patients with xerostomia have impaired cognitive functions, hence the autoregulatory mode of the device may be a useful option, although alternatively, the device can be remote controlled by a relative or a nurse. The osteointegrated implant is positioned in the region of the lower third molar (wisdom tooth) to ensure close proximity to the lingual nerve that carries both afferent and efferent salivary impulses and to avoid interference with normal oral function. The necessary surgery is relatively straightforward, and the posterior location of the device ensures that there are no aesthetic concerns (Figure 3). A clinical trial to investigate the longterm effect of this third-generation neuro-electrostimulator upon salivary function and symptoms of xerostomia is currently under way, and if the results are promising, it would be expected that this could become the most convenient and safe means of enhancing salivary gland function in patients with SS.

Conclusion and perspectives. Hyposalivation and xerostomia have multiple causes, but almost all of them, regardless of their etiology, affect in particular the resting (moisturizing) salivary flow. Neuro-electrostimulation of salivary glands takes the still remaining salivation reserves into therapeutic use. For patients with hyposalivation and xerostomia-related impaired quality of life and who require longterm therapy, the second and third-generation intra-oral neuro-electrostimulating devices may offer a new non-medicinal means of treatment. Preliminary results have demonstrated the effectiveness of intra-oral neuro-electrostimulating devices, which immediately increase salivary secretion, and it seems that the distressing symptom of mouth dryness progressively improves in the long term, which suggests improved efficacy of the stimulus-response coupling. Nevertheless, the outcomes of previous trials should be considered with caution, as some of them are weakened by poor research methodology, small study groups, and most important, short evaluation periods. Larger better-planned trials are under way that will investigate more rigorously the effectiveness of these devices on at least 100 patients enrolled in a randomized, double-blind sham-controlled multinational study over a period of 12 months, with results expected in 2009-2010 (21). These trials have been designed to have as primary objective a significant improvement in dry mouth symptoms in the long term and as secondary objective an increase in salivary flow, with outcome measures including a validated xerostomia questionnaire, visual analog scale for grading xerostomia, and sialometry. Their outcomes will provide more information on the utilization of neurostimulation of salivary function as a means of managing any attendant, longstanding xerostomia in patients with rheumatological disease.

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REFERENCES
11. Jonsson R, Gordon TP, Konttinen YT. Recent advances in


