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SYSTEMATIC REVIEW

A Guide to Medications Inducing Salivary Gland Dysfunction, Xerostomia, and Subjective Sialorrhea: A Systematic Review Sponsored by the World Workshop on Oral Medicine VI

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Abstract

Background Medication-induced salivary gland dysfunction (MISGD), xerostomia (sensation of oral dryness), and subjective sialorrhea cause significant morbidity and impair quality of life. However, no evidence-based lists of the medications that cause these disorders exist.

Objective Our objective was to compile a list of medications affecting salivary gland function and inducing xerostomia or subjective sialorrhea.

Data Sources Electronic databases were searched for relevant articles published until June 2013. Of 3867 screened records, 269 had an acceptable degree of relevance, quality of methodology, and strength of evidence. We found 56 chemical substances with a higher level of evidence and 50 with a moderate level of evidence of causing the above-mentioned disorders. At the first level of the Anatomical Therapeutic Chemical (ATC) classification system, 9 of 14 anatomical groups were represented, mainly the alimentary, cardiovascular, genitourinary, nervous, and respiratory systems. Management strategies include substitution or discontinuation of medications whenever possible, oral or systemic therapy with sialogogues, administration of saliva substitutes, and use of electro-stimulating devices.

Limitations While xerostomia was a commonly reported outcome, objectively measured salivary flow rate was rarely reported. Moreover, xerostomia was mostly assessed

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as an adverse effect rather than the primary outcome of medication use. This study may not include some medications that could cause xerostomia when administered in conjunction with others or for which xerostomia as an adverse reaction has not been reported in the literature or was not detected in our search.

Conclusions We compiled a comprehensive list of medications with documented effects on salivary gland function or symptoms that may assist practitioners in assessing patients who complain of dry mouth while taking medications. The list may also prove useful in helping practitioners anticipate adverse effects and consider alternative medications.

Key Points

We compiled a comprehensive list of medications with documented effects on salivary gland function or symptoms that may assist practitioners assessing patients who complain of dry mouth while taking medications.

The list may also prove useful in helping practitioners anticipate oral adverse effects and consider alternative medications.

1 Introduction

Increased life expectancy, aging populations, and the association of these with polypharmacy have been intriguing topics over the last few decades. The World Health Statistics of 2014 published on the World Health Organization website reports a life expectancy of 55–87 years in its various constituent countries, with even the lower economy countries reporting rapid increases in life expectancy. However, with increased age comes a greater number of ailments, which in turn is indicative of a higher intake of medications.

Medications for the treatment of various diseases may also cause adverse effects, including those related to the oral cavity by their effects on the salivary glands. Apart from medications used to treat salivary gland disorders, other medications can also have the following adverse effects: salivary gland dysfunction (SGD), including salivary gland hypofunction (SGH) (an objectively measured decrease in salivation) or objective sialorrhea (an excessive secretion of saliva), xerostomia (subjective feeling of dry mouth), or subjective sialorrhea (feeling of having too much saliva). Medication-induced SGH and objective sialorrhea are collectively termed medication-induced salivary gland dysfunction (MISGD). The possible adverse effects associated with these disorders, especially SGH, include dental caries, dysgeusia, oral mucosal soreness, and oral candidiasis.

Current literature guiding clinicians in the prescribing of medications while considering the relevant adverse effects on salivary glands is very scarce. Most of the available literature attempting to list relevant drugs comprises a compendium based on manufacturers' drug profiles, narrative reviews, and case reports, or original research papers not containing a overall list of medications [1–10]. A systematic evidence-based list that identifies and lists medications that could objectively be associated with MISGD, xerostomia, or subjective sialorrhea is lacking. Hence, the MISGD group of the World Workshop on Oral Medicine VI (WWOM VI) aimed to review the current knowledge on this subject and compile a list of medications and their objective effects on salivary gland function, based on a high level of evidence and relevance.

2 Materials and Methods

The MISGD group comprised five reviewers (AA, RJ, NN, YS, and AlV), six consultants (senior experts in fields related to MISGD: DA, CD, JE, AMP, GP, and ArV), one research librarian (RM), one group head (AW), and two supervisors on behalf of the WWOM VI Steering Committee (SBJ and ARK). This review addresses one of the MISGD topics covered by the group, an updated classification of medications reported to cause objective SGD. The research method was based on the policies and standards set forth by a task force for WWOM IV [11] and by the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) statement [12], which was adapted to the current review.

2.1 Step 1: Scope Definition

The current review covered seven research questions, as follows:

Which medications have been reported to induce:

1. SGD in humans?
2. SGD in animals?
3. xerostomia but *not* SGD?
4. drooling but *not* SGD?
5. xerostomia-related oral symptoms (but *not* SGD) other than excessive dryness/wetness?
6. xerostomia but have *not been tested yet* for induction of SGD?
7. drooling but have *not been tested yet* for induction of SGD?

2.2 Step 2: Search Term Selection

The following keywords and subject headings were selected for each research question:

Q1. Medication/drugs/humans AND salivary gland dysfunction, xerostomia, dry mouth, reduced salivary flow rate, hyposalivation, sialorrhea, drooling.
Q2. Medication/drugs/animals AND salivary gland dysfunction, reduced salivary flow rate, hyposalivation, drooling.
Q3. Medication/drugs AND xerostomia, dry mouth, hyposalivation AND NOT salivary dysfunction.
Q4. Medication/drugs AND drooling/sialorrhea/hypersalivation/ptyalism/increased salivary flow rate AND NOT salivary dysfunction.
Q5. Medication/drugs AND salivary glands/saliva/xerostomia/dry mouth/hyposalivation AND NOT salivary gland dysfunction, oral sensory complaints.
Q6. Medication/drugs AND salivary glands/saliva/xerostomia/dry mouth/hyposalivation AND NOT salivary gland dysfunction/assessment.
Q7. Medication/drugs AND drooling/sialorrhea/hypersalivation/ptyalism AND NOT salivary gland dysfunction/assessment.

2.3 Step 3: Literature Search

Our literature search was conducted, through June 2013, in the PubMed, Embase, and Web of Science databases based on our chosen keywords and subject headings where applicable and was not limited by publication date, publication type or language. In addition, group members were encouraged to submit articles of interest located through referral or hand searching. The search was completed by a hand search of the reference lists in the eligible papers. After duplicates were removed, 3867 records were retained for Step 4.

2.4 Step 4: Record Screening for Eligibility

Each of the 3867 records was screened independently by the reviewers, who were supervised by the consultants. Papers were either retained for further analysis or excluded because they lacked relevance to any of the research questions; 269 papers relevant to the aforementioned topics were retained.

2.5 Step 5: Paper Selection for Type of Study, Relevance, and Level of Evidence

This step started with calibration among the reviewers to ensure they applied similar standards in the performance of their reviews. Papers were then divided among the reviewers, who analyzed publication titles, abstracts, and the materials and methods sections for key parameters.

2.6 Medication General Inclusion and Exclusion Criteria

1. Particular drugs for which MISGD has been reported were included.
2. A group of drugs or a combination of two or more drugs without specifying the individual MISGD of each drug under the group or combination were excluded.
3. Drugs reported to induce SGD or used in therapeutic aspects of SGD were excluded. Thus, parasympathomimetics (e.g., pilocarpine and cevimeline) and the anti-cholinesterases (e.g., physostigmine and neostigmine), which are used for stimulation of salivary flow in patients experiencing a dry mouth, were not included.
4. Research drugs that were not yet marketed by the time of writing this manuscript, or that were subsequently removed from the market, were excluded.

Next, the retained articles were given scores based on the following assessments:

(1) The degree of relevance: level A (study dedicated to MISGD or xerostomia) or level B (study dedicated to adverse effects of medications).
(2) The strength of methodology provided in the paper: level 1 (typically meta-analyses, systematic reviews, and randomized controlled trials [RCTs]), level 2 (typically open-label trials, observational studies, animal studies, and epidemiological studies), or level 3 (typically narrative reviews and textbooks).

