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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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...
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:

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/hyper-salivation/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/hyper-salivation/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 ophthalmologica. 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).
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), tolvaptan (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) mucin production 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 |
|                                   |                                    | Belladonna alkaloids, semisynthetic, quaternary ammonium compounds | Hyoscyamine | A03BA03 |
|                                   |                                    | Other anti-emetics | Scopolamine/ hyoscine | A03BB01 |
| **Anti-emetics and anti-nauseants** |                                |                                |                                |          |
| **Anti-obesity preparations, excl. diet products** |                                | Centrally acting anti-obesity products | Phentermine | A08AA01 |
|                                   |                                |                                | Dexamfluramine | A08AA04 |
|                                   |                                | Peripherally acting anti-obesity products | Sibutramine | A08AA05 |
|                                   |                                |                                | Orlistat | A08AB01 |
|                                   |                                | Serotonin–noradrenaline–dopamine reuptake inhibitor | Tesofensine | ND |
| **Cardiovascular system** | Cardiac therapy | Anti-arrhythmics, class Ib | Mexiletine | C01BB02 |
|                                   | Anti-hypertensives | Methylidopa | Methylidopa | 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 |
|                                   |                                | Tropesium | 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 |
|                                   |                                | Nevirapine | J05AG01 |
|                                   |                                | Etravirine | J05AG04 |
|                                   |                                | Raltegravir | J05AX08 |
|                                   |                                | Maraviroc | J05AX09 |
| **Anti-neoplastic and immunomodulating agents** | Anti-neoplastic agents | Monoclonal antibodies | Bevacizumab | L01XC07 |
| 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  |
|                                  |                                   | Phenylpiperidine derivatives  | Dihydrocodeine                  | N02AA08  |
|                                  |                                   | Oripavine derivatives         | Fentanyl                        | N02AB03  |
|                                  |                                   | Morphinan derivatives         | Buprenorphine                   | N02AE01  |
|                                  | Other opioids                     | Other anti-migraine preparations | Clonidine                      | N02CX02  |
|                                  | Fatty acid derivatives            | Sodium valproate/valproic acid|                                |          |
| Anti-epileptics                  | 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                         |
|                                  | Diazepines, oxazepines, thiazepines, and oxepines | Loxapine          | N05AH01                         |
|                                  |                                   | Clozapine                     | N05AH02                         |
|                                  |                                   | Olanzapine                    | N05AH03                         |
|                                  |                                   | Quetiapine                    | N05AH04                         |
|                                  |                                   | Asenapine                     | N05AH05                         |
|                                  |                                   | Benzamides                    | N05AN01                         |
|                                  |                                   | Lithium                       | N05AN01                         |
|                                  |                                   | Other anti-psychotics         | Risperidone                     | N05AX08  |
|                                  |                                   | Aripiprazole                  | N05AX12                         |
|                                  |                                   | Paliperidone                  | N05AX13                         |
|                                  |                                   | Benzodiazepine derivatives (anxiolytics) | Clobazam | N05BA09  |
|                                  |                                   | Benzodiazepine-related drugs  | Zolpidem                        | N05CF02  |
|                                  |                                   | Other hypnotics and sedatives | Scopolamine/hyoscine            | N05CM05  |
|                                  |                                   |                               |                               | N05CM18  |
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 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 |
|                                   | Dexamethylphenidate                | 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 |
| Respiratory system                | Nasal preparations                | Azelastine | R01AC03 |
| Drugs for obstructive airway diseases | Anti-allergic agents, excl. corticosteroids | Tiotropium | R03BB04 |
| Anti-histamines for systemic use   | Aminoalkyl ethers                  | Doxylamine | R06AA09 |
|                                   | Piperazine derivatives              | Cetirizine | R06AE07 |
|                                   | Other anti-histamines for systemic use | Levocetirizine | R06AE09 |
|                                   |                                    | Ebastine | R06AX22 |
|                                   |                                    | Desloratadine | R06AX27 |
| Sensory organs                    | Ophthalmologials                   | Brimonidine | S01EA05 |
|                                   | Sympathomimetics in glaucoma therapy | Atropine | S01FA01 |
|                                   | Anti-cholinergics                  | Azelastine | S01GX07 |

