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.