It should be noted that, in addition to the type of study (RCT, review, etc.), the quality of study design and performance were considered in assigning the level of evidence. Hence, articles were assigned scores in order of decreasing levels of evidence as follows: A1 > B1 > A2 > B2 > A3 > B3.

2.7 Step 6: In-Depth Analysis

In-depth analysis was based on expert interpretation of the evidence. Supervised by the group head and consultants CD and JE, reviewer RJ screened the remaining 332 selected publications by reading the full text. Another 63 papers were excluded for reasons such as assessing MISGD and xerostomia as an outcome of minor importance, leaving 269 articles for in-depth analysis. Figure 1 depicts the steps of our work process and the distribution of the selected publications according to their score for level of evidence.

As a consequence of step 6, we derived three lists of medications:

1. 56 medications with strong evidence that were quoted in articles with scores A1 or B1.
2. 50 medications with moderate evidence that were quoted in articles with scores A2 or B2 but not A1 or B1.
3. 48 medications with weak evidence that were quoted in articles with scores not higher than A3 or B3.

3 Results

3.1 Anatomical Therapeutic Chemical (ATC) Classification of Drugs

The World Health Organization Collaborating Centre for Drug Statistics Methodology developed the Anatomical Therapeutic Chemical (ATC) classification system with defined daily doses (DDDs) as a system to classify therapeutic drugs. This system, which we also used, divides drugs into five different groups according to the organ or system on which they act and their chemical, pharmacological, and therapeutic properties. The first level contains 14 main groups according to anatomical site of action, with therapeutic subgroups (second level). The third and fourth levels are pharmacological and chemical subgroups, respectively, and the fifth level is the chemical compound itself.

We found that nine of the 14 groups in the first level contained medications reported with a strong or moderate level of evidence to be associated with SGD, xerostomia, or subjective sialorrhea: alimentary tract and metabolism, cardiovascular system, genitourinary system and sex hormones, anti-infectives for systemic use, anti-neoplastic and immunomodulating agents, musculoskeletal system, nervous system, respiratory system, and sensory organs. Among the 94 subgroups under the second level, 26 contain agents were reported to be associated with SGD, with 22 having strong evidence, namely drugs for functional gastrointestinal disorders, anti-emetics and anti-nauseants, anti-obesity preparations, anti-hypertensives, diuretics, beta-blocking agents, calcium channel blockers, urologicals, anti-neoplastic agents, muscle relaxants, drugs for the treatment of bone diseases, analgesics, anti-epileptics, anti-Parkinson drugs, psycholeptics, psychoanaleptics, other nervous system drugs, anti-muscarinic drugs for obstructive airway diseases, anti-histamines for systemic use, and ophthalmologicals. The third level is not included in Table 1 since it would add very little information. For the fourth level and its 882 subgroups described in the ATC/DDD system, 64 medication classes were found to be associated with SGD, and in 37 of these subgroups the association of SGD with the medications had stronger evidence. At the fifth level, 106 substances of the 4679 specified in the system were reported with a strong or moderate level of evidence to be associated with SGD. Of those, 56 drugs had a higher level of evidence of association with SGD (see Table 2).

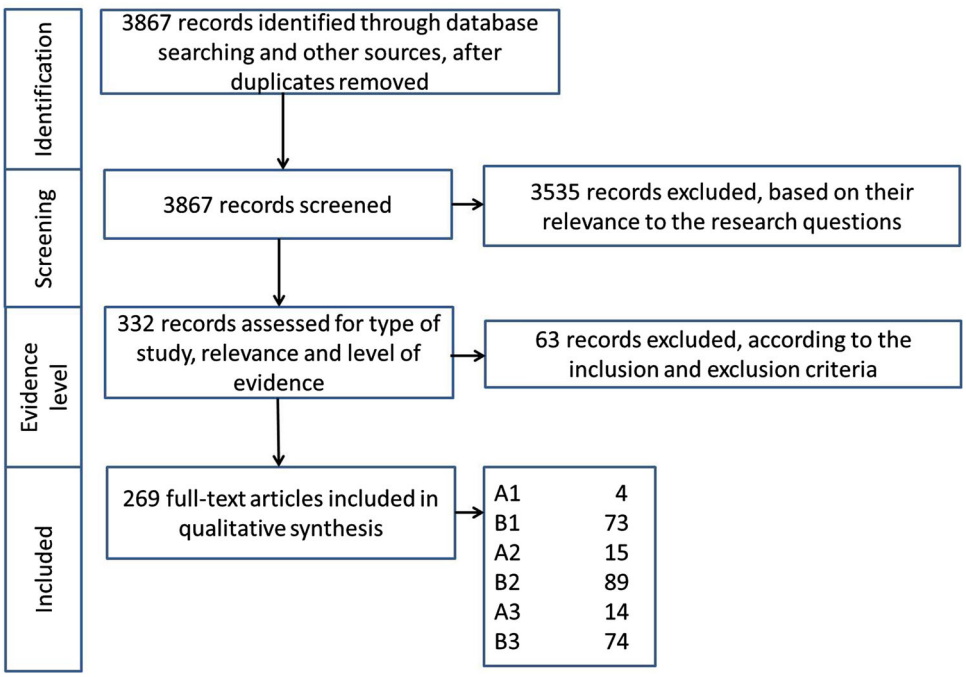

Fig. 1 Adapted PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) flowchart of the paper-selection process

3.2 Medications with Strong Evidence

Fifty-six medications had strong evidence of interference with salivary gland function. These medications could be categorized into the following eight of the ten anatomical main groups (first level in the ATC system): alimentary tract and metabolism (A), cardiovascular system (C), genitourinary system and sex hormones (G), anti-neoplastic and immunomodulating agents (L), musculoskeletal system (M), nervous system (N), respiratory system (R), and sensory organs (S). More than half (36) belong to the ATC main category of nervous system, and the most cited in the literature are oxybutynin (21 papers), tolterodine (19), duloxetine (19), quetiapine (14), bupropion (12), olanzapine (11), solifenacin (11), clozapine (9), fluoxetine (9), and venlafaxine (8). Oxybutynin, tolterodine, and solifenacin are urologicals, while the remainder act on the nervous system. All medications on this list except alendronate, bendroflumethiazide, and clonidine have been reported to cause xerostomia, whereas SGH has been verified (via measurement of salivary flow rate) for alendronate, amitriptyline, atropine, bendroflumethiazide, clonidine, fluoxetine, furosemide, oxybutynin, paroxetine, propiverine, propiverine, scopolamine, sertraline, solifenacin, and tolterodine. Sialorrhea was found to be an adverse effect of clozapine, olanzapine, and venlafaxine, as objectively assessed excess salivation, and of quetiapine and risperidone, as a symptom. Animal experiments offer an explanation for the dual action (oral dryness and sialorrhea) of clozapine [63, 120]. Dysgeusia was reported after administration of amitriptyline, bevacizumab, buprenorphine, fluoxetine loxapine, quetiapine, and sertraline; dental caries were associated with chlorpromazine and lithium; oral candidiasis was associated with olanzapine; and burning mouth sensation was associated with amitriptyline (not in Table 2). The properties of the various drugs listed in column 3 of Tables 2 and 3 were primarily derived from the textbook *Goodman and Gilman's The Pharmacological Basis of Therapeutics* [202].

