Oral Implications of Polypharmacy in the Elderly

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KEYWORDS

• Saliva • Medications • Salivary hypofunction • Elderly • Polypharmacy

KEY POINTS

- The elderly population is increasing and has the highest number of users of prescription and over-the-counter (OTC) medication.
- Age-related changes occur in the body, which affect pharmacokinetics and pharmacodynamics.
- Prescription and OTC medications can cause myriad side effects in the oral cavity, and the elderly are more vulnerable.
- The adverse events in the oral cavity may cause discomfort and loss of function and decrease quality of life in the elderly.

INTRODUCTION

Early diagnoses and treatment of diseases have led to longer life expectancy. However, the treatments of these diseases involve pharmacologic agents, and as people age, they develop multiple health ailments, which can lead to polypharmacy. There are age-related changes in the systems of the body, which alter the pharmacokinetics and pharmacodynamics of medications and make the elderly more vulnerable to adverse events. A major side effects of medications is the qualitative and quantitative change the cause in saliva (salivary hypofunction), by their anticholinergic effects. Saliva plays a pivotal role in the homeostasis of the oral cavity because of its protective and

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functional properties, which include facilitating speech, swallowing, enhancing taste, buffering and neutralizing intrinsic and extrinsic acid, remineralizing teeth, maintaining the oral mucosal health, preventing overgrowth of noxious microorganisms and xerostomia. With salivary hypofunction, a plethora of complications arise, resulting in decreased quality of life in the elderly. However, the anticholinergic effects of medications can be overcome, and the oral cavity can be restored to normalcy.

CHANGES IN THE ELDERLY POPULATION

With improvements in health care, nutrition, lifestyles, habits, and safety practices, the life expectancy of people in the United States is increasing. This trend is true regardless of race or sex. From 1950 to 2010, the life expectancy of Americans of all races, both male and female, rose from 68.2 years to 78.7 years. The average life expectancy for white Americans (78.9 years) is longer than that of black or African Americans (75.1 years). Further, the life expectancy of white women is 81.3 years, compared with that of white men at 76.5 years. The life expectancy of black women is also longer than that of black men, at 78 years and 71.8 years, respectively.[1]

Globally, with the increase in life expectancy, the demographics of the total population are changing. In 2011, 14% of the total population of the United States was older than 65 years. It is estimated that in 2020, this percentage will increase to 16.76%, and by 2050, the percentage of people, both male and female, older than 65 years in the total population will increase to 20.95%.[2]

AGE-RELATED EFFECTS ON THE BODY

Chronologic aging is a process that affects various biological and physiologic processes in the human body. With advancing age, the functional abilities of organ systems tend to decrease. Although there is variability in the age-related changes that take place within each individual, aging generally affects all of the major biological and physiologic systems of the body.

For example, as one ages, there is a change in the composition of the body leading to a decrease in total body water and lean body mass, countered by an increase in body fat. Together, these age-related changes result in a diminished ability to distribute, metabolize, and excrete (clear) certain drugs. This situation causes water-soluble medications to be processed differently and less effectively. Lipophilic drugs because they have an increased volume of distribution, causing a prolonged half life, whereas water-soluble drugs have a smaller volume of distribution and a shorter half life.[3]

The liver is affected in several ways as the body ages. Specifically, there is a decrease in hepatic mass, hepatic blood flow, and enzymatic efficiency. The kidneys also undergo age-related alterations, such as a decrease in renal plasma flow, glomerular filtration rate, and tubular secretion. After these changes, as one ages, there is an increased sensitivity to medications, which can result in medication-induced hepatotoxicity and nephrotoxicity. In the cardiovascular system, the elasticity of blood vessels begins to decrease with age. This stiffening of blood vessels results in the decreased mechanical effectiveness of the heart. Furthermore, in the gastrointestinal system, the secretion of hydrochloric acid and pepsin decreases with the aging of the body. This situation then results in changes in absorption in the gastrointestinal tract.[4]

In the salivary glands, the aging process may cause the number of acinar cells to be reduced and to be replaced by fibrous and fatty tissue. This process may cause the composition of saliva to change.[5–7]