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

* Bold type indicates higher level of evidence.
| Drug name                  | ATC code       | Mechanism and site of action                                                                 | Number of citations for | Sources per level of evidence | Total publications | References |
|---------------------------|----------------|--------------------------------------------------------------------------------------------|-------------------------|------------------------------|-------------------|------------|
|                           |                |                                                                                             | Oral 'dryness' | Sialorrhea | Xerostomia | SGH | Subjective | Objective | Al | B1 | A2 | B2 | A3 | B3 |              |
| Alendronate (anti-bone-resorptive activity) | M05BA04        | Bisphosphonate—inshibits 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 | 1 | 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 | 0 | 1 | 0 | 0 | 0 | 0 | 1 | [29] |
| Bevacizumab (antineoplastic) | L01XC07        | Monoclonal antibody; inhibits vascular proliferation and tumor growth                         | 1 | 0 | 0 | 0 | 0 | 1 | 0 | 0 | 0 | 0 | 1 | [30] |
| Brimonidine (anti-glucoma) | S01EA05        | α2-Adrenergic agonist                                                                       | 3 | 0 | 0 | 0 | 0 | 0 | 1 | 0 | 0 | 1 | 3 | [26, 31, 32] |
| Buprenorphine (opioid-analgesic) | N02AE01, N07BC01 | Mixed receptor actions; κ-opioid antagonist and partial μ-opioid antagonist                   | 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-antagonan                                           | 1 | 0 | 0 | 0 | 0 | 1 | 0 | 0 | 0 | 0 | 1 | [46] |
| Drug name                          | ATC code | Mechanism and site of action                                                                 | Number of citations for Oral ‘dryness’ Sialorrhea | Sources per level of evidence Total publications | References |
|-----------------------------------|----------|-----------------------------------------------------------------------------------------------|---------------------------------------------------|-------------------------------------------------|------------|
|                                   |          |                                                                                              | 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 0                                       | 0 1 0 0 0 0 1                                       | [47]       |
| Citalopram (anti-depressant)      | N06AB04  | Selective 5-HT reuptake inhibitor                                                              | 3 0 0 0 0 0                                       | 0 1 1 1 0 0 3                                       | [34, 48, 49]|
| Clonidine (anti-hypertensive/anti-migraine) | C02AC01, N02CX02 | $\alpha_2$-Adrenergic agonist                                                                  | 0 1 0 0 0 1                                       | 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 $\alpha_1$-adrenergic antagonist | 2 0 0 0 0 7                                       | 3 2 1 2 1 0 9                                       | [55–57a, 58–61, 62a, 63]|
| Cyclobenzaprine (skeletal muscle relaxant—centrally acting) | M03BX08  | Histamine (H1) and muscarinic antagonist                                                        | 4 0 0 0 0 0                                       | 0 3 0 0 0 0 3                                       | [64–66]    |
| Dexamylphenidate (psychostimulant—ADHD) | N06BA11  | Indirect sympathomimetic and NE/dopamine reuptake inhibitor                                    | 1 0 0 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 0                                       | 0 1 0 0 0 0 1                                       | [68]       |
| Doxylamine (hypnotic)             | R06AA09  | Anti-histamine; histamine (H1) and muscarinic antagonist                                        | 1 0 0 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                                       | 0 1 0 10 0 8 19                                     | [34, 70–87]|
| Escitalopram (anti-depressant)    | N06AB10  | Selective 5-HT reuptake inhibitor                                                              | 4 0 0 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 0                                       | 0 2 1 3 0 3 9                                       | [17, 34, 48, 90–95] |
| Drug name                          | ATC code | Mechanism and site of action                                                                 | Number of citations for Oral 'dryness' | Sialorrhea | Sources per level of evidence | Total publications (n) | References |
|-----------------------------------|----------|-----------------------------------------------------------------------------------------------|----------------------------------------|------------|-------------------------------|------------------------|------------|
| Furosemide (strong diuretic)      | C03CA01  | Inhibits NaCl reabsorption in the thick ascending loop of Henle                               | 2                                      | 3          | Subjective Objective          | 2 0 0 0 0 1 0 3     | [14, 29, 96]|
| Gabapentin (anti-convulsant)      | N03AX12  | Proposed action: stimulates GABA synthesis and GABA release                                    | 1                                      | 0          | Objective                      | 0 1 0 0 0 0 1     | [97]       |
| Imidafenacin (urological—reduces bladder activity) | ND       | Anti-muscarinic                                                                             | 1                                      | 0          | Objective                      | 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 α1-adrenergic receptors | 2                                      | 0          | Objective                      | 0 1 0 0 0 1 2     | [99, 100]  |
| Lisdexamfetamine (psychostimulant—ADHD) | N06BA12 | 5-HT/NE reuptake inhibitor                                                                   | 2                                      | 0          | Objective                      | 0 1 0 1 0 0 2     | [101, 102]|
| Lithium (anti-psychotic)          | N05AN01  | Mood stabilizer; inhibits dopamine/NE release and intracellular Ca2+ mobilization            | 2                                      | 0          | Objective                      | 0 1 0 1 1 1 4     | [103, 104–106]|
| Loxapine (anti-psychotic)         | N05AH01  | Dopamine/5-HT antagonist                                                                      | 1                                      | 0          | Objective                      | 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          | Objective                      | 0 2 0 2 0 1 5     | [37, 108–111]|
| Nortriptyline (anti-depressant)   | N06AA10  | NE reuptake inhibitor, antagonist to histamine (H1), 5-HT, α1-adrenergics, and muscarinics    | 2                                      | 0          | Objective                      | 0 1 0 0 0 1 2     | [97, 112]  |
| Drug name                        | ATC code | Mechanism and site of action                                                                 | Number of citations for Oral ‘dryness’ | Sialorrhea | Sources per level of evidence | Total publications | References |
|----------------------------------|----------|----------------------------------------------------------------------------------------------|----------------------------------------|-------------|--------------------------------|-------------------|------------|
|                                  |          |                                                                                              | Xerostomia | SGH | Subjective | Objective | A1 | B1 | A2 | B2 | A3 | B3 |          |          |
| Olanzapine (atypical anti-psychotic) | N05AH03  | Antagonist to dopamine, 5-HT, histamine, muscarinics, and α1-adrenergics                     | 10         | 0   | 0         | 1         | 0 | 4 | 1 | 5 | 0 | 1 | 11 | [20, 56, 113–120, 121] |
| Oxybutynin (urological—reduces bladder activity) | G04BD04  | Anti-muscarinic                                                                               | 20         | 3   | 0         | 0         | 0 | 7 | 0 | 10 | 0 | 4 | 21 | [122–142, 138–140] |
| Paliperidone (atypical anti-psychotic) | N05AX13  | Antagonist to dopamine, 5-HT, α(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 α1-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 (antiperistaltic/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] |
| Quetiapine (atypical anti-psychotic) | N05AH04  | Dopamine, 5-HT, α(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 Oral ‘dryness’ | Xerostomia | SGH | Subjective | Objective | Sources per level of evidence (n) | Total publications (n) | References                      |
|-------------------------------|----------------|-----------------------------------------------------------------------------------------------|--------------------------------------|------------|-----|------------|-----------|----------------------------------|------------------------|--------------------------------|
| Risperidone (anti-psychotic)  | N05AX08        | Antagonist to dopamine, serotonin, histamine (H1), and α1,2 adrenergic receptors            | 1                                    | 0          | 1   | 0          | 0         | 0 1 0 0 1 0 1 2                  | [113, 164]                  |
| Rotigotine (anti-Parkinson)   | N04BC09        | Dopamine and 5-HT agonist, α2 adrenergic antagonist                                           | 2                                    | 0          | 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         | 0 1 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 NE5-HT/dopamine                                                        | 2                                    | 0          | 0   | 0          | 0         | 0 1 0 1 0 2                  | [169, 170]                  |
| Solifenacin (urological—reduces bladder activity) | G04BD08 | Anti-muscarinic                                                                              | 9                                    | 2          | 0   | 0          | 0         | 0 2 0 5 4 0 11                | [133, 134, 137–139, 171–176] |
| Tesofensine (appetite suppressant) | ND | NE5-HT/dopamine reuptake inhibitor                                                             | 1                                    | 0          | 0   | 0          | 0         | 1 0 0 0 0 0 1                  | [177]                      |
| Timolol (anti-glaucoma)       | C07AA06        | Non-selective β-adrenergic antagonist                                                          | 1                                    | 0          | 0   | 0          | 0         | 0 1 0 0 0 0 1                  | [32]                       |
| Tiotropium (anti-asthmatic)   | R03BB04        | Prevents bronchoconstriction, anti-muscarinic                                                 | 2                                    | 0          | 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         | 0 4 1 10 1 3 19                | [124, 128, 129, 133–135, 138, 142, 180–190a, 191] |
| Venlafaxine (anti-depressant) | N06AX16        | NE5-HT reuptake inhibitor                                                                       | 8                                    | 0          | 0   | 0          | 1         | 0 1 0 7 0 0 8                  | [17, 34, 52, 89, 192–195]    |
| Veralapril (anti-hypertensive/anti-angina) | C08DA01 | Calcium channel blocker—arterial vasoconstrictor, anti-muscarinic                           | 1                                    | 0          | 0   | 0          | 0         | 0 1 0 0 0 0 1                  | [196]                      |
| Vortioxetine (anti-depressant) | N06AX26        | 5-HT reuptake inhibitor                                                                       | 2                                    | 0          | 0   | 0          | 0         | 0 1 0 1 0 0 2                  | [75, 197]                   |
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.
| 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 |
|------------------------|----------|-----------------------------|--------------------------|----------------------------------|-----------------------|------------|
|                        |          |                             | Xerostomia | Sialorrhea | 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] |
| Asenapine (atypical anti-psychotic) | N05AH05 | Antagonist to dopamine, 5-HT, histamine (H1) and α(1,2) adrenergic receptors | 2 | 0 | 0 | 0 | 0 | 1 | 0 | 1 | 2 | [115, 204] |
| Atenolol (anti-hypertensive/anti-arrhythmic) | C07AB03 | β1-Adrenergic antagonist | 1 | 0 | 0 | 0 | 0 | 1 | 0 | 0 | 1 | [205] |
| Azelastine (anti-allergic) | R01AC03, R06AE07 | Histamine (H1) antagonist | 1 | 0 | 0 | 0 | 0 | 1 | 0 | 0 | 1 | [206] |
| Cetirizine (anti-allergic) | R06AX22 | Histamine (H1) antagonist | 2 | 0 | 0 | 0 | 0 | 1 | 0 | 1 | 2 | [206, 207] |
| Clobazam (anxiolytic/anti-convulsant) | N05BA09 | Benzodiazapine—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] |
| 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) | N06AX22 | 5-HT and NE reuptake inhibitor | 5 | 0 | 0 | 0 | 0 | 3 | 0 | 2 | 5 | [52, 212–215] |
| Dexamfetamine (appetite suppressant) | A08AA04 | Releases 5-HT | 2 | 0 | 0 | 0 | 0 | 1 | 0 | 1 | 2 | [216, 217] |
| Dexametomidine (hypnotic sedative) | N05CM18 | α2-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] |
| Dolasetron (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), α1-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] |
| 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’             |                                   |                       |            |
|                        |          |                             | Xerostomia                | SGH                               | Subjective           | Objective  |
|                        |          |                             | A2                        | B2                                | A3                    | B3         |            |
|                        |          |                             | A                          | B                                 | A                      | B          |            |
| **Enalapril (anti-**   | C09AA02  | ACE inhibitor                | 2                         | 0                                 | 1                     | 0          | 1          | [205]     |
| **hypertensive**       |          |                             |                           |                                   |                       |            |            |            |
| **Eszopiclone (hypnotic-** | N05CF04 | Enhances the GABA effect on its receptors | 3                         | 0                                 | 0                     | 0          | 1          | 0          | 2          | 3          | [225–227] |
| **sedative**           |          |                             |                           |                                   |                       |            |            |            |
| **Etravirine (anti-viral—** | J05AG04 | Non-nucleoside reverse transcriptase inhibitor | 1                         | 0                                 | 0                     | 0          | 1          | 0          | 0          | 1          | [219]     |
| **HIV-1 therapy**      |          |                             |                           |                                   |                       |            |            |            |
| **Fentanyl (opioid-**   |          | Strong l-opioid receptor agonist | 1                         | 0                                 | 0                     | 0          | 0          | 0          | 1          | 1          | [218]     |
| **analgesic**          |          |                             |                           |                                   |                       |            |            |            |
| **Fesoterodine (urological—** | G04BD11 | Anti-muscarinic              | 4                         | 0                                 | 0                     | 0          | 3          | 0          | 1          | 4          | [181, 183, 228–230] |
| **reduces bladder activity** |          |                             |                           |                                   |                       |            |            |            |
| **Haloperidol (anti-**  | N05AD01  | Antagonist to dopamine, 5-HT, histamine (H1), muscarinic and σ(1,2)adrenergic receptors | 2                         | 0                                 | 1                     | 0          | 2          | 0          | 0          | 2          | [24, 119] |
| **psychotic**          |          |                             |                           |                                   |                       |            |            |            |
| **Hyoscyamine (anti-**  | A03BA03  | Anti-muscarinic              | 1                         | 0                                 | 0                     | 0          | 0          | 1          | 0          | 1          | [231]     |
| **peristaltic/pasymolytic** |        |                             |                           |                                   |                       |            |            |            |
| **Isradipine (anti-**   | C08CA03  | Calcium channel blocker—arterial vasodilator effects | 1                         | 0                                 | 0                     | 0          | 0          | 1          | 0          | 1          | [205]     |
| **hypertensive**       |          |                             |                           |                                   |                       |            |            |            |
| **Lamivudine (anti-viral—** | J05AF05 | Nucleoside analog reverse transcriptase inhibitor | 1                         | 0                                 | 0                     | 0          | 1          | 0          | 0          | 1          | [219]     |
| **HIV, hepatitis B**   |          |                             |                           |                                   |                       |            |            |            |
| **Levocetirizine (anti-** | R06AE09 | Histamine (H1) receptor antagonist | 1                         | 0                                 | 0                     | 0          | 0          | 1          | 0          | 1          | [232]     |
| **allergic**           |          |                             |                           |                                   |                       |            |            |            |
| **Lisinopril (anti-**   | C09AA03  | ACE inhibitor                | 1                         | 0                                 | 0                     | 0          | 1          | 0          | 0          | 1          | [233]     |
| **hypertensive**       |          |                             |                           |                                   |                       |            |            |            |
| **Lurasidone (anti-**   | N05AE05  | 5-HT/dopamine antagonist, σ2 adrenerg receptor antagonist, partial 5-HT(7)-agonist | 1                         | 0                                 | 0                     | 0          | 1          | 0          | 0          | 1          | [234]     |
| **psychotic**          |          |                             |                           |                                   |                       |            |            |            |
| **Maraviroc (anti-viral—** | J05AX09 | Prevents HIV from entering the cells | 1                         | 0                                 | 0                     | 0          | 1          | 0          | 0          | 1          | [219]     |
| **Methyldopa (anti-**   | C02AB01  | False transmitter; synthesis of the less potent α-methyl-NE instead of NE | 2                         | 0                                 | 1                     | 0          | 1          | 0          | 1          | 2          | [50, 53]  |
| **hypertensive**       |          |                             |                           |                                   |                       |            |            |            |
| **Metoprolol (anti-**   | C07AB02  | β1-Adrenergic receptor antagonist | 1                         | 1                                 | 0                     | 0          | 1          | 1          | 0          | 2          | [14, 235] |
| **hypertensive/anti-**  |          |                             |                           |                                   |                       |            |            |            |
| **arrhythmic**         |          |                             |                           |                                   |                       |            |            |            |
| **Mexiletine (anti-**   | C01BB02  | Sodium channel blocker      | 1                         | 0                                 | 0                     | 0          | 0          | 1          | 0          | 1          | [236]     |
| **arrhythmic**         |          |                             |                           |                                   |                       |            |            |            |
| **Morphine (opioid-analgesic)** | N02AA01 | Strong agonist on the μ-receptor | 2                         | 0                                 | 0                     | 0          | 2          | 0          | 0          | 2          | [237, 238] |
| 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’          | Xerostomia | Sialorrhea | Subjective | Objective | A2 | B2 | A3 | B3 |                        |
| Naltrexone (treatment of alcoholism) | N07BB04 | Opioid receptor antagonist | 1 | 0 | 0 | 0 | 0 | 1 | 0 | 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 | 0 | 2 | [240, 241] |
| Orlistat (anti-obesity) | A08AB01 | Inhibits lipase, that breaks down dietary triglycerides | 1 | 0 | 0 | 0 | 0 | 1 | 0 | 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 α2-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 | 0 | 1 | [114] |
| Tapentadol (opioid-analgesic) | N02AX06 | Weak µ-opioid antagonist, and neuronal NE-reuptake inhibitor | 1 | 0 | 0 | 0 | 0 | 1 | 0 | 0 | 0 | 1 | [247] |
| Terazosin (urological—decreases urinary flow obstruction/anti-hypertensive) | G04CA03 | α1-Adrenergic receptor antagonist | 1 | 0 | 0 | 0 | 0 | 1 | 0 | 0 | 0 | 1 | [248] |
| Tizanidine (anti-muscle-spasticity) | M03BX02 | Releases GABA from spinal cord inhibitory interneurons, in addition weak α2-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 | 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 | 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] |
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-