3.3 Medications with Moderate Evidence

Fifty medications had a moderate level of evidence of effects on salivary glands. These medications belonged to the following seven of the ten main anatomical groups (first level according to the ATC classification system): alimentary tract and metabolism, cardiovascular system, genitourinary system and sex hormones, anti-infectives for systemic use, nervous system, and respiratory system. Medications under the ATC category 'nervous system' were also the most commonly quoted medications in Table 3. Xerostomia is an adverse effect of all the drugs listed in Table 3 except clobazam, whereas SGH was reported with darifenacin and metoprolol. Enalapril, haloperidol, and methyldopa were reported to cause a subjective feeling of sialorrhea. Objective sialorrhea was reported only with clobazam. Three medications (azelastine, enalapril, and fluvoxamine) were reportedly associated with dysgeusia, and one (haloperidol) was associated with dental caries (not in Table 3).

3.4 Medications with Weak Evidence

In total, 48 medications were reported to cause a range of adverse oral effects, such as xerostomia, SGH, sialorrhea, burning mouth sensation, dysgeusia, and dental caries (Table 4).

4 Discussion

Saliva plays a crucial role in maintaining the health and functioning of the mouth. Its functions include (1) maintaining a moist oral mucosa, (2) mucinous content acting as a lubricant in the mouth and oesophagus, (3) taste recognition by acting as a medium for suspension of tastants, (4) digestion of starches with the help of amylase, (5) acid buffering in the mouth and oesophagus mainly by bicarbonate, (6) protection of teeth from acids by being supersaturated with respect to tooth mineral and by contributing to the acquired enamel pellicle, (7) modulation of the oral microbiota with the help of anti-bacterial, anti-viral, and anti-fungal components, and (8) facilitating wound healing in the oral cavity [272]. Medications may act on the central nervous system and/or at the neuroglandular junction, explaining the pathogenesis of MISDG. The secretory cells are supplied with muscarinic M1 and M3 receptors, α1- and β1-adrenergic receptors, and certain peptidergic receptors that are involved in the initiation of salivary secretion [273]. It is therefore understandable that drugs that have antagonistic actions on the autonomic receptors but that are used to treat dysfunctions in the various effectors of the autonomic nervous system may also affect the functions of salivary glands and thus cause oral dryness. However, in some cases, the cause of oral dryness is not as evident, as with the bisphosphonate alendronate that was reported to reduce the unstimulated secretion of saliva [13].

The anti-muscarinic drugs are well-known inducers of oral dryness as they prevent parasympathetic (cholinergic) innervation from activating the secretory cells. Surprisingly, clinical studies directly focusing on the secretion of saliva and the flagship of the anti-muscarinics, atropine, seem few. This is in contrast to numerous studies on animals, starting with the observations of the pioneers of salivary physiology in the 1870s.

Table 1 Medications reported to induce xerostomia, salivary gland hypofunction, or sialorrhea with higher and moderate level of evidence, grouped according to their inclusion in first, second, fourth, and fifth ACT levels

First level, anatomical main group	Second level, therapeutic subgroup	Fourth level, chemical subgroup	Fifth level, chemical substance	ATC code
Alimentary tract and metabolism	**Drug for functional GI disorder**	**Synthetic anti-cholinergics, quaternary ammonium compounds**	**Propantheline**	**A03AB05**
		Belladonna alkaloids, tertiary amines	**Atropine**	**A03BA01**
			Hyoscyamine	A03BA03
		Belladonna alkaloids, semisynthetic, quaternary ammonium compounds	**Scopolamine/ hyoscine**	**A03BB01**
	Anti-emetics and anti-nauseants	**Other anti-emetics**	**Scopolamine/ hyoscine**	**A04AD01**
	Anti-obesity preparations, excl. diet products	**Centrally acting anti-obesity products**	**Phentermine**	**A08AA01**
			Dexfenfluramine	A08AA04
			Sibutramine	**A08AA10**
		Peripherally acting anti-obesity products	Orlistat	A08AB01
		Serotonin–noradrenaline–dopamine reuptake inhibitor	Tesofensine	ND
Cardiovascular system	Cardiac therapy	Anti-arrhythmics, class Ib	Mexiletine	C01BB02
	Anti-hypertensives	Methyldopa	Methyldopa	C02AB01
		Imidazoline receptor agonists	**Clonidine**	**C02AC01**
	Diuretics	**Thiazides, plain**	**Bendroflumethiazide**	**C03AA01**
		Sulfonamides, plain	Furosemide	C03CA01
		Vasopressin antagonists	Tolvaptan	C03XA01
	Beta-blocking agents	**Beta-blocking agents, non-selective**	**Timolol**	**C07AA06**
		Beta-blocking agents, selective	Metoprolol	C07AB02
			Atenolol	C07AB03
	Calcium channel blockers	Dihydropyridine derivatives	Isradipine	C08CA03
		Phenylalkylamine derivatives	**Verapamil**	**C08DA01**
	Agents acting on the renin-angiotensin system	ACE inhibitors, plain	Enalapril	C09AA02
			Lisinopril	C09AA03
Genitourinary system and sex hormones	**Urologicals**	**Drugs for urinary frequency and incontinence**	**Oxybutynin**	**G04BD04**
			Propiverine	**G04BD06**
			Tolterodine	**G04BD07**
			Solifenacin	**G04BD08**
			Trospium	G04BD09
			Darifenacin	G04BD10
			Fesoterodine	G04BD11
			Imidafenacin	**ND**
		Alpha-adrenoreceptor antagonists	Alfuzosin	G04CA01
			Terazosin	G04CA03
Anti-infectives for systemic use	Anti-virals for systemic use	Protease inhibitors	Saquinavir	J05AE01
		Nucleoside and nucleotide reverse transcriptase inhibitors	Didanosine	J05AF02
			Lamivudine	J05AF05
		Non-nucleoside reverse transcriptase inhibitors	Nevirapine	J05AG01
			Etravirine	J05AG04
		Other anti-virals	Raltegravir	J05AX08
			Maraviroc	J05AX09
Anti-neoplastic and immunomodulating agents	**Anti-neoplastic agents**	**Monoclonal antibodies**	**Bevacizumab**	**L01XC07**

Table 1 continued

First level, anatomical main group	Second level, therapeutic subgroup	Fourth level, chemical subgroup	Fifth level, chemical substance	ATC code
Musculoskeletal system	**Muscle relaxants**	**Other centrally acting agents**	**Baclofen**	**M03BX01**
			Tizanidine	**M03BX02**
			Cyclobenzaprine	**M03BX08**
	Drugs for treatment of bone diseases	**Bisphosphonates**	**Alendronate**	**M05BA04**
Nervous system	Anesthetics	Opioid anesthetics	Fentanyl	N01AH01
	Analgesics	Natural opium alkaloids	Morphine	N02AA01
			Dihydrocodeine	N02AA08
		Phenylpiperidine derivatives	Fentanyl	N02AB03
		Oripavine derivatives	**Buprenorphine**	**N02AE01**
		Morphinan derivatives	**Butorphanol**	**N02AF01**
		Other opioids	Tramadol	N02AX02
			Tapentadol	N02AX06
		Other anti-migraine preparations	**Clonidine**	**N02CX02**
	Anti-epileptics	Fatty acid derivatives	Sodium valproate/valproic acid	N03AG01
		Other anti-epileptics	**Gabapentin**	**N03AX12**
			Pregabalin	N03AX16
	Anti-Parkinson drugs	**Dopamine agonists**	**Rotigotine**	**N04BC09**
	Psycholeptics	**Phenothiazines with aliphatic side-chain**	**Chlorpromazine**	**N05AA01**
		Phenothiazines with piperazine structure	**Perphenazine**	**N05AB03**
		Butyrophenone derivatives	Haloperidol	N05AD01
		Indole derivatives	Sertindole	N05AE03
			Ziprasidone	**N05AE04**
			Lurasidone	N05AE05
		Diazepines, oxazepines, thiazepines, and oxepines	**Loxapine**	**N05AH01**
			Clozapine	**N05AH02**
			Olanzapine	**N05AH03**
			Quetiapine	**N05AH04**
			Asenapine	N05AH05
		Benzamides	Amisulpride	N05AL05
		Lithium	**Lithium**	**N05AN01**
		Other anti-psychotics	**Risperidone**	**N05AX08**
			Aripiprazole	**N05AX12**
			Paliperidone	**N05AX13**
		Benzodiazepine derivatives (anxiolytics)	Clobazam	N05BA09
		Benzodiazepine-related drugs	**Zolpidem**	**N05CF02**
			Eszopiclone	N05CF04
			Zopiclone	N05CF01
		Other hypnotics and sedatives	**Scopolamine/ hyoscine**	**N05CM05**
			Dexmedetomidine	N05CM18