THE ELDERLY AND MEDICATIONS

The elderly population is more susceptible to acute and chronic medical problems. Hence, to cure or treat the ailments, either prescription medications or nonprescription (over-the-counter [OTC]) medications are introduced in the body system. In 2007 to 2008, more than 88% of Americans older than 60 years took at least 1 prescription medication, 76% used 2 or more prescription medications, and 37% used 5 or more. The use of at least 1 prescription medication follows a linear trend as the aging process advances. This trend is different in men and women, with women using more prescription drugs than men. Significantly more non-Hispanic whites take medications than non-Hispanic blacks or Mexican Americans. Even although the elderly represent only 13% of the population, one-third of the prescriptions written are dispensed to this population.[8]

In addition, as more prescription medications are being changed to OTC status, increasingly older adults self-manage medications to treat common medical conditions, especially the common cold, pain, diarrhea, constipation, indigestion, and headache.[9] Surveys[10] indicate that the elderly use 2 to 4 nonprescription medications daily, most commonly nonsteroidal antiinflammatory drugs, antihistamines, antacids (H_2 blockers), laxatives, and sedatives.[11]

Also, the increased use of illicit drugs by senior has become an emerging issue which prompted the National Institutes of Health to circulate an alert in 2012 about improper use of substances, to strengthen public awareness of substance use disorders in the elderly.[12]

Most Common Anticholinergic Medications

The most common anticholinergic medications are listed in **Table 1**.

Side Effects of Medications

Apart from their therapeutic effect, pharmacologic agents also bind to other unwanted potential sites causing side effects that affect the central nervous system (CNS) and/or the peripheral nervous system. Central side effects include confusion/disorientation, hallucinations, sleepiness, clumsiness or unsteadiness, convulsions, mental status/behavior changes such as distress, excitement, nervousness, attention deficits, cognitive decline (memory loss), and delirium. Peripheral side effects of medications can be salivary hypofunction, difficulty in speech and swallowing, mucous membrane dryness of the nose and skin, blurred vision, light sensitivity, increased breathing difficulty, difficulty urinating, bloating, and constipation in older adults.[13,14]

The perception of dry mouth has been reported to be directly proportional to the total number of drugs taken per day. Dry.org reports 1800 drugs in 80 drug classes that have the capacity to induce xerostomia.[15] Because there are more new medications in the pipeline in production to cure and treat diseases, the list of salivary hypofunction-inducing medications will only increase.

How Does Anticholinergic Medication Work?

To achieve therapeutic benefits and manage diseases, medications with anticholinergic properties are used. Anticholinergic medications competitively block or prevent acetylcholine molecules, which are neurotransmitters, from adhering to receptors of the cell membrane in both the central and peripheral nervous systems. Molecular cloning has defined 5 distinct muscarinic cholinergic receptor subtypes, designated M_1 to M_5, with each subtype being encoded by distinct cellular genes.[16]

Table 1
Common medications with significant anticholinergic properties and potential adverse consequences

Indication	Drug
First-generation antihistamines (as single agent or as part of combination products)	Chlorpheniramine Cyproheptadine Brompheniramine Carbinoxamine Chlorpheniramine Clemastine Cyproheptadine Dexbrompheniramine Diphenhydramine (oral) Doxylamine Hydroxyzine Promethazine Triprolidine
Antidepressants SSRI and SNRI	SSRI Fluoxetine Paroxetine Sertraline Fluvoxamine Citalopram SNRI Venlafaxine Duloxetine Desvenlafaxine
Antidiarrheal	Diphenoxylate atropine
Anti-Parkinson	Amantadine benztropine Biperiden trihexyphenidyl
Muscle relaxants	Cyclobenzaprine dantrolene Orphenadrine
Antivertigo	Meclizine scopolamine Phenothiazine
Tricyclic antidepressants, alone or in combination	Amitriptyline Chlordiazepoxide-amitriptyline Clomipramine Doxepin Imipramine Perphenazine Trimipramine
Cardiovascular	Furosemide Digoxin Nifedipine Disopyramide
Antispasmodic medications	Belladonna alkaloids Clidinium–chlordiazepoxide Dicyclomine Hyoscyamine Propantheline Scopolamine
Antiulcer	Cimetidine ranitidine
Antipsychotic	Chlorpromazine clozapine Olanzapine thioridazine Mesoridazine
Urinary incontinence	Oxybutynin probantheline Solifenacin tolterodine Trospium
Antiemetics	Prochlorperazine promethazine

Adapted from Minnesota Department of Health. Available at: http://www.health.state.mn.us/divs/fpc/cww/D02_Transmittal22ExcerptTableII.pdf Accessed January 1, 2014; and American Geriatrics Society Beers criteria for potentially inappropriate medication use in older adults. Available at: http://www.americangeriatrics.org/files/documents/beers/PrintableBeersPocketCard.pdf Accessed January 1, 2014.