| 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’ | Xerostomia SGH Subjective | | | | | |
| Zopiclone (hypnotic) | N05CF01 | Non-benzodiazepine—enhances the GABA effect on its receptors | 1 | 0 | 0 | 0 | 0 | 1 | [25] |
| 5-HT | 5-hydroxytryptamine (serotonin), ACE angiotensin-converting enzyme, ACE Anatomical Therapeutic Chemical, GABA gamma-aminobutyric acid, NE norepinephrine, SGH salivary gland hypofunction | | | | | | |

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.

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

| Drug name                  | Oral 'dryness' | Sialorrhea | | | | | References |
|----------------------------|----------------|------------|----------|----------|----------|------------|-------------|
|                            | 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 | 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] |
| Cyclohexiazide             | 0 | 1 | 0 | 0 | 1 | 0 | 1 | [14] |
| Cytrisine                  | 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 | 0 | 1 | 0 | 1 | [14] |
| Fluoxetine                 | 1 | 0 | 0 | 0 | 0 | 1 | 1 | [14] |
| 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 | 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 | 0 | 1 | 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] |
| Nefazodine                 | 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] |
| Pseudopethidine            | 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 | 0 | 1 | 0 | 1 | [271] |
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 inves-
tigate 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, amfepra-
mone, mazindol, etilamfetamine, cathine, cloben-
zorex, mfenorex, 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 sub-
groups 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 anatom-
ical 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 saliva effects of many

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*Adis*
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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Compliance with Ethical Standards

Conflict of interest AW owns stocks in Saliwell Ltd., a company that deals with electrostimulation devices to treat xerostomia. RJK, JE, DA, AMLP, GP, NN, A Villa, YWS, AA, RM, ARK, SBJ, A Vissink, and CD have no conflicts of interest that are directly related to the content of this article.

