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Oral adverse effects

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Published in:
Oral diseases

DOI:
[10.1111/odi.13680](https://doi.org/10.1111/odi.13680)

IMPORTANT NOTE: You are advised to consult the publisher's version (publisher's PDF) if you wish to cite from it. Please check the document version below.

Document Version
Publisher's PDF, also known as Version of record

Publication date:
2021

[Link to publication in University of Groningen/UMCG research database](#)

Citation for published version (APA):

Aziz, Y., Rademacher, W. M. H., Hielema, A., Wishaw, S. B. P., van Diermen, D. E., de Lange, J., Vissink, A., & Rozema, F. R. (2021). Oral adverse effects: drug-induced tongue disorders. *Oral diseases*, 27(6), 1528-1541. <https://doi.org/10.1111/odi.13680>

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Oral adverse effects: drug-induced tongue disorders

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Abstract

Objectives: Due to a worldwide increase in drug consumption, oral healthcare professionals are frequently confronted with patients using one or more drugs. A large number of drugs can be accompanied with adverse drug reactions in the orofacial region, amongst others of the tongue. This paper aims to give an overview of drugs that are known to be accompanied with tongue disorders.

Materials and methods: The national drug information database for Dutch pharmacists, composed of scientific drug information, guidelines and summaries of product characteristics, was analysed for drug-induced tongue disorders. “MedDRA classification” and “Anatomical Therapeutic Chemical codes” were used to categorize the disorders.

Results: The database comprises of 1645 drugs of which 121 (7.4%) are documented to be accompanied with tongue disorders as an adverse effect. Drug-induced tongue disorders are predominantly observed in the following drug categories: “nervous systems,” “anti-infectives for systemic use” and “alimentary tract and metabolism”. The most common drug-induced tongue disorders are glossitis, tongue oedema, tongue discoloration and burning tongue.

Conclusion: Healthcare professionals are frequently confronted with drugs that can cause tongue disorders. The overview of drugs reported in this article supports clinicians in their awareness, diagnosis and treatment of drug-induced tongue disorders.

KEYWORDS

burning tongue, drug-induced tongue disorders, glossitis, tongue oedema, tongue discoloration

1 | INTRODUCTION

The global consumption of drugs to treat acute and chronic diseases continues to increase (WHO, 2011). Inevitably, healthcare professionals are frequently confronted with patients using one or more drugs on a daily basis. These drugs can cause several adverse effects in the oral region such as a sensation of oral dryness (xerostomia),

hyposalivation, mucositis and taste disorders (Rademacher et al., 2019). Due to the large number of drugs available and their wide range of adverse effects, it is difficult and time-consuming for healthcare professionals to take all the potential consequences into account during their daily practice. To support oral healthcare professionals in their decision making, the Journal of Oral Diseases is publishing a series of articles discussing the most frequent adverse

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effects of drugs in the oral region. The first paper discussed drug-induced taste disorders (Rademacher et al., 2019). This paper focuses on drug-induced tongue disorders.

Tongue disorders, which are rather frequently observed, can be divided into congenital and acquired tongue disorders. Aglossia, ankyloglossia, hypoglossia, macroglossia, cleft tongue and glossoptosis are examples of congenital tongue disorders (Mangold et al., 2016). Drug-induced tongue disorders belong to the category acquired tongue disorders.

Several studies have reported cases of drug-induced tongue disorders (Alharbi et al., 2018; Balaji et al., 2014; Braggio et al., 2018; Brown, 1949; Gurvits & Tan, 2014; Healy et al., 2004; Hubiche et al., 2013; Kalogirou et al., 2017), but a comprehensive overview of drugs associated with tongue disorders as an adverse effect is not available. Such an overview will support oral healthcare providers in the recognition, diagnosis and eventual treatment of drug-induced tongue disorders.