M_3 receptors are found in the CNS, airway smooth muscles, and glandular tissues (such as salivary gland tissue). When the anticholinergics adhere to the receptors, especially on the M_3 receptors of the salivary gland, cell membrane changes are prevented (like the inhibition of adenylate cyclase, or the alteration in calcium permeability that leads to cholinergic responses).[17] When multiple medications are being taken at the same time for the treatments of various ailments of the elderly, their anticholinergic properties are potentiated. The cumulative anticholinergic burden of multiple medications and metabolites, rather than of a single compound causes the toxicities that are seen in the elderly.[18] Each year, adverse drug events affect millions causing considerable morbidity and mortality.[19]

Anticholinergic agents compete with the muscarinic receptors in the salivary glands and alter their function, but do not interact with or prevent the formation of acetylcholine.

Beers criteria

Mark Beers, MD, a geriatrician, created the Beers criteria which catalogs medications that cause adverse drug events in older adults because of their pharmacologic properties and/or the physiologic changes of aging. In 2011, the American Geriatrics Society (AGS) updated the criteria, assembling a team of experts, using an enhanced, evidence-based methodology. Each criterion is rated using the American College of Physicians' Guideline Grading system, which is based on the Grading of Recommendations Assessment, Development and Evaluation (GRADE) developed by Guyatt and colleagues.[20]

ROLE OF SALIVA

Saliva is produced by 3 pairs of major salivary glands and 400 to 600 minor salivary glands. The serous (watery) portion of the saliva is mostly produced by the parotid and submandibular (mixed serous and mucous) glands, and the mucus (mucin-containing) part is produced by the submandibular, sublingual, and minor salivary glands. Ninety-five percent of the saliva is produced by the salivary glands. The rate of whole unstimulated salivary flow is about 0.3 mL/min (average), and stimulated is on average 1.5 mL/min (with large individual variability). The critical level of saliva is considered to be less than between 0.1 and 0.16 mL/min when the complications from the salivary hypofunction arise.[21,22] Bicarbonates, Sialin, ammonia, urea and water in saliva buffer and neutralize the intrinsic and extrinsic acid and restore the normal pH in the oral cavity. Because of lubricating actions, saliva is necessary for speech, the bolus formation, and swallowing. Saliva also aids in flushing away food debris, dead tissue, and biofilm. Antimicrobial proteins and peptides in saliva (eg, histatins, lysozyme, lactoperoxidase, and lactoferrin) keep the deleterious microorganisms in check in the microenvironment of the oral cavity.[23]

Because secretory salivary IgA and mucins are reduced in the healthy elderly, the oral soft tissues become more susceptible to environmental factors as a result of a reduction of both immunologic and nonimmunologic defense systems of the oral cavity.[24]

ADVERSE EVENTS OF SALIVARY HYPOFUNCTION IN THE ORAL CAVITY

The peripheral side effects of anticholinergic drugs can lead to a plethora of dental and oral complications. Some of the common complications are listed later. The Anticholinergic Risk Scale (ARS) is useful tool that helps to assess the risk of adverse effects caused by anticholinergic drugs. Within the scale, medications are categorized with,

each category being assigned points. To use the ARS, the points are added up with the higher the total points, having the greater the risk.[25]

Xerostomia

The subjective sensation of dryness in the oral cavity is called xerostomia.[26] The aging process may cause the number of acinar cells to be reduced and to be replaced by fibrous and fatty tissue, but the composition remains the same in nonmedicated elders. Xerostomia is not a natural consequence of aging, but its prevalence increases with age.[27] When the basal volume of unstimulated saliva, which usually coats the soft and hard tissue, is decreased by 50% to 70% of the original volume, the subjective sensation of dryness occurs, resulting in xerostomia. Initially, the serous portion of the whole saliva is lost, leaving primarily the mucous portion. Consequently, secretion of thick and viscous saliva leads to a perception of having excessive saliva in the oral cavity. The anticholinergic load of drug(s) determines the severity of the reduction of salivary production that leads to xerostomia. It is more prevalent in the elderly population, primarily because of their increased use of drugs and their susceptibility to disease. Many drugs and drug classes have been linked to xerostomia; the xerogenic effect increases with poly pharmacy.[28]