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References

1. Smith RG, Burtner AP. Oral side-effects of the most frequently prescribed drugs. Spec Care Dentist. 1994;14:96–102.
2. Sreebny LM, Schwartz SS. A reference guide to drugs and dry mouth. Gerodontontology. 1997;14:33–7.
3. Sreebny LM. The causes of dry mouth: a broad panoply. In: Sreebny LM, Vissink A, editors. Dry mouth, the malevolent symptom: a clinical guide. Ames: Wiley-Blackwell; 2010. p. 103–22.
4. Wolff A, Stahl B. Reference guide to xerogenic drugs in Israel. J Isr Dent Assoc. 1999;16:51–76.
5. Scully C. Drug effects on salivary glands: dry mouth. Oral Dis. 2003;9:165–76.
6. Scully C, Bagan-Sebastian JV. Adverse drug reactions in the orofacial region. Crit Rev Oral Biol Med. 2004;15:221–40.
7. Smidt D, Torpet LA, Nauntofte B, Heegaard KM, Pedersen AM. Associations between oral and ocular dryness, labial and whole salivary flow rates, systemic diseases and medications in a sample of older people. Community Dent Oral Epidemiol. 2011;39:276–88.
8. Smidt D, Torpet LA, Nauntofte B, Heegaard KM, Pedersen AM. Associations between labial and whole salivary flow rates, systemic diseases and medications in a sample of older people. Community Dent Oral Epidemiol. 2010;38:422–35.
9. Nguyen CT, MacEntee MI, Mintzes B, Perry TL. Information for physicians and pharmacists about drugs that might cause dry mouth: a study of monographs and published literature. Drugs Aging. 2014;31:55–65.
10. Lynge Pedersen AM, Nauntofte B, Smidt D, Torpet LA. Oral mucosal lesions in older people: relation to salivary secretion, systemic diseases and medications. Oral Dis. 2015;21:721–9.
11. Baccaglioni I, Brennan MT, Lockhart PB, Patton LL. World Workshop on Oral Medicine IV. Process and methodology for systematic review and developing management recommendations. Reference manual for management recommendations writing committees. Oral Surg Oral Med Oral Pathol Oral Radiol Endod. 2007;103(Suppl S3):c1–19.
12. Moher D, Liberati A, Tetzlaff J, Altman DG, PRISMA Group. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. Ann Intern Med. 2009;151:264–9.
13. Eviö S, Tarkkila L, Sorsa T, Furuholm J, Välimäki MJ, Ylikorva O, et al. Effects of alendronate and hormone replacement therapy, alone and in combination, on saliva, periodontal conditions and gingival crevicular fluid matrix metalloproteinase-8 levels in women with osteoporosis. Oral Dis. 2006;12:87–93.
14. Narhi TO, Meurman JH, Ainamo A. Xerostomia and hyposalivation: causes, consequences and treatment in the elderly. Drugs Aging. 1999;15:103–16.
15. Pawar PS, Woo DA. Extrapyramidal symptoms with concomitant use of amitriptyline and amiodarone in an elderly patient. Am J Geriatr Pharmacother. 2010;8:595–8.
16. Rani PU, Naidu MU, Prasad VB, Rao TR, Shobha JC. An evaluation of antidepressants in rheumatic pain conditions. Anesth Analg. 1996;83:371–5.
17. Sauer H, Huppertz-Helmhold S, Dierkes W. Efficacy and safety of venlafaxine ER vs. amitriptyline ER in patients with major depression of moderate severity. Pharmacopsychiatry. 2003;36:169–75.
18. Montgomery SA. Safety of mirtazapine: a review. Int Clin Psychopharmacol. 1995;10(Suppl 4):37–45.
19. Nagata E. Antidepressants in migraine prophylaxis. Brain Nerve. 2009;61:1131–4.
20. Jain T, Bhandari A, Ram V, et al. Drug interactions and adverse drug reactions in hospitalized psychiatric patients: a critical element in providing safe medication use. German J Psychiatry. 2011;14:26–34.
21. Biederman J, Mick E, Spencer T, Doyle R, Hoshi G, Hamerness R, et al. An open-label trial of aripiprazole monotherapy in children and adolescents with bipolar disorder. CNS Spectr. 2007;12:683–9.
22. Montgomery SA. Safety of mirtazapine: a review. Int Clin Psychopharmacol. 1995;10(Suppl 4):37–45.
23. Tramontina S, Zeni CP, Pheula GF, Pheula GF, Narvaez J, Rohde LA. Aripiprazole in juvenile bipolar disorder comorbid with attention-deficit/hyperactivity disorder: an open clinical trial. CNS Spectr. 2007;2:758–62.
24. Veselinovic T, Schorn H, Vernaleken I, Hiemke C, Zemig M, Gur R, et al. Effects of antipsychotic treatment on psychopathology and motor symptoms. A placebo-controlled study in healthy volunteers. Psychopharmacol. 2011;218:733–48.
25. Hewer RD, Jones PM, Thomas PS, McKenzie DK. A prospective study of atropine premedication in flexible bronchoscopy. Aust N Z J Med. 2000;30:466–9.
26. Diamond JP. Systemic adverse effects of topical ophthalmic agents. Implications for older patients. Drugs Aging. 1997;11:352–60.
27. Dawes C. Physiological factors affecting salivary flow rate, oral sugar clearance, and the sensation of dry mouth in man. J Dent Res. 1987;66(Spec Iss):648–53.
28. Chou R, Peterson K, Helfand M. Comparative efficacy and safety of skeletal muscle relaxants for spasticity and musculoskeletal conditions: a systematic review. J Pain Symptom Manag. 2004;28:140–75.
29. Nederfors T, Nauntofte B, Twetman S. Effects of furomethamide and bendrofluamethiazide on saliva flow rate and composition. Arch Oral Biol. 2004;49:507–13.
30. Fang P, Hu JH, Cheng ZG, Liu ZF, Wang JL, Jiao SC. Efficacy and safety of bevacizumab for the treatment of advanced hepatocellular carcinoma: a systematic review of phase II trials. PLoS One. 2012;7:e49717.
31. Walters TR. Development and use of brimonidine in treating acute and chronic elevations of intraocular pressure: a review of safety, efficacy, dose response, and dosing studies. Surv Ophthalmol. 1996;41(Suppl 1):S19–26.
32. Schuman JS, Horwitz B, Choplin NT, David R, Albracht D, Chen K A. 1-year study of brimonidine twice daily in glaucoma and ocular hypertension. A controlled, randomized, multicenter clinical trial. Chronic Brimonidine Study Group. Arch Ophthalmol. 1997;115:847–52.
33. Gordon A, Callaghan D, Spink D, Cloutier C, Dzongowski P, O’Mahoney W. Buprenorphine transdermal system in adults with chronic low back pain: a randomized, double-blind, placebo-controlled crossover study, followed by an open-label extension phase. Clin Ther. 2010;32:844–60.
34. Cipriani A, Santilli C, Furukawa TA, Signoretti A, Nakagawa A, McGuire H, et al. Escitalopram versus other antidepressive agents for depression. Cochrane Database Syst Rev. 2009;(2):CD006532.
35. Graham J, Coghill D. Adverse drug reactions in hospital inpatients: a pilot study. CNS Drugs. 2008;22:213–37.
36. Hewett K, Chrzanowski W, Schmitz M, Milanova V, Gee M, Walters TR. Development and use of brimonidine in treating acute and chronic elevations of intraocular pressure: a review of safety, efficacy, dose response, and dosing studies. Surv Ophthalmol. 1996;41(Suppl 1):S19–26.
37. Schuman JS, Horwitz B, Choplin NT, David R, Albracht D, Chen K A. 1-year study of brimonidine twice daily in glaucoma and ocular hypertension. A controlled, randomized, multicenter clinical trial. Chronic Brimonidine Study Group. Arch Ophthalmol. 1997;115:847–52.
38. Gordon A, Callaghan D, Spink D, Cloutier C, Dzongowski P, O’Mahoney W. Buprenorphine transdermal system in adults with chronic low back pain: a randomized, double-blind, placebo-controlled crossover study, followed by an open-label extension phase. Clin Ther. 2010;32:844–60.
39. Cipriani A, Santilli C, Furukawa TA, Signoretti A, Nakagawa A, McGuire H, et al. Escitalopram versus other antidepressive agents for depression. Cochrane Database Syst Rev. 2009;(2):CD006532.
40. Semenchuk MR, Sherman S, Davis B. Double-blind, randomized trial of bupropion SR for the treatment of neuropathic pain. Ann Neurol. 2001;57:1583–8.
41. Hewett K, Chrzanowski W, Schmitz M, Milanova V, Gee M, Walters TR. Development and use of brimonidine in treating acute and chronic elevations of intraocular pressure: a review of safety, efficacy, dose response, and dosing studies. Surv Ophthalmol. 1996;41(Suppl 1):S19–26.
42. Schuman JS, Horwitz B, Choplin NT, David R, Albracht D, Chen K A. 1-year study of brimonidine twice daily in glaucoma and ocular hypertension. A controlled, randomized, multicenter clinical trial. Chronic Brimonidine Study Group. Arch Ophthalmol. 1997;115:847–52.
43. Andrews JM, Nemeroff CB. Contemporary management of depression. Am J Med. 1994;97(6A):24S–32S.
44. Muller F, Wehbe L. Smoking and smoking cessation in Latin America: a review of the current situation and available treatments. Int J COPD. 2008;3:285–93.
45. Kalman D, Herz L, Monti P, Kahler CW, Mooney M, Rodrigues S, et al. Incremental efficacy of adding bupropion to the nicotine patch for smoking cessation in smokers with a recent history of alcohol dependence: results from a randomized, double-blind, placebo-controlled study. Drug Alcohol Depend. 2011;118:111–8.
46. Wang F, Shen X, Liu Y, Xu S, Guo X. Continuous infusion of butorphanol combined with intravenous morphine patient-controlled analgesia after total abdominal hysterectomy: a randomized, double-blind controlled trial. Eur J Anaesthesiol. 2009;26:28–34.
47. Adams CE, Rathbone J, Thornley B, Clarke M, Borrill J, Wahlbeck K, et al. Chlordiazepoxide for schizophrenia: a Cochrane systematic review of 50 years of randomised controlled trials. BMC Med. 2005;3:15.
48. de Almeida Pdel V, Gregio AM, Brancher JA, de Lima AA, Azevedo LR. Effects of antidepressants and benzodiazepines on stimulated salivary flow rate and biochemistry composition of the saliva. Oral Surg Oral Med Oral Pathol Oral Radiol Endod. 2008;106:58–65.
49. Hellerstein DJ, Batchelder S, Miozzo R, Kreditor D, Hlgyer S, Gangure D. Citalopram in the treatment of dysthymic disorder. Int Clin Psychopharmacol. 2004;19:143–8.
50. Webster J, Koch HF. Aspects of tolerability of centrally acting antihypertensive drugs. J Cardiovasc Pharmacol. 1996;27(Suppl 3):S49–54.
51. Geyer O, Schmidt KG, Pianka P, Neudorfer M, Lazar M. Clonidine provides an allergy-free alternative in glaucoma patients with proven allergy to apraclonidine. Graefes Arch Clin Exp Ophthalmol. 2000;238:149–52.
52. Villaseca P. Non-estrogen conventional and phytochemical treatments for vasomotor symptoms: what needs to be known for practice? Climacteric. 2012;15:115–24.
53. van Zwieten PA. Centrally acting antihypertensives: a renaissance of interest. Mechanisms and haemodynamics. J Hypertens Suppl. 1997;15:S3–8.
54. Planitz V. Crossover comparison of moxonidine and clonidine in mild to moderate hypertension. Eur J Clin Pharmacol. 1984;27:147–52.
55. Essali A, Al-Haj Haasan N, Li C, Rathbone J. Clonazepam versus typical neuroleptic medication for schizophrenia. Cochrane Database Syst Rev. 2009;(1):CD000059.
56. Tollefson GD, Birckett MA, Kiesler GM, Wood AJ, Double-blind comparison of olanzapine versus clonazepam in schizophrenic patients clinically eligible for treatment with clonazepam. Biol Psychiatry. 2001;49:52–63.
57. Ekstrom J, Godoy T, Riva A. Clonazepam: agonistic and antagonistic salivary secretory actions. J Dent Res. 2010;89:276–80.
58. Soler Roibal MA, Oca Bravo L, Montejo Iglesias LM. The saliva and its effects on drug delivery. Oral Surg Oral Med Oral Pathol Oral Radiol Endod. 2004;238:149–52.
59. Immadisetty V, Agrawal P. A successful treatment strategy for depression in the elderly. J Clin Psychiatry. 1999;50:408–11.
60. Bennett JP Jr, Landow ER, Schuh LA. Suppression of dyskinesias by double-blind, randomized, double-blind controlled trial. Eur J Clin Pharmacol. 1984;27:147–52.
61. Essali A, Al-Haj Haasan N, Li C, Rathbone J. Clonazepam versus typical neuroleptic medication for schizophrenia. Cochrane Database Syst Rev. 2009;(1):CD000059.
diagnosis and treatment. Berlin: Springer-Verlag; 2012. p. 19–47.
62. Godoy T, Riva A, Ekström J. Clozapine-induced salivation: interaction with N-desmethylclozapine and amisulpride in an experimental rat model. Eur J Oral Sci. 2011;119:275–81.
63. Praharaj SK, Jana AK, Goswami K, Das PR, Goyal N, Sinha VK. Salivary flow rate in patients with schizophrenia on clozapine. Oral Dis. 2012;18:680–91.
64. Darwish M, Hellriegel ET. Steady-state pharmacokinetics of once-daily cyclobenzaprine extended release: a randomized, double-blind, 2-period crossover study in healthy volunteers. Clin Ther. 2011;33:746–53.
65. Moldofsky H, Harris HW, Archambault WT, Kwong T, Leiderman S. Effects of bedtime very low dose cyclobenzaprine on symptoms and sleep physiology in patients with fibromyalgia syndrome: a double-blind randomized placebo-controlled study. J Rheumatol. 2011;38:2653–63.
66. Weil AJ, Ruoff GE, Nalamachu S, Altman CA, Xie F, Taylor DR. Efficacy and tolerability of cyclobenzaprine extended release for acute muscle spasm: a pooled analysis. Postgrad Med. 2010;122:158–69.
67. Lower EE, Fleishman S, Cooper A, Zeldis J, Faleck H, Yu Z, et al. Efficacy of dexamethasone for the treatment of fatigue after cancer chemotherapy: a randomized clinical trial. J Pain Symptom Manage. 2009;38:650–62.
68. Doody RS, Gavrilova SI, Sano M, Thomas RG, Aisen PS, et al. Efficacy and tolerability of duloxetine added to oral nonsteroidal anti-inflammatory drugs for treatment of knee pain due to osteoarthritis: results of a randomized, double-blind, placebo-controlled trial. J Neuropsychiatr Clin Neurosci. 2010;22:376–82.
69. Koren G, Clark S, Hankins GDV, Caritis SN, Miodovnik M, Oelke M. Duloxetine in the treatment of stress urinary incontinence. Womens Health (Lond). 2005;1:345–58.
70. Smith HS, Bracken D, Smith JM. Pharmacotherapy for fibromyalgia. Front Pharmacol. 2011;2:17.
71. Frakes EP, Risser RC, Ball TD, Hochberg MC, Wohlgemuth MM. Duloxetine added to oral nonsteroidal anti-inflammatory drugs for treatment of knee pain in patients with osteoarthritis: a randomized, double-blind, placebo-controlled trial. J Rheumatol. 2012;39:2361–72.
72. Guerdjikova AI, McIntyre SL, Kotwal R, Welge JA, Nelson E, Lake K. High-dose escitalopram in the treatment of binge-eating disorder with obesity: a placebo-controlled monotherapy trial. Hum Psychopharmacol. 2008;23:1–11.
73. Montgomery SA, Anderssen HF. Escitalopram versus venlafaxine XR in the treatment of depression. Int Clin Psychopharmacol. 2006;21:297–309.
74. Bhat A, El Solh AA. Management of narcolepsy. Exp Opin Pharmacother. 2008;9:1721–33.
75. Atkinson JH, Slater MA, Capparelli EV, Wallace MS, Zisook S, Abramson I, et al. Efficacy of noradrenergic and serotonergic antidepressants in chronic back pain: a preliminary concentration-controlled trial. J Clin Psychopharmacol. 2007:27:135–42.
76. Baker B, Dorian P, Sandor P, Shapiro C, Schell C, Mitchell J, et al. Electrocardiographic effects of fluoxetine and doxepin in patients with major depressive disorder. J Clin Psychopharmacol. 1997;17:15–21.
77. Newhouse PA, Krishnan KRR, Doraiswamy PM, Richter EM, Batzar ED, Clary CM. A double-blind comparison of sertraline and fluoxetine in depressed elderly outpatients. J Clin Psychiatry. 2000;61:559–68.
78. Steiner M, Steinberg S, Stewart D, Carter D, Berger C, Reid R, et al. Fluoxetine in the treatment of premenstrual dysphoria. N Engl J Med. 1995;332:1529–34.
Homma Y, Yamaguchi O. A randomized, double-blind, placebo- and propiverine-controlled trial of the novel antis tu- carinic agent imidafenac in Japanese patients with overactive bladder. Int J Urol. 2009;16:499–506.