2 | MATERIALS AND METHODS

An elaborated description of the Materials and Methods used in the current study is described by Rademacher et al. (2019). In short, the data on oral adverse effects of medications were derived from the Informatorium Medicamentorum of the Royal Dutch Pharmacists Association (KNMP), the leading drug information database and reference work for pharmacists in the Netherlands (KNMP, 2019). This database is composed of scientific drug information, guidelines and summaries of product characteristics. It includes not only entries derived from scientific publications (randomized control trials, observational studies, case reports, etc.), but also data from the Netherlands pharmacovigilance centre LAREB, the Dutch knowledge centre for adverse drug reactions. The Informatorium Medicamentorum is regularly updated with the latest obtainable information from scientific publications, warnings of authorities and summaries of product characteristics of the European Medicines Agency and Medicines Evaluation Board in the Netherlands. The Informatorium Medicamentorum database was last searched on 1 August 2018. All drugs of which was reported that they may cause tongue disorders were extracted from this database. For each drug, the following information was recorded: generic name of the drug, term of the adverse effect, incidence of the adverse effect and Anatomical Therapeutic Chemical (ATC) code of the drug (WHO, 2003). The MedDRA classification was manually applied after the selection of drugs that have been linked to causing tongue disorders (MedDRA, 2018a, 2018b). This system categorizes medical terminology in five levels. The "Lowest Level Term (LLT)" and the "Preferred Term (PT)" were used to categorize drug-induced tongue disorders (Rademacher et al., 2019). The most common definitions were used to describe drug-induced tongue disorders. Microsoft® Excel (version 16.16.1) was used to create a database with acquired information on drug-induced tongue disorders. Descriptive statistics were applied where applicable.

TABLE 1 Number of medications associated with particular tongue disorders

Adverse effects of medication related to tongue	Number of medication
Burning tongue	10
Dysaesthesia of tongue	2
Glossitis	36
Hairy tongue	4
Hypertrophy of tongue papillae	1
Pruritus of tongue	1
Glossodynia	6
Tongue disorders NOS [*]	5
Coated tongue	4
Irritation of the tongue	2
Tongue oedema	22
Tongue ulceration	4
Tongue discoloration	21
Tongue numbness	3
Total	121

*NOS, not otherwise specified.

3 | RESULTS

The Informatorium Medicamentorum database comprises information on 1645 drugs with approximately 65,000 unique combinations between a drug and an adverse effect as each drug can cause multiple adverse effects. About 2335 (3.5%) of these unique combinations enclose adverse effects of medication in the orofacial region.

In total, 121 (7.4%) drugs out of the 1645 drugs have been associated with tongue disorders as adverse drug reaction (Table 1). Drug-induced tongue disorders are predominantly reported in the following drug categories: "nervous systems," "anti-infectives for systemic use" and "antineoplastic and immunomodulating agents" (Table 2). The most common drug-induced tongue disorders are

glossitis, tongue oedema, tongue discoloration and burning tongue.

A wide variety of terminology is found in the literature to describe a particular tongue disorder related to the use of a drug and vice versa. Some of these terms may even overlap each other. As it was not possible to identify the exact definitions that were used to denominate a reported adverse drug reaction by coders, we have chosen to categorize the drug-induced tongue disorders as follows:

1. Alteration in colour of the tongue (glossitis, tongue discoloration, hairy tongue, coated tongue)
2. Increase in volume of the tongue (tongue oedema, hypertrophy of tongue papillae)
3. Alteration in sensitivity of the tongue (burning tongue, dysaesthesia of tongue, pruritus of tongue, glossodynia, tongue numbness)
4. Defect of surface of the tongue (tongue ulceration)
5. Other tongue disorders (tongue irritation, tongue disorders NOS)

TABLE 2 Number of drugs associated with tongue disorders per ATC level 1 category

ATC level 1 Category	Drug-induced tongue disorders
Alimentary tract and metabolism	13
Anti-infectives for systemic use	35
Antineoplastic and immunomodulating agents	11
Antiparasitic products, insecticides and repellents	0
Blood and blood-forming organs	2
Cardiovascular system	9
Dermatologicals	6
Genitourinary system and sex hormones	1
Musculoskeletal system	2
Nervous system	26
Respiratory system	4
Sensory organs	1
Systemic hormonal preparations, excl.	1
Various	10
Total:	121

**FIGURE 1** Drug-induced median rhomboid glossitis (B. Stegenga, 2013). Reprinted with permission [Colour figure can be viewed at wileyonlinelibrary.com]