Dental Carious Lesions

Just like bone, teeth are mineralized tissues that constantly undergo demineralization and remineralization controlled by saliva.[29] Saliva is normally supersaturated with calcium and phosphate ions acid either extrinsic or intrinsic leaches mineral from teeth. Fluoride acts as a catalyst to promote remineralization and is incorporated in the crystal to create a harder less soluble tooth structure, thus maintaining homeostasis in the oral cavity.

In salivary hypofunction, because of a decreased quantity of saliva and the loss of the antimicrobial functions of saliva, the number of cariogenic microorganisms (*Streptococcus mutans* lactobacilli) and *Candida* increases. In addition, the food (carbohydrate) substrate and dead cells are no longer debrided/lavaged well, thereby providing more substrate from which microorganisms produce bacterial acid to demineralize the tooth structure. Also, the loss of saliva enhances aggregation and adherence of noxious microorganisms, resulting in an increased population of bacteria. Normally, the demineralized structures are remineralized, but in the compromised microenvironment of the oral cavity, the potential to remineralize is decreased, thus increasing the risk of developing new and recurrent carious lesions. With elderly Americans living longer, retaining their teeth longer, resulting in a significant reduction in edentulism. With this change, along with receding gingival levels, more root surfaces are exposed, leading to an increased surface at risk (SAR) (**Figs. 1** and **2**). More than half of the individuals older than 65 years have experienced root caries.[30]

Candidiasis

The decrease in qualitative and quantitative saliva disposes to oral candidiasis. Studies have found the presence of *Candida* spp in association with mutans streptococci and lactobacilli in the saliva associated with dental decay and decreased microhardness of enamel.[31,32] In patients with oral candidiasis, salivary levels of lactoferrin, secretory immunoglobulins, salivary proteins, and peptides may be decreased and give rise to the growth and adhesion of candidial species to the oral tissue. Fissuring of the tongue, denture prosthesis, the presence of other (autoimmune) diseases affecting salivary gland function, and oral hygiene habits can increase aggregation, adherence, and penetration into deeper tissues and subsequently increase the risk of candidiasis.

Fig. 1. In older adults, more root surfaces are exposed, leading to an increased SAR.

When the opportunistic candidial microorganisms overgrow on the mucosa of the oral cavity, it may present with no obvious clinical presentation or present as erythematous, pseudomembranous, hyperplastic or angular chelitis. In salivary hypofunction, even the dental prostheses in the oral cavity can provide additional surfaces for the adherence and growth of the candidial population (Fig. 3).

Burning Tongue

Loss of the lubricating function of saliva may lead to increased friction between the tongue and hard tissue in the oral cavity. Candidiasis, fissuring of the tongue, sensitivity to allergens, strong tastants, and supertaster status can contribute to the burning sensation of the tongue.

Tooth Surface Loss

Tooth surface loss and caries are due to the irreversible loss of the tooth minerals. Enamel dissolves at the critical pH of 5.8 and dentin at 6.9. In the presence of fluoride, tooth structure is remineralized with the formation of hydroxyfluoroapatite crystals, but frequent acid exposures tips the balance to demineralization, resulting in caries, erosion, abrasion, and attrition.

Saliva is the most critical biological factor to prevent erosion. In the absence of the buffering action of saliva, there is a decreased potential of forming a pellicle (a protective barrier to the hard tissue), which helps prevent the direct exposure of the teeth to

Fig. 2. In older adults, more root surfaces are exposed, leading to an increased SAR.

Fig. 3. In salivary hypofunction, even the dental prostheses in the oral cavity can provide additional surfaces for the adherence and growth of the candidial population.

extrinsic and intrinsic acidic challenges in the oral cavity. Erosive lesions follow. There occurs a characteristic cupping or saucerlike appearance of the cuspal tips and incisal edges, a thinning of enamel, and subsequent yellowing of teeth. Lesions in which the width is greater than the depth, with loss of luster and matted look, can be found on the smooth surfaces, resulting from the process of erosion. Because of tooth surface loss around restorations, restorations may look as though they are protruding out of the tooth surfaces. These restorations are called proud restorations.