Kasper S, Moller HJ, Montgomery SA, Zondag E. Antidepressant efficacy in relation to item analysis and severity of depression: a placebo-controlled trial of fluvoxamine versus imipramine. Int Clin Psychopharmacol. 1995;9(Suppl 4):3–12.

Billiard M. Narcolepsy: current treatment options and future approaches. Neuropsych Dis Treatment. 2008;4:557–66.

Brown TE, Brams M, Gao J, Gasior M, Childress A. Open-label administration of lisdexamfetamine dimesylate improves executive function impairments and symptoms of attention-deficit/hyperactivity disorder in adults. Postgrad Med. 2010;122:7–17.

Wigal T, Brams M, Gasior M, Gao J, Gribin J. Effect size of lisdexamfetamine dimesylate in adults with attention-deficit/hyperactivity disorder. Postgrad Med. 2011;123:169–75.

Bowden CL, Grunze H, Mullen J, Brecher M, Paulsson B, Jones M, et al. A randomized, double-blind, placebo-controlled efficacy and safety study of quetiapine or lithium as monotherapy for mania in bipolar disorder. J Clin Psychiatry. 2005;66:111–21.

O’Connell AC, Bowen WH. Composition and flow rate of saliva and caries development in young rats following administration of lithium. Caries Res. 1994;28:342–7.

Donaldson SR. Sialorrhea as a side effect of lithium: a case report. Am J Psychiatry. 1982;138:1350–1.

Young AH, McElroy SL, Bauer M, Philips N, Chang W, Olausson B, et al. A double-blind, placebo-controlled of quetiapine and lithium monotherapy in adults in the acute phase of bipolar depression (EMBOLDEN 1). J Clin Psychiatry. 2010;71:150–62.

Allen MH, Feifel D, Lesem MD, Zimbroff DL, Ross R, Munzar M, et al. Efficacy and safety ofloxapine for inhalation in the treatment of agitation in patients with schizophrenia: a randomized, double-blind, placebo-controlled trial. J Clin Psychiat. 2011;72:1313–21.

Blader JC, Pliszka SR, Jensen PS, Schoeller NR, Kafantaris V. Stimulant-responsive and stimulant-refractory aggressive behavior among children with ADHD. Pediatrics. 2010;126:e796–806.

Devos D, Krystkowiak P, Clement F, Dujardin A, Cottencin O, Waucquier N, et al. Improvement of gait by chronic, high doses of methylphenidate in patients with advanced Parkinson’s disease. J Neurol Neurosurg Psychiatry. 2007;78:470–5.

Lasheen W, Walsh D, Mahmoud F, Davis MP, Rivera N, Khoshknabi DS. Methylphenidate side effects in advanced cancer: a retrospective analysis. Am J Hosp Palliat Care. 2010;27:16–23.

Biederman J, Mick E, Surman C, Doyle R, Hammerness P, Harpold T, et al. A randomized, placebo-controlled trial of OROS methylphenidate in adults with attention-deficit/hyperactivity disorder. Biol Psychiatry. 2006;59:829–35.

Volz HP, Gietler CH. Monoamine oxidase inhibitors. A perspective on their use in the elderly. Drugs Aging. 1998;13:341–55.

Johnsen E, Jorgensen HA. Effectiveness of second generation atypical antipsychotics: a systematic review of randomized trials. BMC Psychiatry. 2008;8:1–14.

Kumar A, Gupta M, Jiloha RC, Tekur U. Efficacy of olanzapine and sodium valproate given alone or as add-on therapy in acute mania. A comparative study. Methods Find Exp Clin Pharmacol. 2010;32:319–24.

