The impact of certain conditions and medications on the production and secretion of saliva

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ABSTRACT: Xerostomia is defined as a condition or feeling of dry mouth resulting in biochemical changes in the amount and composition of the saliva which may present further complications in the oral health.

Hyposalivation is defined as an objective assessment of a reduced rate of salivary flow. Benzodiazepines and antidepressants constitute the most frequently prescribed drugs with anxiolytic activity that can give rise to hyposalivation.

Diabetes mellitus, although a metabolic disorder, usually sent with one of the first oral symptoms such as xerostomia.

Taste receptors are permanently exposed in smokers where primary effect is stimulation of saliva from hypersalivation acquired by chronic use of cigarettes to pass in hyposalivation.

This paper reviews the current knowledge of the drugs that cause impairment of the creation and flow of saliva and certain conditions that are shipped with the dryness of the mouth.

INTRODUCTION

Oral medication reactions are common with affecting the quality of life of patients. Almost all classes of medications, especially those used continuously, such as antidepressants, antihypertensives, anxiolytics, hypnotics, diuretics, antipsychotics and many others, including vitamins, minerals and pharmaceutical products that can give oral changes. If not properly treated, they can worsen the general condition of the patient and oral health.

Prescribed drugs commonly used in large quantities especially in adults over 65 years of age. Abusing the use of drugs, mainly in elderly patients may result in a change in the oral cavity.

The number of US prescriptions prescribed for therapeutic purposes for different medical conditions increased particularly in geriatric population. Josephe et al1 reported that 21% of 1800 examined dental patients using antidepressants. Suspected is prevalence and the increased level of oral lesions correlates with the necessary drugs, mainly to treat a chronic disease. More than 200 drugs are involved in negative reactions and side effects of oral tissues. Smith and Burtner2 discovered that the most frequent adverse effects with oral prescription medications include dry mouth (80.5%), dysgeusia (47.5%) and stomatitis (33.9%).

Xerostomia, a subjective sensation of dry mouth, occurs as a negative effect on nearly 400 medical drugs. Moreover, one of the main problems in the US currently affecting millions of the population. Reduction or absence of saliva may account effects on emotional well-being, causing significant morbidity and dysfunction of the quality of life of patients .Taking dental and medical records for each patient individually is necessary, with appropriate upgrading of drugs that currently apply because the patient can

be a reason for a possible interaction between them. It is also important dentists to be aware of the problems associated with medication and their impact on the diagnosis and plan of therapy3.

AIM OF STUDY

Realizing the actuality of the problem and the need for better information taken over investigation in order to make an overview of current knowledge about drugs and the conditions that cause changes in the work of the salivary glands, and to try to give an explanation of the manner of their activity.

MATERIAL AND METHOD OF STUDY

To achieve the set goal was performed literature search under keywords medications impaired function of the salivary glands .Aquired data were systematized and selected and displayed in the paper.

DISCUSSION

Psychotropic medications belong to the group of drugs that affect the central nervous system (CNS) producing alterations in behavior, mood, ability in understanding and also can lead to addiction. The use of psychotropic increased in recent decades in several countries. This data or this rate of increase is due to increased frequency of diagnoses psychiatric disorder in the population, introduction of new psychopharmaceutical products in pharmaceutical market and new therapeutic indications with existing psychotropic drugs4.

Patients who use psychotropic medications for long periods may experience a negative impact on oral health. These medications can cause lethargy, fatigue, and reduced motor skills and memory can reduce the ability of an individual to practice proper technique and good oral hygiene. In addition, many medications used in the treatment of psychiatric disorders, the effect of causing dry mouth, decreased salivar flow or change in the composition of saliva. Zaclikevis et al5 noticed that psychotropic medications cause hyposalivation in rats and acinic hypertrophy in their parotid glands. De Almeida et al6 have shown that among users of psychotropic substances is significantly reduced the amount of stimulated saliva flow in comparison with a control group.