3.1 | Alteration in colour of the tongue

In total, 36 (2.2% of 1645 drugs) drugs were associated with glossitis (Figure 1) as an adverse drug reaction (Table 1). Glossitis was defined as inflammation of the tongue with loss of filiform papillae, leading to

pain, swelling and erythema (Byrd et al., 2003). It was reported in 10 of the 14 ATC level 1 categories of the ATC classification. The drug categories “anti-infectives for systemic use” (36%) and “nervous systems” (13.9%) contain most medications that have been associated with glossitis. Both categories account for almost 50% of drug-induced glossitis. Drug-induced glossitis is rather “common” in 11.1% (4 out of 36 drugs), “uncommon” in 41.7% (15 out of 36 drugs), “rare” in 30.5% (11 out of 36 drugs) and “very rare” in 11.1% (4 out of 36 drugs) of the drugs. The frequency of occurring of glossitis was not reported for methotrexate.

In the Informatorium Medicamentorum database, 21 drugs (1.28 % of 1645 drugs) were associated with the development of tongue discoloration (Figure 2) as an adverse drug reaction. Tongue discoloration was defined as pigmentation of the tongue as a result of the drug or its metabolites deposition or by increasing the production of melanin. The discoloration may be blue, brown, grey or black (Rosebush et al., 2019). Tongue discoloration was reported in 7 of the 14 ATC level 1 categories. Tongue discoloration was predominantly reported in the drug categories “anti-infectives for systemic use” (52.4%) and “dermatologicals” (19%). Frequency of drug-induced tongue discoloration was “uncommon” in 19% (4 out of 21 drugs), “rare” in 14.3% (3 out of 21 drugs), “very rare” in 47.6% (10 out of 21 drugs) and “unknown” in 19% (4 out of 21 drugs) of the drugs.

Hairy tongue is a transitory and harmless condition characterized by hypertrophy and prolongation of filiform papillae on the surface of the tongue (Figure 3). The colour of the tongue can vary from yellow to brown or black (Reamy et al., 2010). Hairy tongue as an adverse effect was reported for 4 drugs (0.24% of 1645 drugs). Two of these drugs belong to the drug category “anti-infectives for systemic use.” Coated tongue describes any area of the tongue with a coating on it. Coated tongue as an adverse effect was reported for 4 drugs (0.24% of 1645 drugs). These 4 drugs belong to the drug categories “nervous system,” “anti-infectives for systemic use,” “dermatologicals” and “alimentary tract and metabolism.” In 3 out of 4 drugs is coated tongue a “rare” adverse drug reaction. An overview of all drugs that may alter the colour of the tongue is given in Table 3.

3.2 | Increase in volume of the tongue

Tongue oedema was reported in 22 drugs (1.3% of 1645 drugs). Tongue oedema was defined as swelling of the tongue due to loss of vascular integrity causing extravasation of fluid into interstitial tissue. This adverse effect was mentioned in 9 out of 14 ATC level 1 categories. Occurrence of tongue oedema (Figure 4) was mainly reported in the drug category “nervous systems” (45.5%). Frequency of drug-induced tongue oedema was “common” in 13.6% (3 out of 22 drugs), “uncommon” in 31.8% (7 out of 22 drugs), “rare” in 31.8% (7 out of 22 drugs) and “very rare” in 22.7% (5 out of 22 drugs) of the drugs.

A rare adverse effect of Imipenem is hypertrophy of tongue papillae. Imipenem, belonging to the drug category “anti-infectives for systemic use,” is the only drug that causes this adverse drug reaction. An overview of all drugs that may cause tongue oedema and hypertrophy of tongue papillae is shown in Table 4.