Table 1 continued

First level, anatomical main group	Second level, therapeutic subgroup	Fourth level, chemical subgroup	Fifth level, chemical substance	ATC code
	Psychoanaleptics	**Non-selective monoamine reuptake inhibitors**	Desipramine	N06AA01
			Imipramine	**N06AA02**
			Amitriptyline	**N06AA09**
			Nortriptyline	**N06AA10**
			Doxepin	N06AA12
			Dosulepin	N06AA16
		Selective serotonin reuptake inhibitors	**Fluoxetine**	**N06AB03**
			Citalopram	**N06AB04**
			Paroxetine	**N06AB05**
			Sertraline	**N06AB06**
			Escitalopram	**N06AB10**
		Other anti-depressants	**Bupropion**	**N06AX12**
			Venlafaxine	**N06AX16**
			Reboxetine	**N06AX18**
			Duloxetine	**N06AX21**
			Desvenlafaxine	N06AX23
			Vortioxetine	**N06AX26**
		Centrally acting sympathomimetics	**Methylphenidate**	**N06BA04**
			Dexmethylphenidate	**N06BA11**
			Lisdexamfetamine	**N06BA12**
	Other nervous system drugs	Drugs used in nicotine dependence	Nicotine	N07BA01
		Drugs used in alcohol dependence	Naltrexone	N07BB04
		Drugs used in opioid dependence	**Buprenorphine**	**N07BC01**
	ND	**ND**	**Dimebon**	**ND**
			Tesofensine	ND
Respiratory system	Nasal preparations	Anti-allergic agents, excl. corticosteroids	Azelastine	R01AC03
	Drugs for obstructive airway diseases	**Anti-cholinergics**	**Tiotropium**	**R03BB04**
	Anti-histamines for systemic use	**Aminoalkyl ethers**	**Doxylamine**	**R06AA09**
		Piperazine derivatives	Cetirizine	R06AE07
			Levocetirizine	R06AE09
		Other anti-histamines for systemic use	Ebastine	R06AX22
			Desloratadine	R06AX27
Sensory organs	**Ophthalmologicals**	**Sympathomimetics in glaucoma therapy**	**Brimonidine**	**S01EA05**
		Anti-cholinergics	**Atropine**	**S01FA01**
		Other anti-allergics	Azelastine	S01GX07

ACE angiotensin-converting enzyme, *ATC* Anatomical Therapeutic Chemical, *GI* gastrointestinal, *ND* not determined

[a] Bold type indicates higher level of evidence

The number of patients adversely affected by a specific drug, as well as the severity of the effect of this drug, are usually dose dependent. Figures for these parameters are not presented in the current study. Lack of saliva is often manifested as the sensation of dry mouth (xerostomia). A number of studies have suggested an association between the incidence of xerostomia and the number and dose of medications [274]. That study also discussed secondary effects of MISGD in promoting caries or oral mucosal alterations.

Management of MISGD has mainly been based on a trial-and-error approach. Use of intraoral topical agents, such as a spray containing malic acid, sugar-free chewing gums or candy, saliva substitutes, or non-alcoholic mouthwashes to moisten or lubricate the mouth have served as the mainstay of treatment for patients with a dry

Table 2 Medications reported to induce xerostomia, salivary gland hypofunction, or sialorrhea with higher level of evidence

Drug name	ATC code	Mechanism and site of action	Number of citations for				Sources per level of evidence (*n*)						Total publications (*n*)	References
			Oral 'dryness'		Sialorrhea									
			Xerostomia	SGH	Subjective	Objective	A1	B1	A2	B2	A3	B3		
Alendronate (anti-bone-resorptive activity)	M05BA04	Bisphosphonate—inhibits osteoclastic bone resorption	0	1	0	0	1	0	0	0	0	0	1	[13]
Amitriptyline (anti-depressant)	N06AA09	Non-selective 5-HT/NE reuptake inhibitor, anti-muscarinic	5	1	0	0	0	1	0	3	1	1	6	[14–19]
Aripiprazole (atypical anti-psychotic)	N05AX12	Dopamine stabilizer; partial dopamine (D2) and 5-HT1A agonist, 5-HT2A antagonist	5	0	0	0	0	1	0	4	0	0	5	[20–24]
Atropine (GI disorders/mydriatic)	A03BA01, S01FA01	Anti-muscarinic	3	2	0	0	0	1	1	0	1	1	4	[14, 25–27]
Baclofen (skeletal muscle relaxant—centrally acting)	M03BX01	GABA agonist: reduces release of excitatory glutamate	2	0	0	0	0	1	0	0	0	0	1	[28]
Bendroflumethiazide (weak diuretic)	C03AA01	Inhibits reabsorption of NaCl in distal tubule of nephron	0	1	0	0	1	0	0	0	0	0	1	[29]
Bevacizumab (anti-neoplastic)	L01XC07	Monoclonal antibody: inhibits vascular proliferation and tumor growth	1	0	0	0	0	1	0	0	0	0	1	[30]
Brimonidine (anti-glaucoma)	S01EA05	α_2-Adrenergic agonist	3	0	0	0	0	1	0	0	1	1	3	[26, 31, 32]
Buprenorphine (opioid-analgesic)	N02AE01, N07BC01	Mixed receptor actions; κ-opioid antagonist and partial μ-opioid agonist	1	0	0	0	0	1	0	0	0	0	1	[33]
Bupropion (anti-depressant)	N06AX12	NE/dopamine reuptake inhibitor	12	0	0	0	0	5	0	3	0	4	12	[34–45]
Butorphanol (opioid-analgesic)	N02AF01QR05A90	Mixed receptor actions; κ-agonist and μ-antagonist	1	0	0	0	0	1	0	0	0	0	1	[46]

Table 2 continued

Drug name	ATC code	Mechanism and site of action	Number of citations for				Sources per level of evidence (*n*)						Total publications (*n*)	References
			Oral 'dryness'		Sialorrhea									
			Xerostomia	SGH	Subjective	Objective	A1	B1	A2	B2	A3	B3		
Chlorpromazine (anti-psychotic)	N05AA01	Antagonist to dopamine, 5-HT, histamine (H1), muscarinic and $\alpha_{(1,2)}$-adrenergic receptors	2	0	0	0	0	1	0	0	0	0	1	[47]
Citalopram (anti-depressant)	N06AB04	Selective 5-HT reuptake inhibitor	3	0	0	0	0	1	1	1	0	0	3	[34, 48, 49]
Clonidine (anti-hypertensive/anti-migraine)	C02AC01, N02CX02	α_2-Adrenergic agonist	0	1	0	0	0	1	0	0	1	4	6	[14, 50–54]
Clozapine (atypical anti-psychotic)	N05AH02	Dopamine antagonist, partial 5-HT and partial muscarinic (M1) agonist, muscarinic (M3) antagonist, and α_1-adrenergic antagonist	2	0	0	7	3	2	1	2	1	0	9	[55–57[a], 58–61 62[a], 63]
Cyclobenzaprine (skeletal muscle relaxant—centrally acting)	M03BX08	Histamine (H1) and muscarinic antagonist	4	0	0	0	0	3	0	0	0	0	3	[64–66]
Dexmethylphenidate (psychostimulant—ADHD)	N06BA11	Indirect sympathomimetic and NE/dopamine reuptake inhibitor	1	0	0	0	0	1	0	0	0	0	1	[67]
Dimebon (anti-dementia)	ND	Unknown action—proposed histamine (H1) and 5-HT antagonist	1	0	0	0	0	1	0	0	0	0	1	[68]
Doxylamine (hypnotic)	R06AA09	Anti-histamine; histamine (H1) and muscarinic antagonist	1	0	0	0	0	1	0	0	0	0	1	[69]
Duloxetine (anti-depressant)	N06AX21	5-HT/NE reuptake inhibitor	19	0	0	0	0	1	0	10	0	8	19	[34, 70–87]
Escitalopram (anti-depressant)	N06AB10	Selective 5-HT reuptake inhibitor	4	0	0	0	0	1	0	2	0	1	4	[34, 84, 88, 89]
Fluoxetine (anti-depressant)	N06AB03	Selective 5-HT reuptake inhibitor	9	1	0	0	0	2	1	3	0	3	9	[17, 34, 48, 90–95]