McIntyre RS, Cohen M, Zhao J, Alphs L, Macek TA, Panagides J. Asenapine versus olanzapine in acute mania: a double-blind extension study. Bipolar Disord. 2009;11:815–26.

Bridle C, Palmer S, Bagnall AM, Darba J, Duffy S, Sculpter M, et al. A rapid and systematic review and economic evaluation of the clinical and cost-effectiveness of newer drugs for treatment of mania associated with bipolar affective disorder. Health Technol Assess. 2004;8:iii–iv,1–187.

Budman CL, Gayer A, Lesser M, Shi Q, Bruun RD. An open-label study of the treatment efficacy of olanzapine for Tourette’s disorder. J Clin Psychiatry. 2001;62:290–4.

Conley RR, Meltzer HY. Adverse events related to olanzapine. J Clin Psychiatry. 2000;61:6–30.

Fulton B, Goa KL. Olanzapine. A review of its properties and therapeutic efficacy in the management of schizophrenia and related psychoses. Drugs. 1997;53:281–98.

Godoy T, Riva A, Ekstrom J. Salivary secretion effects of the antipsychotic drug olanzapine in an animal model. Oral Dis. 2013;19:151–61.

Stauffer VL, Sniadecki JL, Piezer KW, Gatz J, Kollack-Walker S, Hoffmann VP, et al. Impact of race on efficacy and safety during treatment with olanzapine in schizophrenia, schizophreniform or schizoaffective disorder. BMC Psychiatry. 2010;10:89–99.

Barkin J, Corcos J, Radomski S, Jammal MP, Micelli PC, Reiz JL. A randomized, double-blind, parallel-group comparison of controlled- and immediate-release oxybutynin chloride in urge urinary incontinence. Clin Therapeutics. 2004;26:1026–36.

Aaron LE, Morris TJ, Jahshan P, Reiz JL. An evaluation of patient and physician satisfaction with controlled-release oxybutynin 15 mg as a one-step daily dose in elderly and non-elderly patients with overactive bladder: results of the STOP study. Curr Med Res Opin. 2012;28:1369–79.

Homma Y, Paick JS, Lee JG, Kawabe K. Clinical efficacy and tolerability of extended-release tolterodine and immediate-release oxybutynin in Japanese and Korean patients with an overactive bladder: a randomized, placebo-controlled trial. BJU Int. 2003;92:741–7.

Lucente VR, Staskin DR, De E. Development of oxybutynin chloride topical gel for overactive bladder. Open Access J Urol. 2011;3:35–42.

Staskin DR, Rosenberg MT, Dahl NV, Polishtuk PV, Zinner NR. Effects of oxybutynin transdermal system on health-related quality of life and safety in men with overactive bladder and prostate conditions. Int J Clin Pract. 2008;62:27–38.

Madersbacher H, Halaska M, Voigt R, Alloussi S, Höfner K. A placebo-controlled, multicentre study comparing the tolerability and efficacy of propiverine and oxybutynin in patients with urgency and urge incontinence. BJU Int. 1999;84:646–51.

Garely AD, Burrows LJ. Current pharmacotherapeutic strategies for overactive bladder. Exp Opin Pharmacother. 2002;3:827–33.

Hay-Smith J, Herbsion P, Ellis G, Moore K. Anticholinergic drugs versus placebo for overactive bladder syndrome in adults. Cochrane Database Syst Rev. 2002;(3):CD003781.

Kay GG, Staskin DR, MacDiarmid S, McIlwain M, Dahl NV. Cognitive effects of oxybutynin chloride topical gel in older healthy subjects: a 1-week, randomized, double-blind, placebo- and active-controlled study. Clin Drug Invest. 2012;32:707–14.

Lauti M, Herbison P, Hay-Smith J, Ellis G, Wilson D. Anticholinergic drugs, bladder retaing and their combination for urge urinary incontinence: a pilot randomised trial. Int Urogynecol J Pelvic Floor Dysfunct. 2008;19:1533–43.

MacDiarmid SA, Anderson RU, Armstrong RB, Dmochowski RR. Efficacy and safety of extended release oxybutynin for the treatment of urge incontinence: an analysis of data from 3 flexible dosing studies. J Urol. 2005;174(4 Pt 1):1301–5 (discussion 1305).
Guide to Medications Inducing Salivary Gland Dysfunction, Xerostomia and Subjective Sialorrhea

133. Nabi G, Cody JD, Ellis G, Herbsion P, Hay-Smith J. Anticholinergic drugs versus placebo for overactive bladder syndrome in adults. Cochrane Database Syst Rev. 2006;(4):CD003781.

134. Hashim H, Abrams P. Drug treatment of overactive bladder: efficacy, cost and quality-of-life considerations. Drugs. 2004;64:1643–56.

135. Hegde SS, Eglen RM. Muscarinic receptor subtypes modulating smooth muscle contractility in the urinary bladder. Life Sci. 1999;64:419–28.

136. Michel MC. A benefit-risk assessment of extended-release oxybutynin. Drug Saf. 2002;25:867–76.

137. Abrams P, Andersson KE. Muscarinic receptor antagonists for overactive bladder. BJU Int. 2007;100:987–1006.

138. Naruganahalli KS, Sinha S, Hegde LG, Meru AV, Chugh A, Kumar N, et al. Comparative in vivo uroselectivity profiles of anticholinergics, tested in a novel anesthetized rabbit model. Eur J Pharmacol. 2007;572:207–12.

139. Oki T, Takeuchi C, Yamada S. Comparative evaluation of exocrine muscarinic receptor binding characteristics and inhibition of salivation of solifenacin in mice. Biol Pharm Bull. 2006;29:1397–400.

140. Sakaguchi M, Goto K, Ichiki H, Hattori N, Iizuka A, Yamamoto M, et al. Effects of Byakko-ka-ninin-to on salivary secretion and bladder function in rats. J Ethnopharmacol. 2005;102:164–9.

141. Sathyan G, Chancellor MB, Gupta SK. Effect of OROS controlled-release delivery on the pharmacokinetics and pharmacodynamics of oxybutynin chloride. Br J Clin Pharmacol. 2001;52:409–17.

142. Armstrong RB, Luber KM, Peters KM. Comparison of dry mouth in women treated with extended-release formulations of oxybutynin or tolterodine for overactive bladder. Int Urol Nephrol. 2005;37:247–52.

143. Canuso CM, Turkoz I, Sheehan JJ, Bossie CA. Efficacy and safety of paliperidone extended-release in schizophrenia patients with prominent affective symptoms. J Affect Disord. 2010;120:193–9.

144. Viaet E, Nuamah IF, Lim P, Yuen EC, Palumbo JM, Hough DW, et al. A randomized, placebo- and active-controlled study of paliperidone extended release for the treatment of acute manic and mixed episodes of bipolar I disorder. Bipolar Disord. 2010;12:230–43.

145. Kodish I, Rockhill C, Varley C. Pharmacotherapy for anxiety disorders in children and adolescents. Dialogues Clin Neurosci. 2011;13:439–52.

146. Gadde KM, Allison DB, Ryan DH, Peterson CA, Truong B, Schwiers ML, et al. Effects of low-dose, controlled-release, phentermine plus topiramate combination on weight and associated comorbidities in overweight and obese adults (CONQUER): a randomised, placebo-controlled, phase 3 trial. Lancet. 2011;377:1341–52.

147. Kim KK, Cho HJ, Kang HC, Youn BB, Lee KR. Effects on weight reduction and safety of short-term phentermine administration in Korean obese people. Yonsei Med J. 2006;47:614–25.

148. Allison DB, Gadde KM, Garvey WT, Peterson CA, Schwiers ML, Najarian T, et al. Controlled-release phentermine/topiramate in severely obese adults: a randomized controlled trial (EQUIP). Obesity (Silver Spring). 2012;20:330–42.

149. Scheep JR, Braun PM, Junemann KP, Alken P. Effects of propiverine and its metabolite propiverine-N-oxide on bladder contraction and salivation in minipigs. Urol Int. 2008;81:468–73.

150. Cutler AJ, Montgomery SA, Feifel D, Lazarus A, Aström M, Brecher M. Extended release quetiapine fumarate monotherapy in major depressive disorder: a placebo- and duloxetine-controlled study. J Clin Psychiatry. 2009;70:526–39.

151. El-Khalili N, Joyce M, Atkinson S, Buynak RJ, Datto C, Lindgren P, et al. Extended-release quetiapine fumarate (quetiapine XR) as adjunctive therapy in major depressive disorder (MDD) in patients with an inadequate response to ongoing antidepressant treatment: a multicentre, randomized, double-blind, placebo-controlled study. Int J Neuropsychopharmacol. 2010;13:917–32.

152. Suppes T, Datto C, Minkwitz M, Nordenhem A, Walker C, Darko D. Effectiveness of the extended release formulation of quetiapine as monotherapy for the treatment of acute bipolar depression. J Affect Disord. 2010;121:106–15.