FIGURE 2 Chlorhexidine-induced tongue discoloration (B. Stegenga, 2013). Reprinted with permission [Colour figure can be viewed at wileyonlinelibrary.com]



FIGURE 3 Antibiotic-induced hairy tongue [Colour figure can be viewed at wileyonlinelibrary.com]

3.3 | Alteration in sensitivity of the tongue

Burning tongue was reported in 10 drugs (0.61% of 1645 drugs) which belong to 5 ATC level 1 categories. Burning tongue was defined as a burning sensation of tongue caused by drugs without specifying the affected region explicitly (Imamura et al., 2019). The appearance of the tongue can be changed, but there is no need for an identifiable change in the appearance of the tongue. The drug category "alimentary tract and metabolism" (30%) consists of most drugs that may cause burning tongue. The frequency of burning tongue was

"common" in 30% (3 out of 10 drugs), "uncommon" in 20% (2 out of 10 drugs), "rare" in 10% (1 out of 10 drugs) and "very rare" in 30% (3 out of 10 drugs) of the drugs. The frequency of burning tongue was most frequently ("very common," 10%) reported for cabozantinib. Dysaesthesia of the tongue is an abnormal unpleasant sensation of the tongue. This adverse effect was reported for metoclopramide and oxaliplatin. These drugs belong to the following drug categories, respectively, "alimentary tract and metabolism" and "antineoplastic and immunomodulating agents." Numbness of the tongue was defined as loss of sensation in the tongue not due to peripheral nerve injury. Numbness of the tongue was reported in 3 drugs from the drug category "nervous system." The frequency of this adverse drug reaction is uncommon. Pruritus of tongue was defined as an itchy sensation of the tongue as a result of exposure to medications. It was only reported for allergen extracts and was a common side effect of sublingually administered allergen extracts. Glossodynia was described as burning sensation of the tongue due to an identifiable cause, viz., drugs. Glossodynia was reported in 6 drugs (0.36% of 1645 drugs) in the following drug categories; "anti-infectives for systemic use" (33.3%), "antineoplastic and immunomodulating agents" (33.3%), "cardiovascular system" (16.7%) and "various" (16.7%). The frequency of glossodynia was "common" in the drug categories "anti-infectives for systemic use" and "various" (3 out of 6 drugs). In the drug categories "antineoplastic and immunomodulating agents" and "cardiovascular system" was the frequency "very rare" (3 out of 6 drugs). Table 5 gives an overview of all drugs that may cause alteration in sensitivity of the tongue.

3.4 | Defect of surface of the tongue

Four drugs are reported to cause ulceration of the tongue (0.30% of 1645 drugs). These drugs belong to the following drug categories: "antineoplastic and immunomodulating agents" (1 drugs), "cardiovascular system" (1 drug) and "nervous system" (2 drugs). The frequency of tongue ulceration was "rare" in 3 out of 4 drugs (Table 6).

3.5 | Other tongue disorders

Unspecified tongue disorders were reported in 5 drugs (0.30% of 1645 drugs) in the following drug categories: "nervous system" (2 drugs), "antineoplastic and immunomodulating agents" (1 drug), "anti-infectives for systemic use" (1 drug) and "various" (1 drug). The frequency of tongue disorders NOS was "common" in 20% (1 out of 5 drugs), "uncommon" in 40% (2 out of 5 drugs) and "unknown" in 40% (2 out of 5 drugs) of these drugs. Iloprost and cholestyramine were reported to cause irritation of the tongue. They pertain to the drug category, respectively, "blood and blood-forming organs" and "cardiovascular system." An overview of all drugs that may cause irritation of the tongue and tongue disorders NOS can be found in Table 7.



TABLE 3 Alteration in colour of the tongue (glossitis, tongue discoloration, hairy tongue, coated tongue)