Table 2 continued

Drug name	ATC code	Mechanism and site of action	Number of citations for				Sources per level of evidence (*n*)						Total publications (*n*)	References
			Oral 'dryness'		Sialorrhea									
			Xerostomia	SGH	Subjective	Objective	A1	B1	A2	B2	A3	B3		
Furosemide (strong diuretic)	C03CA01	Inhibits NaCl reabsorption in the thick ascending loop of Henle	2	3	0	0	2	0	0	0	1	0	3	[14, 29, 96]
Gabapentin (anti-convulsant)	N03AX12	Proposed action: stimulates GABA synthesis and GABA release	1	0	0	0	0	1	0	0	0	0	1	[97]
Imidafenacin (urological—reduces bladder activity)	ND	Anti-muscarinic	1	0	0	0	0	1	0	0	0	0	1	[98]
Imipramine (anti-depressant)	N06AA02	5-HT/NE-reuptake inhibitor, antagonist to histamine (H1), 5-HT, muscarinic and α_1-adrenergic receptors	2	0	0	0	0	1	0	0	0	1	2	[99, 100]
Lisdexamfetamine (psychostimulant—ADHD)	N06BA12	5-HT/NE reuptake inhibitor	2	0	0	0	0	1	0	1	0	0	2	[101, 102]
Lithium (anti-psychotic)	N05AN01	Mood stabilizer; inhibits dopamine/NE release and intracellular Ca^{2+} mobilization	2	0	0	0	0	1	0	1	1	1	4	[103, 104–106]
Loxapine (anti-psychotic)	N05AH01	Dopamine/5-HT antagonist	1	0	0	0	0	1	0	0	0	0	1	[107]
Methylphenidate (psychostimulant—ADHD)	N06BA04	Indirect sympathomimetic, release of dopamine, and NE/5-HT reuptake inhibitor	5	0	0	0	0	2	0	2	0	1	5	[37, 108–111]
Nortriptyline (anti-depressant)	N06AA10	NE reuptake inhibitor, antagonist to histamine (H1), 5-HT, α_1-adrenergics, and muscarinics	2	0	0	0	0	1	0	0	0	1	2	[97, 112]

Table 2 continued

Drug name	ATC code	Mechanism and site of action	Number of citations for				Sources per level of evidence (*n*)						Total publications (*n*)	References
			Oral 'dryness'		Sialorrhea									
			Xerostomia	SGH	Subjective	Objective	A1	B1	A2	B2	A3	B3		
Olanzapine (atypical anti-psychotic)	N05AH03	Antagonist to dopamine, 5-HT, histamine, muscarinics, and α_1-adrenergics	10	0	0	1	0	4	1	5	0	1	11	[20, 56, 113–120[a], 121]
Oxybutynin (urological—reduces bladder activity)	G04BD04	Anti-muscarinic	20	3	0	0	0	7	0	10	0	4	21	[122–142] ([138–140] are animal studies)
Paliperidone (atypical anti-psychotic)	N05AX13	Antagonist to dopamine, 5-HT, $\alpha_{(1,2)}$ –adrenergics, and histamine	2	0	0	0	0	1	0	0	0	1	2	[143, 144]
Paroxetine (anti-depressant)	N06AB05	5-HT reuptake inhibitor	3	1	0	0	0	1	0	1	0	1	3	[34, 41, 145]
Perphenazine (anti-psychotic)	N05AB03	Antagonist to 5-HT, dopamine, histamine (H1), muscarinic, and α_1-adrenergic receptors	1	0	0	0	0	1	0	0	0	0	1	[113]
Phentermine (appetite suppressant)	A08AA01	Releases NE and to a lesser degree dopamine and 5-HT	3	0	0	0	0	2	0	1	0	0	3	[146–148]
Propantheline (anti-peristaltic/spasmolytic)	A03AB05	Anti-muscarinic	2	1	0	0	0	2	0	0	1	0	3	[14, 129, 133]
Propiverine (urological—reduces bladder activity	G04BD06	Anti-muscarinic	5	1	0	0	0	1	0	2	1	2	6	[98, 127, 129, 133, 134, 149[a]]
Quetiapine (atypical anti-psychotic)	N05AH04	Dopamine, 5-HT, $\alpha_{(1,2)}$-adrenergic, and histamine (H1) antagonist	14	0	2	0	0	12	0	1	0	1	14	[103, 113, 116 144, 150–159]
Reboxetine (anti-depressant)	N06AX18	NE reuptake inhibitor, anti-muscarinic	5	0	0	0	0	1	0	2	0	2	5	[85, 160–163]

Table 2 continued

Drug name	ATC code	Mechanism and site of action	Number of citations for				Sources per level of evidence (*n*)						Total publications (*n*)	References
			Oral 'dryness'		Sialorrhea									
			Xerostomia	SGH	Subjective	Objective	A1	B1	A2	B2	A3	B3		
Risperidone (anti-psychotic)	N05AX08	Antagonist to dopamine, serotonin, histamine (H1), and $\alpha_{1,2}$ adrenergic receptors	1	0	1	0	0	1	0	0	0	1	2	[113, 164]
Rotigotine (anti-Parkinson)	N04BC09	Dopamine and 5-HT agonist, α_2 adrenergic antagonist	2	0	0	0	0	1	0	1	0	0	2	[165, 166]
Scopolamine (anti-nauseant/sedative/GI disorders)	A04AD01, N05CM05 A03BB01	Muscarinic antagonist	2	1	0	0	0	1	0	0	1	1	3	[14, 167, 168]
Sertraline (anti-depressant)	N06AB06	5-HT reuptake inhibitor	4	1	0	0	0	2	1	0	0	1	4	[34, 48, 93, 95]
Sibutramine (anti-depressant)	A08AA10	Reuptake inhibitor of NE/5-HT/dopamine	2	0	0	0	0	1	0	1	0	0	2	[169, 170]
Solifenacin (urological—reduces bladder activity)	G04BD08	Anti-muscarinic	9	2	0	0	0	2	0	5	4	0	11	[133, 134, 137–139, 171–176]
Tesofensine (appetite suppressant)	ND	NE/5-HT/dopamine reuptake inhibitor	1	0	0	0	0	1	0	0	0	0	1	[177]
Timolol (anti-glaucoma)	C07AA06	Non-selective β-adrenergic antagonist	1	0	0	0	0	1	0	0	0	0	1	[32]
Tiotropium (anti-asthmatic)	R03BB04	Prevents bronchoconstriction, anti-muscarinic	2	0	0	0	0	1	0	0	0	1	2	[178, 179]
Tolterodine (urological—reduces bladder activity)	G04BD07	Anti-muscarinic	19	2	0	0	0	4	1	10	1	3	19	[124, 128, 129, 133–135, 138, 142, 180–190[a],191]
Venlafaxine (anti-depressant)	N06AX16	NE/5-HT reuptake inhibitor	8	0	0	1	0	1	0	7	0	0	8	[17, 34, 52, 89, 192–195
Verapamil (anti-hypertensive/anti-angina)	C08DA01	Calcium channel blocker—arterial vasodilator effects	1	0	0	0	0	1	0	0	0	0	1	196]
Vortioxetine (anti-depressant)	N06AX26	5-HT reuptake inhibitor	2	0	0	0	0	1	0	1	0	0	2	[75, 197]