153. Timdahl K, Carlsson A, Stening G. An analysis of safety and tolerability data from controlled, comparative studies of quetiapine in patients with schizophrenia, focusing on extrapyramidal symptoms. Hum Psychopharmacol. 2007;22:315–25.

154. Weisler RH, Montgomery SA, Earley WR, Szamoss J, Lazarus A. Efficacy of extended release quetiapine fumarate monotherapy in patients with major depressive disorder: a pooled analysis of two 6-week, double-blind, placebo-controlled studies. Int Clin Psychopharmacol. 2012;27:27–39.

155. Findling RL, McKenna K, Earley WR, Stankowski J, Pathak S. Efficacy and safety of quetiapine in adolescents with schizophrenia investigated in a 6-week, double-blind, placebo-controlled trial. J Child Adolescent Psychopharmacol. 2012;22:327–42.

156. Merideth C, Cutler AJ, She F, Eriksson H. Efficacy and tolerability of extended release quetiapine fumarate monotherapy in the acute treatment of generalized anxiety disorder: a randomized, placebo controlled and active-controlled study. Int Clin Psychopharmacol. 2012;27:40–54.

157. Gareri P, De Fazio P, De Fazio S, Marigliano N, FERRI, Ibbadu G, De Sarro G. Adverse effects of atypical antipsychotics in the elderly: a review. Drugs Aging. 2006;23:937–56.

158. Katzman MA, Brawman-Mintzer O, Reyes EB, Olausson B, Liu S, Eriksson H. Extended release quetiapine fumarate (quetiapine XR) monotherapy as maintenance treatment for generalized anxiety disorder: a long-term, randomized, placebo-controlled trial. Int Clin Psychopharmacol. 2011;26:11–24.

159. Bauer M, Pretorius HW, Constant EL, Earley WR, Szamoss J, Brecher M. Extended-release quetiapine as adjunct to an antidepressant in patients with major depressive disorder: results of a randomized, placebo-controlled, double-blind study. J Clin Psychiatry. 2009;70:540–9.

160. Schatzberg AF. Clinical efficacy of reboxetine in major depression. J Clin Psychiatry. 2000;61(Suppl 10):31–8.

161. Versiani M, Amin M, Chouinard G. Double-blind, placebo-controlled study with reboxetine in inpatients with severe major depressive disorder. J Clin Psychopharmacol. 2000;20:28–34.

162. López-Muñoz F, Rubio G, Alamo C, García-Garcia P. Reboxetine addition in patients with mirtazapine-resistant depression: a case series. Clin Neuropharmacol. 2006;29:192–6.

163. Rahi F, Tehrani-Doost M, Shahrivar Z, Alaghband-Rad J. Efficacy of reboxetine in adults with attention-deficit/hyperactivity disorder: a randomized, placebo-controlled clinical trial. Hum Psychopharmacol. 2010;25:570–6.

164. Malone RP, Gratz SS, Delaney MA, Hyman SB. Advances in drug treatments for children and adolescents with autism and other pervasive developmental disorders. CNS Drugs. 2005;19:923–34.

165. Wu A, Wagner ML. Rotigotine transdermal system for the treatment of restless legs syndrome. Future Neurol. 2009;4:267–77.

166. Hening WA, Allen RP, Ondo WG, Walters AS, Winkelman JW, Becker P, et al. Rotigotine improves restless legs syndrome: a...
6-month randomized, double-blind, placebo-controlled trial in the United States. Mov Disord. 2010;25:1675–83.

Finlay E, Stratton JB, Gavrin JR. Nausea and vomiting: an overview of mechanisms and treatment in older patients. Geriatr Aging. 2007;10:116–21.

Khajavi D, Farokhnia M, Modabbernia A, Ashrafi M, Abbasi SH, Tabrizi M, et al. Oral scopolamine augmentation in moderate to severe major depressive disorder: a randomized, double-blind, placebo-controlled study. J Clin Psychiatry. 2012;73:1428–33.

Kaya A, Aydin N, Topsever P, Filiz M, Oztürk A, Dağar A, et al. Efficacy of soliubutamine, orlistat and combination therapy on short-term weight management in obese patients. Biomed Pharmacother. 2004;58:582–7.

Willfrey DE, Crow SJ, Mitchell JE, Berkowitz RI, James M, et al. Comparison of fesoterodine and tolterodine extended release and dutasteride in male overactive bladder patients with prostates to head placebo-controlled trial. BJU Int. 2010;105:58–66.

Finlay E, Stratton JB, Gavrin JR. Nausea and vomiting: an overview of mechanisms and treatment in older patients. Geriatr Aging. 2007;10:116–21.
200. Fava M, Asnis GM, Shrivastava RK, Lydiard B, Bastani B, Sheehan DV, et al. Improved insomnia symptoms and sleep-related next-day functioning in patients with comorbid major depressive disorder and insomnia following concomitant zolpidem extended-release 12.5 mg and escitalopram treatment: a randomized controlled trial. J Clin Psychiatry. 2011;72:914–28.

201. Joffe H, Partridge A, Giobbie-Hurder A, Li X, Habin K, Goss P, Winer E, et al. Augmentation of venlafaxine and selective serotonin reuptake inhibitors with zolpidem improves sleep and quality of life in breast cancer patients with hot flashes: a randomized, double-blind, placebo-controlled trial. Menopause. 2010;17:908–16.

202. Brunton LL. Goodman & Gilman’s the pharmacological basis of therapeutics. 12th ed. New York: McGraw-Hill Medical; 2011.

203. Godoy T, Riva A, Ekström J. Atypical antipsychotics—effects of amisulpride on salivary secretion and on clozapine-induced sialorrhea. Oral Dis. 2012;18:680–91.

204. Timpe EM, Chopra RA. Asenapine: a novel atypical antipsychotic agent for schizophrenia and bipolar I disorder. J Pharmaceut Technol. 2010;26:352–61.

205. Croog SH, Elias MS, Colton T, Baume RM, Leiblum SR, Jenkins CD. Effects of antihypertensive medications on quality of life in elderly hypertensive women. Am J Hypertens. 1994;7:329–39.

206. Henz BM, Metzenauer P, O'Keefe E, Zuberbier T. Differential composition, nutrient intake and cardiovascular risk factors. Int J Obes Relat Metab Disord. 1996;20:1033–40.

207. Wellington K, Jarvis B. Cetirizine/pseudoephedrine. Drugs. 1993;7:329–39.

208. Pollack M, Kimrys G, Krystal A, McCull W, Roth T, Schaefer K, et al. Eszopiclone coadministered with escitalopram in patients with insomnina and comorbid generalized anxiety disorder. Arch Gen Psychiatry. 2008;65:551–62.

209. Tzefos M, Dolder C, Olin JL. Fesoterodine for the treatment of overactive bladder. Ann Pharmacotherapy. 2009;43:1992–2000.

210. Storms WW. Clinical studies of the efficacy and tolerability of ebastine 10 or 20 mg once daily in the treatment of seasonal allergic rhinitis in the US. Drugs. 1996;52(Suppl 1):20–5.

211. Wilken JA, Daly AF, Sullivan CL, Kim H. Desloratadine for the relief of nasal and non-nasal allergy symptoms: an observational study. Arch Drug Inf. 2001;36:141–57.

212. Aberer W. Desloratadine for the relief of nasal and non-nasal allergy symptoms: an observational study. Arch Drug Inf. 2001;36:2–17.

213. Kornstein SG, Clayton AH, Soares CN, Padmanabhan SK, Ganguly R, Liebowitz MR, Manley AL, Padmanabhan SK, et al. Impact of CYP2C19 polymorphisms on efficacy of clofazimine treatment. Pharmacogenomics. 2008;9:527–37.

214. Pollack M, Kinrys G, Krystal A, McCall WV, Roth T, Schaefer K, et al. Eszopiclone coadministered with escitalopram in patients with insomnia and comorbid generalized anxiety disorder. Arch Gen Psychiatry. 2008;65:551–62.

215. Tourian KA, Pitrosky B, Padmanabhan SK, Rosas GR. A double-blind, multicentre study of levocetirizine for the treatment of chronic idiopathic urticaria in adults. Drugs. 1996;52(Suppl 1):30–4.

216. Kalis B. Double-blind multicentre comparative study of ebastine, terfenadine and placebo in the treatment of chronic idiopathic urticaria in adults. Drugs. 1996;52(Suppl 1):50–4.

217. Davis EC, Green CF, Mottram DR, Pirmohamed M. Adverse drug reactions in hospital in-patients: a pilot study. J Clin Pharm Ther. 2006;31:335–41.

218. Tzevos M, Dolder C, Olin JL. Fesoterodine for the treatment of overactive bladder. Ann Pharmacotherapy. 2009;43:1992–2000.

219. Fava M, Asnis GM, Shrivastava RK, Lydiard B, Bastani B, Sheehan DV, et al. Improved insomnia symptoms and sleep-related next-day functioning in patients with comorbid major depressive disorder and insomnia following concomitant zolpidem extended-release 12.5 mg and escitalopram treatment: a randomized controlled trial. J Clin Psychiatry. 2011;72:914–28.