Antidepressants are drugs that are prescribed to patients almost all age groups for the treatment of different variations of psychiatric disorders (depression, affective disease, insomnia, anxiety, panic syndrome, and bipolar disorder). In some cases they are also prescribed to treat certain medical conditions such as rheumatoid arthritis, eating disorders, fibromyalgia, migraines, trigeminal neuralgia, premenstrual tension7

Antidepressant drugs were first discovered in the early 1950s, with the development of monoamine oxidase inhibitors (MAOIs). MAO is an enzyme responsible for the degradation of different other neurotransmitters including adrenaline, serotonin, norepinephrine and dopamine. It is believed that MAO inhibition alleviates depression, allowing serotonin and norepinephrine to accumulate synaptic connection in the CNS and sympathetic independent sistem8. In addition there MAOIs and tricyclic antidepressants (TCAs) are relatively non-selective, affecting not only serotonergic and noradrenergic systems, but also of muscarinic, histaminergic, and alpha-adrenergic system. Their efficacy is associated with increase in serotonin and noradrenaline lower level of dopamine in the synaptic gap. Amitriptyline, imipramine, clomipramine and nortriptyline are some examples of tricyclic antidepressants.

Most antidepressants are associated with a significant number of oral reactions9. These complications including xerostomia, sialoadenitis, gingivitis, dysgeusia, glossitis, edema of the tongue, discoloration and stomatitis, are almost always associated with salivary gland dysfunction induced by drugs.

Saliva is a real mirror of the body which contains a number of organic and inorganic compounds, and can be quite important health indicator. Salivary secretion is controlled by the autonomic nervous system through receptors responsible for the salivary glands. Many studies show that as far as the quality and quantity of salivary secretion medical conditions can affect the function of salivary glands10 11.

Salivary secretion is complex and occurs subsequently after neurotransmition incentives. The main control of secretion is derived from parasympathetic and sympathetic innervation which regulates the secretory function on level of acinic cells and controls the process in reabsorption in striated ducts of the salivary glands. Parasympathetic stimulation increases the level of saliva secretion, where sympathetic stimulation mainly affects the content and composition of proteins. Salivary glands can serve as a model to determine the effect of various peripheral antidepressants of monoaminergic and cholinergic systems. The function of the salivary glands depends on the integrity of the parasympathetic and sympathetic innervation. Normal salivation is essential for oral health because of its significant contributions to the oral defense mechanism. Reduced salivary secretion may lead to serious disease and deterioration of the mucosa. Saliva has more functions with respect to the oral cavity, including oral mucosa protection, chemical barrier digestion, antimicrobial activity, and maintain the integrity of teeth. Due to its glycoprotein, saliva has a viscous character that protect oral mucosa from harmful stimuli, microbial toxins and minor traumas forming a barrier. Its natural liquid removes cell debris and non-adherent bacteria.

The term means xerostomia subjective feeling or sensation of dryness in the mouth and is manifested as a symptom associated with a patient. It may appear as part of a systemic disease or condition (salivary aplasia, dehydration, sarcoidosis, cystic fibrosis, psychogenic, primary biliary cirrhosis, vasculitis, anxiety, diabetes type 1 or 2 diabetes insipidus, depression, chemotherapy), or as a consequence of applying drugs (antidepressants, diuretics, antispasmodics, barbiturates, anticonvulsants, antidysrithmics, decongestants, cytokines, cytotoxic agents). Patients with xerostomia manifest varying degrees of discomfort or discomfort that is associated with quality of life according to the etiology of their situation12. Nearly 1 to 5 patients complain of dryness in the mouth, with an increased incidence in the elderly it is essential to have a full understanding of this problem13.

