**Introduction:**

Xerostomia is a symptom of oral dryness that occurs when salivary flow is not sufficient to compensate the fluid loss from the oral cavity. In the majority of the

cases it results from salivary gland hypofunction.1 According to several reports,

its prevalence in the adult population (i.e. people reporting that xerostomia afflicts them always or frequently), ranges between 10 and a 29%, affecting more women

than men.2,3 Xerostomia is particularly prevalent among adults.4 Nevertheless, an increase of cases of xerostomía has been recently reported among young adults.5

Xerostomia can be caused by systemic diseases or iatrogenic effects. Diseases associated with salivary flow reduction include autoimmune diseases (particularly

Sjögren’s Syndrome), Alzheimer’s disease, depression and diabetes. Infections caused by sialotrophic viruses such as hepatitis C virus (HCV) or human immunodeficiency virus (HIV), sarcoidosis, lymphoma or graft vs host disease can lead to inflammatory damage of salivary glands, which consequently generates dysfunction and xerostomia .6 On the other hand, reduction of salivary flow can be induced by medical treatments, either medication intake, head and neck radiotherapy, chemotherapy or bone marrow transplantation.7,8 Nearly 400 medicines may lead to xerostomia as side effect.9 Among these drugs, it is worthwhile to mention: anti-cholinergic, anti-depression, anti-psychotic, anti-hypertensive, antidiuretic antidiuretic, anti-histamine, and steroidal and non-steroidal anti-inflammatory agents, tranquilizers, muscular relaxants, and narcotic analgesics.10 The majority of those medications are taken during long periods of time and even for lifetime, and their deleterious effects increase along the intake period. The salivary flow is reduced significantly when two or more xerogenic medicines are taken simultaneously.11

Saliva fulfils important functions such as lubrication of the oral and oropharyngeal

mucosa, as well as facilitating mastication, swallowing and formation of the nutritional bolus. In average, a healthy person produces 500 ml of saliva in

a 24 hours period. Salivary flow-rate is 0,3 ml/min in resting condition, but it increases to 4 or 5 ml/min during mastication.1 The salivary fluid is crucial for defense against viral, bacterial and fungal infections, for remineralización of dental enamel and dentine and for taste sensation.12,13 Reduction in salivary flow-rate entails a compromise in oral defense mechanisms and lubrication; the oral mucosa can become painful, with burning sensation, ulcerated and atrophic.10 Hence xerostomia has the potential to give rise to a spectrum of problems that include infections (e.g., caries, gingivitis, acute suppurative sialadenitis, oral candidiasis), 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.13,14

The assessment of severity of xerostomia is done by subjective and objective techniques. The visual analogue scale, Zimmerman xerostomia questionnaire and late effect of normal tissues subjective objective management analysis (LENT SOMA) scale are some of the methods to find and grade the severity of xerostomia. The salivary gland secretory ratio (SGSR), determined by dynamic salivary 99mTcscintigraphy, is an objective measure of salivary gland function.15,16

Rydholm and associates conducted a study to explore the global effects of xerostomia, with a specific focus on the psychological and social consequences. Four main categories were identified in the study:17

1. Subjective discomfort: e.g. dryness or burning sensation.
2. Loss of function: e.g. articulation or swallowing.
3. Increased infection: e.g. oral thrush and ulcerations.
4. Psychological effects: Including shame, increased feelings of being a patient rather than a person and tendency to avoid social contact resulting in loneliness.