Table 2 continued

Drug name	ATC code	Mechanism and site of action	Number of citations for				Sources per level of evidence (*n*)						Total publications (*n*)	References
			Oral 'dryness'		Sialorrhea									
			Xerostomia	SGH	Subjective	Objective	A1	B1	A2	B2	A3	B3		
Ziprasidone (atypical anti-psychotic)	N05AE04	5-HT, dopamine and α-adrenergic antagonist	3	0	0	0	0	3	0	0	0	0	3	[113, 198, 199]
Zolpidem (hypnotic/sedative)	N05CF02	Agonist at the benzodiazepine site of the $GABA_A$ receptor, enhancing the inhibitory effect of GABA	2	0	0	0	0	2	0	0	0	0	2	[200, 201]

5-HT 5-hydroxytryptamine (serotonin), *ADHD* attention-deficit/hyperactivity disorder, *ATC* Anatomical Therapeutic Chemical, *GABA* gamma-aminobutyric acid, *GI* gastrointestinal, *ND* not determined, *NE* norepinephrine, *SGH* salivary gland hypofunction

[a] Animal studies

mouth. Parasympathomimetic agents with potent muscarinic-stimulating properties, such as pilocarpine and cevimeline, and anti-cholinesterases, which reduce the rate of acetylcholine metabolism, have been used as systemic sialogogues. Although they increase salivation significantly, the adverse effect profile of these drugs upon systemic administration restricts their use in patients with MISGD. A local application of these categories of drugs onto the oral epithelium, with the aim of activating the underlying minor glands, may be an alternative approach. It is also necessary to ensure salivary gland functionality before administering these medications. Newer management methods include electrostimulation. Other management options for MISGD include possibly reducing the number of medications or the dosage or replacing them with medications or formulations with fewer xerogenic effects. Little evidence is available on this important topic; however, when dental treatment is needed, close communication between the dentist (who has to deal with the adverse effects) and the prescribing physician is warranted to obtain the best outcome for the patient [275].

The present paper tries to fill the lacunae in regard to evidence-based listing of the effects of medications on salivary function as found in the current scientific literature. We conducted an extensive search of the literature related to MISGD, followed by meticulous scrutiny and analysis of the articles. However, it is still possible that a few medications were missed, and the lists in Tables 2 and 3 may not be exhaustive. Grading the evidence and relevance of each scientific article was a major issue. Consequently, the number of medications with strong or moderate evidence of being associated with SGD and xerostomia in our lists is much smaller than in other lists [1–6, 9]. Moreover, some studies may have recorded salivary disorders only in an adverse effect table, and these would have been missed by our search. An additional issue is that our study does not include preparations containing more than one agent. However, any medication included in a mixed medication in these lists may have the potential to influence the salivary effects of the overall preparation. A further matter that warrants consideration is the possibility that certain drugs, while not exerting xerogenic effect when taken individually (and therefore not appearing in these lists), may do so as a result of drug–drug interaction if consumed together in a polypharmacy context [7, 8]. It should also be noted that, for some medications not included in this review because peer-reviewed publications on their salivary side effects were lacking, such side effects could have been mentioned on their monographs according to their manufacturer's controlled clinical trial. Finally, this article does not report the potency and frequency of salivary effects of the medications, as these data were rarely available.

Table 3 Medications reported to induce xerostomia, salivary gland hypofunction, or sialorrhea with moderate level of evidence

Drug name and function	ATC code	Mechanism and site of action	Number of citations for:				Sources per level of evidence (*n*)				Total publications (*n*)	References
			Oral 'dryness'		Sialorrhea							
			Xerostomia	SGH	Subjective	Objective	A2	B2	A3	B3		
Amisulpride (atypical anti-psychotic)	N05AL05	Antagonist to dopamine and 5-HT	1	0	0	0	1	0	0	1	2	[157, 203[a]]
Asenapine (atypical anti-psychotic)	N05AH05	Antagonist to dopamine, 5-HT, histamine (H1) and $\alpha_{(1,2)}$ adrenergic receptors	2	0	0	0	0	1	0	1	2	[115, 204]
Atenolol (anti-hypertensive/anti-arrhythmic)	C07AB03	β_1-Adrenergic antagonist	1	0	0	0	0	1	0	0	1	[205]
Azelastine (anti-allergic)	R01AC03,	Histamine (H1) antagonist	1	0	0	0	0	1	0	0	1	[206]
Cetirizine (anti-allergic)	R06AE07	Histamine (H1) antagonist	2	0	0	0	0	1	0	1	2	[206, 207]
Clobazam (anxiolytic/anti-convulsant)	N05BA09	Benzodiazepine—enhances the GABA effect on its receptors	0	0	0	1	0	1	0	0	1	[208]
Darifenacin (urological—reduces bladder activity)	G04BD10	Anti-muscarinic	5	1	0	0	1	2	0	3	6	[133–135, 137, 138, 171]
Desipramine (anti-depressant)	N06AA01	Preferential NE-reuptake inhibitor	2	0	0	0	1	1	0	0	2	[91, 209[a]]
Desloratadine (anti-allergic/anti-pruritic)	R06AX27	Histamine (H1)-antagonist, anti-muscarinic	2	0	0	0	0	1	0	1	2	[210, 211]
Desvenlafaxine (anti-depressant)	N06AX23	5-HT and NE reuptake inhibitor	5	0	0	0	0	3	0	2	5	[52, 212–215]
Dexfenfluramine (appetite suppressant)	A08AA04	Releases 5-HT	2	0	0	0	0	1	0	1	2	[216, 217]
Dexmedetomidine (hypnotic sedative)	N05CM18	α_2-Adrenergic agonist	1	0	0	0	0	1	0	0	1	[218]
Didanosine (anti-viral—HIV-1 therapy)	J05AF02	Nucleoside analog reverse transcriptase inhibitor	1	0	0	0	0	1	0	0	1	[219]
Dihydrocodeine (opioid-analgesic)	N02AA08	Weak agonist for the μ-opioid receptor	1	0	0	0	0	1	0	0	1	[220]
Dosulepin (anti-depressant)	N06AA16	Non-selective 5-HT/NE reuptake inhibitor, anti-muscarinic, anti-histamine (H1)	1	0	0	0	0	1	0	0	1	[221]
Doxepin (anti-depressant)	N06AA12	Non-selective 5-HT/NE reuptake inhibitor, anti-muscarinic, anti-histamine (H1), α_1-adrenergic receptor antagonist	2	0	0	0	0	1	0	0	1	[92]
Ebastine (anti-allergic/anti-pruritus)	R06AX22	Histamine (H1) antagonist	2	0	0	0	0	3	0	0	3	[222–224]