Of all the above medical conditions, secondary manifestation of salivary hypofunction is usually after applying the drug-medication. They inhibit cholinergic signals in salivary tissues and thereby reduce excretion of fluid from the glands creating obstacles in the center of the road (and serotoninergics dopaminergics) 14th The normal amount of saliva stimulated salivary ranges between 0.7-1 Ml / min given that hyposalivation is considered when saliva production is below 0.7-1 Ml / min. Minimum age has influence on salivary flow, but with advancing age and the occurrence of chronic disease puts patients receiving drugs that can influence salivary flow up to 40% 15.

The study which was compared with the use of escitalopram and nortriptyline, Uher and aso16 noticed that dryness in the mouth was the most common adverse effect that significantly manifested during treatment with escitalopram or nortriptyline compared to the period where the medication was discontinued. The authors suggest that there is a positive correlation between the dosage of two antidepressants.

There is evidence that the prevalence of dryness in the mouth is correlated with polymedication (Nederfors17). However, Persson and aso18 confirmed that use up to 4 different xerogel medications did not result in significant further disruption in saliva speed and flow in their patients.

Subjective feeling of dryness can occur even in a state of normal flow of saliva who do not have to be connected by reducing the amount of saliva. According to Mandel and Wotman19 quality of salivary secretion (especially the mucin content) it is very important quantity than the sensation of dry

mouth. Such as saliva, process or procedure during collection, composition and source (small or large salivary glands) are factors that may contribute to patient hyposalivation associated with dryness in the mouth. According Nagler20, in one third of cases xerostomia does not reflect the actual reduction of saliva flow. Dryness in the oral cavity or reduction can cause many clinical problems: dental caries, dry mouth, dysgeusia, dry mouth, dysphagia, gingivitis, halitosis, problems with mastication, burning sensation in the mouth, mucositis, candidiasis, ulceration, changes in composition of saliva, periodontal diseases.

Antidepressants have antimuscarinic or anticholinergic action, so that act to block the parasympathetic system by inhibiting the effect of the acetylcholine receptors of salivary glands. This results in dryness in the oral cavity, probably because the predominant part of the sympathetic nervous system and independent blockade of parasympathetic nervous system22. According Douglas23 reduction of saliva is due to the reduction of blood flow to the gland, resulting adrenergic sympathetic vasoconstrictor.

Rather it is important to emphasize that dry mouth or decreased salivary production can occur during periods of stress and / or acute anxiety, frequent occurrence of depressive disorders, predominantly stimulation of sympathetic system regardless of the use of anxiolytic and / or antidepressant lekovi24. Occurrence of isolated depression is associated with reduced salivary secretion and xerostomia due to anticholinergic reaction. Therefore, it can be difficult to determine the origin intensity and side effects if the medical condition that requires treatment or medication that is recommended for this condition or disease, but perhaps due to two reasons.

Patients with the phenomenon of dry mouth, often complain of discomfort in the region of the lips, throat, oral or burning pain, altered taste and bad breath, halitosis. It is also an increased risk of developing thrush. Lack of adequate salivary biofilm may lead to subsequent pathological events in the oral cavity. Patients with dry mouth often try to relieve their symptoms with gum containing sugar or consuming cariogenic and acidic beverages.

According Veerabhadrappa et al., 24 there is a positive relationship between psychological disorders and xerostomia dryness of lips and mucosa. Emotional changes may affect as accelerated factor that can affect the secretion of salivary glands so you could potentially result in the manifestation of oral diseases. They note that a significant high percentage of xerostomia was observed in anxiety patients (51%), followed by depression (47%), bipolar disorder (41%), schizophrenia (39%) and control group (27%). Most patients were diagnosed with moderate to severe xerostomia, while the control group mild xerostomia. Age group pointed to xerostomia as dominant in their examination is between 18-49 years of age.

The presence of xerostomia and hyposalivation is quite common in patients with diabetes mellitus. There are many controversies as to whether the presence of hyposalivation is greater in patients with diabetes mellitus or for those absent.