Xerostomia and associated symptoms have a considerable negative global impact, resulting in shame, anxiety, disappointments and verbal communication difficulties. They should therefore focus more on the management of xerostomia, which is often neglected in the palliative care.18

Treatment with lubricants or salivary substitutes and salivary stimulation by gustatory or masticatory methods may generate an improvement,19 but xerostomia recurs once the active treatment is interrupted. Pharmacological agents, like pilocarpine HCl, have been studied extensively; nevertheless, more than one third of patients display adverse effects similar to those produced by other cholinergic drugs, including: gastric upset, perspiration, tachycardia, bradycardia, arrhythmia,

increases of pulmonary secretions, muscular tone and urinary frequency and blurred vision.20,21

Individuals with xerostomia often wish for a functional and non-pharmacological (“natural”) cure. There thus remains a need for a treatment of xerostomia that is effective, convenient and safe.22

More recently, the use of extraoral 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 (efferent pathway) that supplies the secretomotor drive to the parotid gland.23,24

The therapeutic potential of electro-stimulating nervous and muscular structures has been recognized in many areas of modern medicine. It is being used or investigated in a variety of clinical applications such as in bone healing or the treatment of pain, deafness, bladder dysfunction, cardiac arrhythmia (e.g. pacemaker), muscular weakness or denervation, problems of the respiratory

system (e.g. phrenic nerve dysfunction), seizures, and essential tremor in Parkinson’s disease.25 Given the autonomic control of salivary secretion, a

similar principle can be used in the management of salivary gland hypofunction and xerostomia. Application of electrical impulses on one, two or three components of the salivary reflex should improve both salivary secretions

as well as several long term consequences of hyposalivation. Thus, a significant increase of salivary flow following electrical stimulation application in experimental animals has been observed.26 Application of an electrical current through the oral mucosa on afferent receptors and routes was reported in research

projects aimed at increasing salivary flow and reducing oral dryness in patients with salivary gland hypofunction. It has been suggested that intra-oral electro-stimulation increments salivation in resting condition via the salivary reflex, i.e. through the production of efficient amounts of afferent-efferent stimuli.23.27 The objective of this review is to present the latest advances of neuro-stimulation for the treatment of xerostomia/hyposalivation.

**Salivary pacemakers:**

**First generation electro-stimulating 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).28 The apparatus consisted of a mouth piece and a video cassette recorder sized external control module, both parts interconnected to each other by an electrical cord (Figure1).27 The probe was applied to the intraoral mucosal surfaces by the user (between the dorsum of the tongue and the palate) for a few minutes each day and delivered a stimulating signal to sensitive neurons of the mouth to induce salivation(Figure1) .It was found that such neuroelectrostimulation, when delivered repeatedly, led to 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.27,29 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***.*** Nevertheless it was not used massively due to its large size, high price and cumbersomeness for the user.22To overcome some of the limitations of this first-generation device, a European Commission-funded research consortium developed novel miniature intraoral neuro-electrostimulators to enhance salivary flow (Saliwell project). Two devices were produced, one designed to be part of a removable intraoral splint appliance (second-generation device) and the other to be fixed to an osteointegrated dental implant (third-generation device)30

**Removable intra-oral dental splint-embedded second generation devices-**

The second-generation salivary neuroelectrostimulator (GenNarino Saliwell Ltd. Germany) is a removable intraoral appliance produced for individual patients by using their teeth pattern molds.31

The salivary neuro-electro-stimulator (Saliwell Gen-Narino®) is composed by a dental thermoplastic polyurethane-made apparatus and an electronic miniature stimulating device that contains a signal generator (electrodes), a battery and a circuit that is embedded within the plastic splint. (Figure2)

The electrodes are located on the third molar area mucosa to enable stimulation of the lingual nerve. The electro-stimulator is customized for each patient using the mold of its inferior dental arch. The system also contains a remote control that allows the patient to communicate with Saliwell GenNarino® by means of infrared light transmission at a wavelength of 940nm-950nm. The GenNarino is similar to night guards to treat bruxism, is worn on the Mandibular arch and is inserted and removed by the patient. The distance between the surfaces of the electrodes and the lingual nerve can vary between 1 and 5 mm.32 In addition to the lingual nerve, also the long buccal nerve runs next to GenNarino’s electrodes. As a result of exciting these nerves, all salivary glands are stimulated by the salivary reflex.

This appliance 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 intraoral application.