Table 3 continued

Drug name and function	ATC code	Mechanism and site of action	Number of citations for:				Sources per level of evidence (*n*)				Total publications (*n*)	References
			Oral 'dryness'		Sialorrhea							
			Xerostomia	SGH	Subjective	Objective	A2	B2	A3	B3		
Enalapril (anti-hypertensive)	C09AA02	ACE inhibitor	2	0	1	0	0	1	0	0	1	[205]
Eszopiclone (hypnotic-sedative)	N05CF04	Enhances the GABA effect on its receptors	3	0	0	0	0	1	0	2	3	[225–227]
Etravirine (anti-viral—HIV-1 therapy)	J05AG04	Non-nucleoside reverse transcriptase inhibitor	1	0	0	0	1	0	0	0	1	[219]
Fentanyl (opioid-analgesic)	N01AH01, N02AB03	Strong μ-opioid receptor agonist	1	0	0	0	0	1	0	0	1	[218]
Fesoterodine (urological - reduces bladder activity)	G04BD11	Anti-muscarinic	4	0	0	0	0	3	0	1	4	[181, 183, 228–230]
Haloperidol (anti-psychotic)	N05AD01	Antagonist to dopamine, 5-HT, histamine (H1), muscarinic and $\alpha_{(1,2)}$adrenergic receptors	2	0	1	0	0	2	0	0	2	[24, 119]
Hyoscyamine (anti-peristaltic/spasmolytic)	A03BA03	Anti-muscarinic	1	0	0	0	0	1	0	0	1	[231]
Isradipine (anti-hypertensive)	C08CA03	Calcium channel blocker—arterial vasodilator effects	1	0	0	0	0	1	0	0	1	[205]
Lamivudine (anti-viral—HIV, hepatitis B)	J05AF05	Nucleoside analog reverse transcriptase inhibitor	1	0	0	0	1	0	0	0	1	[219]
Levocetirizine (anti-allergic)	R06AE09	Histamine (H1) receptor antagonist	1	0	0	0	0	1	0	0	1	[232]
Lisinopril (anti-hypertensive)	C09AA03	ACE inhibitor	1	0	0	0	0	1	0	0	1	[233]
Lurasidone (anti-psychotic)	N05AE05	5-HT/dopamine antagonist, α_2-adrenerg receptor antagonist, partial 5-$HT_{(7)}$-agonist	1	0	0	0	0	1	0	0	1	[234]
Maraviroc (anti-viral)	J05AX09	Prevents HIV from entering the cells	1	0	0	0	1	0	0	0	1	[219]
Methyldopa (anti-hypertensive)	C02AB01	False transmitter; synthesis of the less potent α-methyl-NE instead of NE	2	0	1	0	0	1	0	1	2	[50, 53]
Metoprolol (anti-hypertensive/anti-arrhythmic)	C07AB02	β_1-Adrenergic receptor antagonist	1	1	0	0	0	1	1	0	2	[14, 235]
Mexiletine (anti-arrhythmic)	C01BB02	Sodium channel blocker	1	0	0	0	0	1	0	0	1	[236]
Morphine (opioid-analgesic)	N02AA01	Strong agonist on the μ-receptor	2	0	0	0	0	2	0	0	2	[237, 238]

Table 3 continued

Drug name and function	ATC code	Mechanism and site of action	Number of citations for:				Sources per level of evidence (*n*)				Total publications (*n*)	References
			Oral 'dryness'		Sialorrhea							
			Xerostomia	SGH	Subjective	Objective	A2	B2	A3	B3		
Naltrexone (treatment of alcoholism)	N07BB04	Opioid receptor antagonist	1	0	0	0	0	1	0	0	1	[239]
Nevirapine (anti-viral—HIV-1)	J05AG01	Non-nucleoside reverse transcriptase inhibitor	1	0	0	0	1	0	0	0	1	[219]
Nicotine (for smoking cessation)	N07BA01	Agonist to nicotinic receptors	2	0	0	0	0	2	0	0	2	[240, 241]
Orlistat (anti-obesity)	A08AB01	Inhibits lipase, that breaks down dietary triglycerides	1	0	0	0	0	1	0	0	1	[169]
Pregabalin (anti-convulsant by non-GABAergic mechanisms)	N03AX16	Reduces transmitter release	3	0	0	0	0	1	0	2	3	[242–244]
Raltegravir (anti-viral—HIV-1)	J05AX08	Prevents the integration of virus DNA into host chromosomes	1	0	0	0	1	0	0	0	1	[219]
Saquinavir (anti-viral)	J05AE01	HIV protease inhibitor	1	0	0	0	1	0	0	0	1	[219]
Sertindole (anti-psychotic)	N05AE03	Antagonist to dopamine, 5-HT and α_1-adrenergic receptors	2	0	0	0	0	1	0	1	2	[245, 246]
Sodium valproate (anti-convulsant)	N03AG01	Reduces the excitability of nerves by inhibiting the inflow of sodium ions	1	0	0	0	0	1	0	0	1	[114]
Tapentadol (opioid-analgesic)	N02AX06	Weak μ-opioid antagonist, and neuronal NE-reuptake inhibitor	1	0	0	0	0	1	0	0	1	[247]
Terazosin (urological—decreases urinary flow obstruction/anti-hypertensive)	G04CA03	α_1-Adrenergic receptor antagonist	1	0	0	0	0	1	0	0	1	[248]
Tizanidine (anti-muscle-spasticity)	M03BX02	Releases GABA from spinal cord inhibitory interneurons, in addition weak α_2-adrenergic agonist	2	0	0	0	2	0	0	0	2	[28, 249]
Tolvaptan (diuretic)	C03XA01	Vasopressin V2 receptor antagonist preventing the action of the anti-diuretic hormone (ADH)	1	0	0	0	0	1	0	0	1	[250]
Tramadol (opioid-analgesic)	N02AX02	Weak μ-opioid receptor agonist and NE/ 5-HT reuptake inhibitor	1	0	0	0	0	1	0	0	1	[237]
Trospium (urological—reduces bladder activity)	G04BD09	Muscarinic receptor antagonist	4	0	0	0	0	2	0	2	4	[128, 132, 133, 137]

Table 3 continued

Drug name and function	ATC code	Mechanism and site of action	Number of citations for:				Sources per level of evidence (*n*)				Total publications (*n*)	References
			Oral 'dryness'		Sialorrhea							
			Xerostomia	SGH	Subjective	Objective	A2	B2	A3	B3		
Zopiclone (hypnotic)	N05CF01	Non-benzodiazepine—enhances the GABA effect on its receptors	1	0	0	0	0	1	0	0	1	[251]

5-HT 5-hydroxytryptamine (serotonin), *ACE* angiotensin-converting enzyme, *ATC* Anatomical Therapeutic Chemical, *GABA* gamma-aminobutyric acid, *NE* norepinephrine, *SGH* salivary gland hypofunction

[a] Animal study

The study suggests that medications acting on almost all systems of the body may also cause side effects related to the salivary system. At higher levels of the classification tree, the analysis seems to yield more specific details of the medications and their modes of action leading to SGD and xerostomia. Hence, the selection of an alternate drug with a similar effect on the desired system but fewer adverse salivary effects may be attempted based on this list. However, the possibility exists that other drugs that belong to the same level, especially at the fourth level of the ATC/DDD classification, may have a similar effect on salivary glands as the drug to be replaced.

Very few studies used objective measurements of salivary flow rates in the context of a medication adverse effect [7, 8, 13, 48]. Further, few articles seem to have correlated the results of such objective measurements with the subjective feelings of the patients receiving these drugs. Though animal studies have established a reduced salivary flow rate as an effect of medications, the subjective feeling of dryness (xerostomia) obviously cannot be registered in animals; hence, the relationship between changes in salivary flow rate and subjective feelings of dryness/drooling has been ambiguous [104, 120, 138–140, 148].

It has been reported that xerostomia in healthy subjects is not experienced until the unstimulated flow rate of whole saliva has been reduced to 40–50% of normal [27]. Furthermore, whether changes in the composition of the salivary secretion can also affect the subjective feelings of the patient remains to be clarified. However, the main difficulty encountered was the rarity of studies in which salivary flow rate or composition was actually measured before and after patients were prescribed medication. Moreover, baseline data were available for virtually no patients regarding their unstimulated saliva flow rates before they require medications. It seems to be only in Sweden that dental students are taught to measure the salivary flow rates of their patients to provide baseline values for any subsequent salivary problems that may develop. We suggest this is a valuable approach that should also be introduced in other countries.