López-Pintor25 in their comprehensive literature search in international biomedical research documented for xerostomia, hyposalivation and amount of saliva in patients with diabetes mellitus indicate that there is a high prevalence and variation present of xerostomia in patients with diabetes mellitus (12.5% -53.5%) in relation to nondiabetic patients (0-30%). Studies have analyzed the quality of saliva in DM patients compared to nondiabetic patients posted higher flow rates of saliva in non-diabetic than in diabetic patients.

Benzodiazepines as commonly prescribed psychotropic drugs with anxiolytic activity can directly or indirectly cause hyposalivation. It is established that benzodiazepines can cause hypertrophy and reducing the number of acinic cells. Mattioli TM et al26, examined the impact and effect of acinic and myoepithelial cells in rats. They came to the conclusion that animals treated with lorazepam showed a favorable increase in staining of cells

Calponin (calcium binding protein monoclonal antibody) compared to control animals ($p < 0.05$). Midazolam administered with pilocarpine (MP60) induced increased proliferation of acinic and ductal cells and reduce staining of positive cells Calponin, in comparison with the midazolam given with saline (MS60).

Mattioli et al27 in their immunohistochemical study on the effects of antidepressants and pilocarpine (parasympathomimetic alkaloid) in parotid glands of rats, explaining that the positive staining of cells Calponin increased after chronic use of antidepressants. Proliferation index of epithelial cells in rat parotid glands, was changed using antidepressants within 60 days.

Methamphetamine as highly dependent sympathomimetic stimulant widely abused in the world and is associated with devastating effects on oral health. Rommel N and sor28 (2016) studied the sympathomimetic effects of chronic methamphetamine abuse and adverse effects of oral health including 100 chronic patients using such a powerful central nervous system stimulant and 100 other participant for comparison. A significant number of users who abuse the use of methamphetamine reported that they have a sense of dry mouth (72%), and mastication of forks (68%). Methamphetamine abusers showed a significantly low production halls (ml / 5 min) ($p < 0.001$), low pH of saliva ($p < 0.001$) with signs of bruxism ($p < 0.001$).

Drugs or medications used to reduce inflammation and pain, or products with anti-inflammatory action and analgetic manifest influence and affect the secretion of saliva and its quantity.

Shin YH et al29, have analyzed the effect of Caspacin (trans-8-methyl-N-vanilyl-6-nonenamid) as the sole alkaloid agonist vanilloid type 1 which is expressed in nociceptive sensory neurons and a number of secretory epithelia, including salivary glands. Caspacin-by who has analgetic and anti-inflammatory effect on peripheral neurons affects the salivary secretion and inflammation in the salivary glands. They point to the effect of caspacin increase of salivary secretion in human and animal models, modulating in paracellular route in the salivary glands.

Literary findings suggest that nitric oxide plays a key role in the function and health of salivary gland. The specific mechanisms by which can regulate the function of the salivary gland during the initial Diabetes mellitus has yet to be determined. The reduced flow of Saliva can cause complications in the oral cavity, thus enabling excessive accumulation of bacteria that lead to numerous oral infections, extreme thirst (especially at night). Nitric oxide is a free radical was initially defined as a vasodilator which have an important role in the host defence mechanisms and pathogenesis of numerous inflammatory and autoimmune diseases. The results of examinations of Stewart CR30 conducted in female rats (author emphasizes that 85% of patients with diabetes mellitus and xerostomia are females) show that salivary production is correlated with the size of the submandibular and parotid gland. The results showed a reduction in the expression of submandibular cofactor tetrahydrobiopterin (BH4) with the ability to record it, and refers to the mechanism for development of hyposalivation in Diabetes mellitus induced xerostomia.

Oral and dental manifestations in diabetics may manifest due to numerous factors, including elevated levels of salivary secretory immunoglobulin (s-IgA). The study conducted Kakoei S31 was designed to evaluate the concentration of s-IgA in patients with type 2 diabetes mellitus and to investigate the association between levels of s-IgA with oral manifestations of type 2 diabetes mellitus. In patients with diabetes were determined significant concentration levels of s-IgA followed by stomatitis and xerostomia ($P \leq 0.050$).