Those nerves of the salivary reflex arch that are excited by the stimulating GenNarino are:

1- Taste buds of the anterior 2/3 of the tongue →lingual nerve→ facial nerve → salivary center, from which efferent fibers can follow 3 pathways:

a) → facial nerve→lingual nerve→submandibular and sublingual glands.

b) → glossopharyngeal nerve →maxillary nerve → parotid gland.

c) →nerves to all minor salivary glands.

2- Mucosal sensorial receptors (tactile perception) →lingual and long buccal nerves→ trigeminal nerve → salivary center → efferent nerves to salivary glands according to the above description.

The following protocol has been developed for the clinical use of Saliwell GenNarino®:

1. Before taking impression for its preparation the clinician should verify that the dental, periodontal and oral mucosal status is optimal.

2. This system can be used by any patient with xerostomia.

3. In head and neck irradiated patients it is recommended to place the electrodes in the side that is contra-lateral to the irradiation area.

4. Irradiated patients and those treated with bisphosphonates require special precaution to avoid irritationoriginated lesions. In case of mucosal ulceration, the

device needs not to be worn until the lesion has healed.

5. GenNarino can replace pharmacological therapy; in severe cases though, it can be used in combination with sialogogues, especially in patients with dry eye.

6. The patient must be controlled periodically.

7. Concomitant to this therapy, it is recommended to deliver optimal levels of fluorides in toothpastes and mouthwashes.

8. Its use in pregnant patients is not recommended. The use with other extra-oral electro-stimulation devices (e.g. pacemaker) seems to be safe.

9. This device needs to be replaced every year, when the battery runs out of power.

The short term effectiveness of this electro-stimulator in the treatment of the xerostomia was evaluated in a randomized, cross-over, double blind study, comparing the device in active state with the same apparatus in inactive state among patients with dry mouth symptoms due to diverse causes. The main objectives of this study were to assess the diminution of oral dryness (objectively

verified by means of a wetness sensor incorporated in the device) and to establish improvement of symptoms related to xerostomia (by means of subjective measurement of the perception of oral dryness symptoms). The results of this study demonstrated that the device was well tolerated by all the patients and did not cause local or systemic adverse effects. Objective moistening (p<0.0001) and subjective decrease of patient-reported xerostomia (p<0.005) were registered.33 Thus, the electro-stimulator was effective in reducing oral dryness by its application during 10 minutes.22

### Dental implant-based third-generation intraoral device-

This is a dental implant based miniature neuroelectrostimulating device permanently implanted into the oral cavity. This device was developed by the Saliwell Crown Saliwell Ltd. Germany. The device is commonly used in patients who require frequent and/or constant stimulation of the salivary glands. The components of the second-generation device were miniaturized and packaged into a device that has the dimensions and shape of a molar tooth, which avoids the inconvenience associated with the repeated application and removal of a splint-based stimulator. This device can be mounted on a commercially available osteointegrated implant(Figure3) . A wetness sensor has been embedded into the device to detect changes in wetness/dryness.

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 straight forward, and the posterior location of the device ensures that there are no aesthetic concerns.

This third-generation implantable device has been developed not only to generate continuous or frequent stimuli, to be applied into the oral cavity without interfering with regular oral functions and to sense the wetness/dryness status of the oral cavity and automatically increase/decrease the stimulus within a preset range (autoregulatory mode) but also to be controlled by the patient via a remote control.

A clinical trial to investigate the long-term effect of this third-generation neuroelectrostimulatoron 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 to treat xerostomia.22,30

**Conclusion:**

Xerostomia and hyposalivation remain one of the most important causes related to impaired quality of life, thus its prevention and treatment should remain the primary concern of the dentists, medical practitioners and radiation oncologists.

The Neuroelectrostimulation of salivary glands being one of the most important non pharmacological therapeutic use for the treatment of xerostomia, the second-and third-generation intraoral neuroelectrostimulating devices may offer a new non-medicinal means of treatment and result in an increased salivary secretion and progressive improvement of xerostomia symptoms, thus demonstrating the effectiveness of these intraoral devices.

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