220. Fava M, Asnis GM, Shrivastava RK, Lydiard B, Bastani B, Sheehan DV, et al. Improved insomnia symptoms and sleep-related next-day functioning in patients with comorbid major depressive disorder and insomnia following concomitant zolpidem extended-release 12.5 mg and escitalopram treatment: a randomized controlled trial. J Clin Psychiatry. 2011;72:914–28.

221. DiVizio TR, Baranowsky J, Latusch L. Dose-related effects of controlled release dihydrocodeine on oro-cecal transit and pupillary light reflex. A study in human volunteers. Arzneimittelforschung. 2001;51:60–6.

222. Kalis B. Double-blind multicentre comparative study of ebastine, terfenadine and placebo in the treatment of chronic idiopathic urticaria in adults. Drugs. 1996;52(Suppl 1):50–4.

223. Storms WW. Clinical studies of the efficacy and tolerability of ebastine 10 or 20 mg once daily in the treatment of seasonal allergic rhinitis in the US. Drugs. 1996;52(Suppl 1):20–5.

224. Palaz A. Clinical efficacy of ebastine in the treatment and prevention of seasonal allergic rhinitis. Drugs. 1996;52(Suppl 1):35–8.

225. Halas CJ. Cost-effectiveness of eszopiclone for the treatment of chronic insomnia. Expert Rev Pharmacoecon Outcomes Res. 2007;7:9–17.

226. Monti JM, Pandi-Perumal SR. Eszopiclone: its use in the treatment of insomnia. Neuropsychiatr Dis Treat. 2007;3:441–53.

227. Pollack M, Kimrys G, Krystal A, McCull W, Roth T, Schaefer K, et al. Eszopiclone coadministered with escitalopram in patients with insomnia and comorbid generalized anxiety disorder. Arch Gen Psychiatry. 2008;65:551–62.

228. Kampf GM, Marquardt J. Cetirizine in the treatment of allergic rhinitis and urticaria in Taiwanese patients. Chin J Physiol. 2010;53:199–207.

229. Kay GG, Maruff P, Scholfield D, Malhotra B, Whelan L, Darcar A. Evaluation of cognitive function in healthy older subjects treated with fesoterodine. Postgrad Med. 2012;124:7–15.

230. Yamaguichi O, Nishizawa O, Takeda M, Yoshida M, Choo MS, Gu Lee J, et al. Efficacy, safety and tolerability of fesoterodine in Asian patients with overactive bladder. Low Urin Tract Symptoms. 2011;3:43–50.

231. Bova JG, Jurdi RA, Bennett WF. Antipsammatic drugs to reduce discomfort and colonic spasm during barium enemas: comparison of oral hyoscine, i.e., glaconan, and no drug. AJR Am J Roentgenol. 1993;161:965–8.

232. Fang SY, Perng DW, Lin CL, Huangs CY. An open-label, multicentre study of levocetirizine for the treatment of symptoms. 2011;3:43–50.

233. Momo K, Homma M, Osaka Y, Inomata S, Tanaka M, Kohda Y. Effects of new-generation H1-receptor antagonists in pruritic dermatoses. Allergy. 1998;53:180–3.

234. Monti JM, Pandi-Perumal SR. Eszopiclone: Its use in the treatment of insomnia. Neuropsychiatr Dis Treat. 2007;3:441–53.

235. Aneja P, Srinivas A, Biswas AD. Comparative clinical study of fesoterodine versus other antispasmodics in adult patients with overactive bladder. Ann Pharmacother. 2009;43:1992–2000.

236. Momo K, Homma M, Osaka Y, Inomata S, Tanaka M, Kohda Y. Effects of new-generation H1-receptor antagonists in pruritic dermatoses. Allergy. 1998;53:180–3.

237. Vickers MD, Paravicini D. Comparison of tramadol with morphine for post-operative pain following abdominal surgery. Eur J Anaesthesiol. 1995;12:265–71.
257. Friedel HA, Fitton A. Flupirtine. A review of its pharmacological properties, and therapeutic efficacy in pain states. Drugs. 1993;50:493–69.

258. Moreno I, Sahade M, del Giglio A. Low-dose granisetron for prophylaxis of acute chemotherapy-induced nausea and vomiting: a pilot study. Support Care Cancer. 2005;13:850–3.

259. Vongpatanasin W, Kario K, Atlas SA, Victor RG. Central sympatholytic drugs. J Clin Hypertens (Greenwich). 2011;13:658–61.

260. Newnham DM. Asthma medications and their potential adverse effects in the elderly: recommendations for prescribing. Drug Saf. 2001;24:1065–80.

261. Ormseth MJ, Eyler AE, Hammonds CL, Boomershine CS. Milnacipran for the management of fibromyalgia syndrome. J Pain Res. 2010;3:15–24.

262. Blaya C, Seganfredo AC, Dornelles M, Torres M, Paludo A, Heldt E, et al. The efficacy of milnacipran in panic disorder: An open trial. Int Clin Psychopharmacol. 2007;22:153–8.

263. Coskun M, Ahmetoglu E, Ozturk M. Mirtazapine treatment for comorbid anxiety/depressive disorders in young subjects with attention-deficit hyperactivity disorder: case series. Klinik Psikofarmakoloji Bulteni. 2010;20:246–51.

264. Schwartz JRL. Modafinil in the treatment of excessive sleepiness. Drug Des Dev Ther. 2008;2:71–85.

265. Curran MP, Robinson DM. Mosapride in gastrointestinal disorders. Drugs. 2008;68:981–91.

266. Tulkens PM, Arvis P, Kruesemann F. Moxifloxacin safety: an analysis of 14 years of clinical data. Drugs R D. 2012;12:71–100.

267. Prichard BN, Grahm BR. II imidazoline agonists. General clinical pharmacology of imidazoline receptors: implications for the treatment of the elderly. Drugs Aging. 2000;17:133–59.

268. Ellingrod VL, Perry PJ. Nefazodone: a new antidepressant. Am J Health Syst Pharm. 1995;52:2799–812.

269. Davis R, Whittington R, Bryson HM. Nefazodone. A review of its pharmacology and clinical efficacy in the management of depression. Drug Saf. 2001;24:1065–80.

270. Mangel AW, Hicks GA. Asimadoline and its potential for the treatment of diabetes-predominant irritable bowel syndrome: a review. Clin Exp Gastroenterol. 2012;5:1–10.

271. Simpson D, Plosker GL. Atomoxetine: a review of its use in children and adolescents with attention deficit hyperactivity disorder. Drugs. 2004;64:205–22.

272. Bouwer A. Combination cold and flu medicines: an overview of their pharmacokinetics and the effects of their ingredients on the central nervous system. J Health Syst Pharm. 1995;52:2799–812.

273. Curran MP, Robinson DM. Mosapride in gastrointestinal disorders. Drugs. 2008;68:981–91.

274. Steigerwald I, Muller M, Davies A, Samper D, Sabatowski R, Baron R, et al. Effectiveness and safety of tapentadol prolonged release for severe, chronic low back pain with or without a neuropathic pain component: Results of an open-label, phase 3b study. Curr Med Res Opin. 2012;28:911–36.

275. Lee E, Lee C. Clinical comparison of selective and non-selective alpha 1A-adrenoreceptor antagonists in benign prostatic hyperplasia: studies on tamsulosin in a fixed dose and terazosin in increasing doses. Br J Urol. 1997;80:606–11.

276. Barlow SE, Pedersen AM, Villa A, Proctor GB, Ekstroem J, Lynge E, et al. World Workshop on Oral Medicine VI: clinical implications of medication-induced salivary gland dysfunction. Oral Dis. 2016;22:365–82.

277. Villa A, Wolff A, Narayana N, Dawes C, Aframian DJ, Lynege Pedersen AM, et al. World Workshop on Oral Medicine VI: a systematic review of medication-induced salivary gland dysfunction. Oral Dis. 2016;22:365–82.

278. Ali A, Wolff A, Dawes C, Aframian D, Proctor G, Ekstroem J, et al. World Workshop on Oral Medicine VI: clinical implications of medication-induced salivary gland dysfunction. Oral Surg Oral Med Oral Pathol Oral Radiol. 2015;120:185–206.

279. Villa A, Wolff A, Aframian D, Vissink A, Ekstroem J, Proctor G, et al. World Workshop on Oral Medicine VI: a systematic review of medication-induced salivary gland dysfunction: prevalence, diagnosis, and treatment. Clin Oral Investig. 2015;19:1563–80.

280. WHO Collaborating Centre for Drug Statistics Methodology. ATC/DDD Index. http://www.whocc.no/atc_ddd_index/?code=A08AA&showdescription=yes. Accessed 9 Nov 2016.

281. WHO Collaborating Centre for Drug Statistics Methodology. ATC/DDD Index 2016. http://www.whocc.no/atc_ddd_index/. Accessed 9 Nov 2016.