Also, because of a lack of lubricating action of saliva, tooth to tooth mechanical contact can result in tooth surface loss, called attrition. Tooth attrition takes place during the physiologic aging process, usually resulting in the loss of vertical height of the tooth. In the elderly cohort with salivary hypofunction, attrition can be accentuated, especially if the hardness of a restoration on opposing teeth is different than the tooth structure and pathologic. The vertical occlusal forces can result in the attrition of the incisal edges and abfraction of cervical and proximal surfaces.

The mechanical forces including chewing, deglutition, and parafunctional habits, cause wear facets, which are usually flat and well circumscribed in both opposing arches. Once the attrition reaches the dentin, the loss accelerates (**Fig. 4**).[33]

Fissuring of the Tongue

Aging and genetic predisposition can lead to central furrowing, with lateral extension of the dorsal surface of tongue, with varied depths. Salivary mucins protect the oral cavity against desiccation and environmental insult by coating the mucosal surfaces.[34] Loss of natural protective and environmental factors can cause fissuring of the tongue. Dead tissue and food debris trapped inside these grooves can serve as a feeding and breeding ground for biofilm and cause inflammation and halitosis.

Fig. 4. Once the attrition reaches the dentin, the loss of the tooth structure can be rapid.

Because removal of debris and biofilm from the deeper and fissured tongue is difficult, development of biofilm on other parts of the oral structures may be accelerated. Irritation of exposed or nearly exposed nerve endings on the cracked mucosal lining may induce increased sensitivity to tastants and other particles (Fig. 5).

Difficulty with Swallowing and Speech

The quantitative and qualitative decrease in saliva interferes with speech and swallowing processes as a result of loss of lubrication and decreased capability to form a bolus.

Mucositis

The oral mucosa is vulnerable to inflammation and ulceration because of cells in the process of mitosis, exposure to foreign objects, and reduced functioning of saliva. The mucositis can be accentuated by sharp dental edges, faulty restorations, or ill-fitting dentures.

Loss of Taste Perception

Decreased transfer of tastants by saliva to the receptor cells of the taste buds of the gustatory system, as well as possible coating of the tongue, as a result of microbial growth and accumulation of dead tissue and food debris, may interfere with the taste perception. Taste perception may be exaggerated if denuding of the tongue occurs as

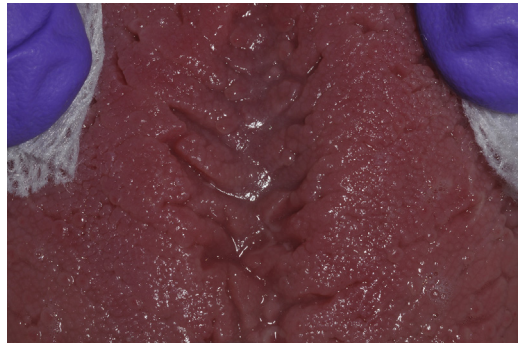

Fig. 5. Irritation of exposed or nearly exposed nerve endings on the cracked mucosal lining may induce increased sensitivity to tastants and other particles.

a result of loss of partial or total loss of papillae or alteration of the papillary architecture. Also, depending on type of medication use, there may be altered taste (eg, a metallic taste).

OVERCOMING ANTICHOLINERGIC EFFECTS

In contrast to the irreversible salivary hypofunction caused by Sjögren's syndrome and the therapeutic radiation of the head and neck area, medications and their side effects cause no physical damage to the salivary gland cells. Both gustatory or mechanical stimulation of the salivary glands promotes salivary flow.

As competitive antagonists, the effect of anticholinergic drugs can be overcome by increasing the concentration of acetylcholine in muscarinic M_3 receptors and increase production of saliva from the salivary glands. The anticholinergics may also cause vasodilation, acid production, and bronchodilatation. Parasympathomimetic drugs (eg, pilocarpine HCl [nonselective muscarinic agonist] and cevimeline HCl [M_1 and M_3 selectivity]), can bind with M_3 receptors and increase the intracellular Ca^{2+} concentration in salivary acini. Also, pilocarpine can increase the blood flow with the pressor response (due to increase in arterial pressure).[35] The stimulatory action of pilocarpine and cevimiline lasts up to 3 hours and 5 hours, respectively. Cevimiline induces salivary secretion at higher doses (30 mg) compared with pilocarpine (5 mg). Cevimeline may have lower sensitivity to Ca^{2+} in salivary glands[36,37] and be less effective in the heart and lungs with M_2 and M_4 muscarinic receptors.