Malicka B32 studying prevalence of xerostomia and salivary flow in patients with diabetes concluded that the phenomenon of dry mouth was more frequent represented in diagnosed type 1 diabetics with low flow of saliva.

According to Aitken-Saavedra33, there is a positive correlation between the level of metabolic controlled measurement HbA1, protein concentration and pH of saliva salivary dysfunction in patients with diabetes mellitus type 2. Of the patients diagnosed with type 2 diabetes mellitus was diagnosed xerostomia in 53%.

Hypertension is generally a condition where abnormally increased blood pressure in the arteries increases the risk of problems such as stroke, aneurysm, heart attack, kidney failure. Habbab et al34 declared that the possibility of oral manifestations in patients treated with cardiovascular drugs accounted for 14.1% of its examination. The most common oral signs and symptoms were recorded xerostomia in 7.5% of patients, lichen planus 3.6% and 1.9% dysgeusia.

Xerostomia measurements are heavier compared to those for hyposalivation that can be performed with sialometry. Direct testing issues a relatively sensitive method that can be used to assess xerostomia. Smoking as a negative habit is perhaps the leading cause to timely prevent with the same preventing outbreaks of disease. Smoking is regarded as one of the risk factors affecting salivation in addition to reducing the occurrence of xerostomia. Saliva is that the first step is in contact with cigarette smoke. Cigarette smoke contains 4,000 bioactive chemicals and 300 carcinogens that can cause structural and functional changes in plunkata35,36.

According to Maryam R36 there was a statistically significant difference between the rate of salivary flow in smokers who was 0.38 compared to where smoking was 0.56. Xerostomia was recorded in 39% of smokers and 19% in non-smokers.

The effect of smoking in the amount of saliva is controversial. Literature data show that for users with short-term use of cigarettes there is an increasing amount of plunka37, 38, while other studies show no statistically significant difference in the amount of saliva between the group of smokers and nepushachi39.

The study of Sujatha Dyasanoor 40, the prevalence of xerostomia in smokers was 37%, while smoking 13% statistically significant difference between the two groups. The prevalence of hyposalivation in their study amounted to 43% in smokers and 8% in the control group (non-smoking).

Weinberger AH41 in their double-blind, placebo-controlled, randomized clinical study determined the safety and efficacy of monoamine oxidase B inhibitor seleginin hydrochloride as an aid to smoking cessation in patients smokers. Monoamine oxidase is an enzyme involved in the catabolism of neurotransmitters such as dopamine, serotonin and norepinefrin42. Ex vivo human studies have shown that smokers have a reduced level of active platelet monoamine oxidase A and B compared to non-smokers. On the other hand selegiline hydrochloride is irreversible (sudiciden) subtype of monoamine oxidase B that is predominantly localized in the brain. According to the results of Weinberger AH 41 study participants who received more selegiline hydrochloride daily dose compared to the placebo group recorded condition of dry mouth in a ratio of 25.5% and 8.2%.

Agha-Hosseini43 suggests that patients with xerostomia there are significant changes in the composition of saliva, so that registered high levels of K, Cl, Ca, IgA and amylase, decreased levels of estrogen and progesterone zaedno44, 45. Calcium, PTH and cortisol with higher levels in women with xerostomia compared with their control grup44-47.

CONCLUSION

Xerostomia represents an important risk factor for diseases of the oral cavity that can affect the quality of life of patients. Providing better oral health is a priority for every therapist in order to ensure effective adequate dental treatment. Early recognition and treatment of xerostomia among this population group may prevent further development of various other oral diseases associated with it. Each dentist doctor should recognize and identify drugs that are

associated with the development of xerostomia and salivary gland dysfunction through a review of medical history.

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