Medications were also reported to cause other oral adverse effects. Aliko et al. [274] point out that although independent reports relate a burning sensation of the oral mucosa and/or dysgeusia with MISGD, the relationship has not been established objectively. A few articles (albeit of moderate or weak level of evidence) mention that candidiasis and dental caries are associated with the use of certain drugs. None of these studies has tested the relationship between the pharmacokinetics of the drug, its effect on salivary glands, and other oral adverse effects reported [274]. Dawes et al. [272] reported that constituents of saliva have anti-fungal, anti-viral, and anti-

Table 4 Medications reported to induce xerostomia, salivary gland hypofunction, or sialorrhea with weaker level of evidence

Drug name	Number of citations for:				Sources per level of evidence (*n*)		Total publications (*n*)	References
	Oral 'dryness'		Sialorrhea					
	Xerostomia	SGH	Subjective	Objective	A3	B3		
Amiloride	0	1	0	0	1	0	1	[14]
Apraclonidine	1	0	0	0	0	1	1	[26]
Asimadoline	1	0	0	0	0	1	1	[252]
Atomoxetine	1	0	0	0	0	1	1	[253]
Biperiden	1	1	0	0	1	0	1	[14]
Chlorpheniramine	1	0	0	0	0	1	1	[254]
Chlorprothixene	0	1	0	0	1	0	1	[14]
Cisplatin	1	0	0	0	0	1	1	[255]
Clomipramine	3	0	0	0	0	3	3	[90, 95, 145]
Cyclothiazide	0	1	0	0	1	0	1	[14]
Cytisine	1	0	0	0	0	1	1	[256]
Diltiazem	0	1	0	0	1	0	1	[14]
Dimenhydrinate	2	0	0	0	0	2	2	[167, 254]
Diphenhydramine	1	0	0	0	0	1	1	[254]
Disopyramide	1	0	0	0	1	0	1	[14]
Flupirtine	1	0	0	0	0	1	1	[257]
Granisetron	1	0	0	0	0	1	1	[258]
Guanfacine	2	0	0	0	0	2	2	[53, 259]
Interleukin-2a	0	1	0	0	1	0	1	[14]
Ipratropium	1	0	0	0	0	1	1	[260]
Levomepromazine	0	1	0	0	1	0	1	[14]
Maprotiline	1	1	0	0	1	0	1	[14]
Mazindol	1	0	0	0	0	1	1	[100]
Melperone	0	1	0	0	1	0	1	[14]
Mepyramine	1	0	0	0	0	1	1	[254]
Metiamide	0	1	0	0	1	0	1	[14]
Milnacipran	3	0	0	0	0	3	3	[85, 261, 262]
Mirtazapine	2	0	0	0	0	2	2	[18, 263]
Moclobemide	1	0	0	0	0	1	1	[112]
Modafinil	2	0	0	0	0	2	2	[90, 264]
Mosapride	1	0	0	0	0	1	1	[265]
Moxifloxacin	1	0	0	0	0	1	1	[266]
Moxonidine	3	0	0	0	0	3	3	[50, 53, 267]
Nefazodone	2	0	0	0	0	2	2	[268, 269]
Oxitropium	1	0	0	0	0	1	1	[260]
Perindopril	1	0	0	0	0	1	1	[270]
Pethidine	0	1	0	0	1	0	1	[14]
Phenelzine	1	0	0	0	0	1	1	[113]
Pheniramine	0	1	0	0	0	1	1	[254]
Promazine	1	0	0	0	0	1	1	[157]
Protriptyline	2	0	0	0	0	2	2	[90, 100]
Pseudoephedrine	1	0	0	0	0	1	1	[207]
Rilmenidine	2	0	0	0	0	2	2	[53, 266]
Selegiline	1	1	0	0	1	1	2	[14, 112]
Thioridazine	2	1	0	0	1	0	1	[14]
Tianeptine	1	0	0	0	1	0	1	[271]

Table 4 continued

Drug name	Number of citations for:				Sources per level of evidence (*n*)		Total publications (*n*)	References
	Oral 'dryness'		Sialorrhea					
	Xerostomia	SGH	Subjective	Objective	A3	B3		
Triprolidine	1	0	0	0	0	1	1	[254]
Zimelidine	0	1	0	0	1	0	1	[14]

SGH salivary gland hypofunction

bacterial properties, which indicates the role of saliva in controlling the oral microbiota and correlates SGH with occurrence of oral candidiasis. The relationship between SGH, dental caries, and oral candidiasis is well known and established. However, the same has not been tested in the context of MISGD in the current literature.

The present paper may help clinicians and researchers consider whether the medications they prescribe or investigate may lead to SGD or xerostomia. A few scenarios follow:

(a) A clinician needs to evaluate which drugs from the medication list of his/her patient have potential adverse salivary effects. The clinician may take the following steps:

  (i) Search in Tables 2 and 3 for the medications by alphabetical order.
  (ii) If the medications are not found, there is probably no published evidence for a salivary adverse effect.
  (iii) If found and they wish to know more about the medication type, they can search Table 1 using the ATC code(s) found in column 2 of Tables 2 and 3. These codes are in the last column of Table 1 in alphabetical and numerical order.

(b) Before prescribing a medication, a clinician wishes to assess its potential salivary adverse effects. The above decision tree is also recommended in this situation.

(c) A treated patient complains of salivary symptoms but the clinician cannot find any of the medications in Tables 2 or Table 3. However, it is plausible that additional medications not included in these tables could also affect salivary glands if they belong to the same ATC category at any level. For example, the anti-obesity medications fenfluramine, amfepramone, mazindol, etilamfetamine, cathine, clobenzorex, mefenorex, and lorcaserin are all 'centrally acting anti-obesity products', ATC A08AA [276], and may act similarly to dexfenfluramine, which belongs to the same category and appears in Table 3. Such an association may provide an explanation for the patient's symptoms.

(d) A clinician needs to prescribe medication to a patient with Sjögren's syndrome or who has undergone radiotherapy to the head and neck area and wishes to avoid worsening the patient's xerostomia. If, for example, the required drug is a muscle relaxant, the clinician may search the ATC website [277] under 'muscle relaxants' and then double check the subgroups and Table 1. There, they will find that 'other centrally acting agents' may have salivary effects and thus choose a medication belonging to any of the other subgroups.

(e) A researcher wishes to know whether a certain type of medication has salivary effects and at what level of evidence.

  (i) The researcher may start searching Table 1 for the type of medication according to the anatomical site of action (first level), therapeutic effect (second level), chemical characteristic (fourth level), or generic name (fifth level).
  (ii) If no relevant category is found, there is probably no published evidence for adverse salivary effects of this drug type.
  (iii) If the drug type is found at any of the levels in bold text, one of the drugs at the fifth level belonging to the category may be searched for in Table 2, where the medications are in alphabetical order and information is available, i.e., type and number of publications and references.
  (iv) If the drug type is found but not in bold text, the researcher may proceed as in (iii) above but in Table 3 instead of Table 2.

5 Conclusions

Most investigators relied on the subjective opinion of the individuals or patients about whether they had too little or an excessive secretion of saliva. Thus, we conclude that further RCTs that include saliva collection are warranted for the assessment of potential salivary effects of many

medications. Unstimulated and stimulated salivary flow rates should be measured before and at intervals after starting the drug. In addition, a record of changes in the patients' subjective feelings over time should also be kept. Ideally, studies should also aim to assess changes in salivary composition, since these may also relate to SGD.

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