Because of unwanted therapeutic effects of sialogogues, with individual variability, the dosage should be titrated up to the maximum and given for as long as 3 months for full effect.

MECHANICAL AND GUSTATORY STIMULATION

Gustatory and mechanical actions in the oral cavity, via neural reflexes, stimulate saliva, which increases the buffering capability, pH, and supersaturation of the salivary minerals (eg, calcium and phosphate).

Chewing sugar-free gum over a prolonged period results in a functional increase in salivary flow, as well as in increases in pH and buffer capacity which can help reduce plaque acidogenicity.[38] In a Cochrane review,[39] chewing gums increased saliva production in those with residual secretory capacity and was preferred by patients.

Also, manual (massaging) and thermal (moist heat) stimulation of parotid and submandibular glands helps expel mucous plugs and small sialoliths, which may cause salivary gland swelling and damage.

XYLITOL

The effects of xylitol-incorporated lozenges, spray, and gum stimulate and increase saliva, by osmotically drawing water from the tissues, improving pH, and buffering capacity of the saliva in the oral cavity.[40,41] Xylitol is a nonfermentable carbohydrate and inhibits the metabolism of bacterial species, especially mutans streptococci. Xylitol-containing agents aid with the clearance of carbohydrate substrate, dead tissue, and microorganisms, thus reducing the rate of demineralization and inducing remineralization[42] of the hard tissue. This process helps maintain homeostasis of the soft tissue. Recent studies with xylitol lozenges showed a 10% reduction in caries in high risk populations.[43]

SUPERSATURATED CALCIUM AND PHOSPHATE

The use of remineralizing solutions in concentrated doses (eg, Caphosol, Jazz Pharmaceuticals PLC, Dublin, Ireland or Neutrasal, Invado Pharmaceuticals, Pomona, NY, USA) can help provide the physiologic supersaturated level of calcium phosphate that is necessary for remineralization and mucosal healing. This situation is especially so when used with 1.1% Na F amorphous calcium phosphate containing paste, and fortified with 900 ppm fluoride (eg MI Paste and MI Paste Plus, GC America Inc, Alsip, IL, USA). This process may enhance remineralization and decrease demineralization of the calcified tissue in oral cavity.[44,45]

FLUORIDE

Various salts of fluoride are bactericidal and help with the reuptake of calcium and phosphate from the supersaturated saliva and the formation of fluoroapatite crystals, which are more resistant to acidic attacks. Prescription-strength fluoride in the form of toothpastes, gels, and professionally applied varnishes is necessary to prevent caries in a population with salivary hypofunction. Various strengths of fluoride are recommended to people at risk for developing dental carious lesions. As part of the evidence-based approach to care, these clinical recommendations should be integrated with the practitioner's professional judgment and the patient's needs and preferences.[46]

SALIVARY SUBSTITUTES

The evidence for caries protection from salivary substitutes is not sufficient for artificial saliva substitutes. The soothing effect of these substitutes is only temporary and must be administered frequently. Mouth rinses intended to treat dry mouth are expectorated and cleared by swallowing, resulting in only a small residual amount of active agent in the oral cavity. Sprays and gels are also susceptible to rapid dilution as a result of swallowing. Thus, the use of mouth rinses, sprays, and gels is inconvenient and often interruptive of daily activities. The evidence for caries protection is not there for saliva. The Cochrane review reported that,[39] there was no strong evidence for any topical therapy to relieve xerostomia. Oxygenated glycerol triester saliva substitute spray have shown about a 20% improvement over an electrolyte spray.

Commercially available products generally contain mucoadhesive polymers (eg, carboxymethylcellulose or hydroxyethylcellulose), preservatives (eg, methylparaben or propylparaben) and flavoring agents.

REGULAR DENTAL CARE

The frequency of dental office visits for xerostomic elderly patients should be every 3 months. During these visits, the oral cavity should be examined for any development of new dental carious lesions, soft tissue changes to assess any infection or inflammation, review of oral hygiene products, usage of prescriptions, prophylaxis, and most importantly, compliance to the regimen advised to reduce complications in the oral cavity caused by medications.

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