ATC level 1	ATC level 3	Generic name	ATC Code	LLT MedDRA*	Frequency	Specific type of administration
ALIMENTARY TRACT AND METABOLISM	STOMATOLOGICAL PREPARATIONS	Tetracycline	A01AB13	Glossitis	Very rare (<0.01%)	Not given
	INTESTINAL ANTI-INFECTIVES	Amphotericin B	A07AA07	Glossitis	Uncommon (0.1-1%)	After oral administration
	DRUGS FOR PEPTIC ULCER AND	Lansoprazole	A02BC03	Glossitis	Rare ($\geq 0.01\%$ and < 0.1%)	Not given
	OTHER ALIMENTARY TRACT AND METABOLISM PRODUCTS	Betaine	A16AA06	Glossitis	Uncommon (0.1-1%)	Not given
	STOMATOLOGICAL PREPARATIONS	Tetracycline	A01AB13	Tongue discoloration	Very rare (<0.01%)	After oral or oromucosal administration
	INTESTINAL ANTI-INFECTIVES	Miconazole	A07AC01	Tongue discoloration	Very rare (<0.01%)	Not given
	STOMATOLOGICAL PREPARATIONS	Hydrogen peroxide	A01AB02	Hairy tongue	Frequency not known	Not given
	ANTIEMETICS AND ANTINAUSEANTS	Palonosetron	A04AA05	Tongue coated	Rare ($\geq 0.01\%$ and < 0.1%)	Not given
ANTI-INFECTIVES FOR SYSTEMIC USE	BETA-LACTAM ANTIBACTERIALS, PENICILLINS	Benzylpenicillin	J01CE01	Glossitis	Uncommon (0.1-1%)	Not given
	TETRACYCLINES	Minocycline	J01AA08	Glossitis	Rare ($\geq 0.01\%$ and < 0.1%)	Not given
	AMINOGLYCOSIDE ANTIBACTERIALS	Tobramycin	J01GB01	Glossitis	Uncommon (0.1-1%)	Inhalation liquid
	OTHER BETA-LACTAM ANTIBACTERIALS	Ceftriaxone	J01DD04	Glossitis	Very rare (<0.01%)	Not given
	MACROLIDES, LINCOSAMIDES AND STREPTOGRAMINS	Clarithromycin	J01FA09	Glossitis	Uncommon (0.1-1%)	Not given
	OTHER ANTIBACTERIALS	Linezolid	J01XX08	Glossitis	Uncommon (0.1-1%)	Not given
	ANTIMYCOTICS FOR SYSTEMIC USE	Voriconazole	J02AC03	Glossitis	Uncommon (0.1-1%)	Not given
	OTHER ANTIBACTERIALS	Daptomycin	J01XX09	Glossitis	Uncommon (0.1-1%)	Not given
	DIRECT ACTING ANTIVIRALS	Raltegravir	J05AX08	Glossitis	Uncommon (0.1-1%)	Not given
	TETRACYCLINES	Doxycycline	J01AA02	Glossitis	Uncommon (0.1-1%)	Not given
	ANTIVIRALS	Trifluridine	S01AD02	Glossitis	Uncommon (0.1-1%)	In combination with tipiracil
	CARBAPENEMS	Imipenem and ciliastatin	J01DH51	Glossitis	Rare ($\geq 0.01\%$ and < 0.1%)	Not given

(Continues)



TABLE 3 (Continued)

ATC level 1	ATC level 3	Generic name	ATC Code	LLT MedDRA*	Frequency	Specific type of administration
BETA-LACTAM ANTIBACTERIALS, PENICILLINS		Pheneticillin	J01CE05	Tongue discoloration	Very rare (<0.01%)	Not given
TETRACYCLINES		Demeclocycline	J01AA01	Tongue discoloration	Frequency not known	Not given
TETRACYCLINES		Minocycline	J01AA08	Tongue discoloration	Rare ($\geq 0.01\%$ and < 0.1%)	Not given
BETA-LACTAM ANTIBACTERIALS, PENICILLINS		Amoxicillin	J01CA04	Tongue discoloration	Uncommon (0.1-1%)	Not given
DIRECT ACTING ANTIVIRALS		Ribavirin	J05AP01	Tongue discoloration	Very rare (<0.01%)	Not given
MACROLIDES, LINCOSAMIDES AND STREPTOGRAMINS		Clarithromycin	J01FA09	Tongue discoloration	Very rare (<0.01%)	After intravenous administration
MACROLIDES, LINCOSAMIDES AND STREPTOGRAMINS		Azithromycin	J01FA10	Tongue discoloration	Very rare (<0.01%)	Not given
OTHER ANTIBACTERIALS		Linezolid	J01XX08	Tongue discoloration	Uncommon (0.1-1%)	Not given
TETRACYCLINES		Doxycycline	J01AA02	Tongue discoloration	Very rare (<0.01%)	Not given
CARBAPENEMS		Imipenem and cilaastatin	J01DH51	Tongue discoloration	Rare ($\geq 0.01\%$ and < 0.1%)	Not given
SULPHONAMIDES AND TRIMETHOPRIM		Sulphamethoxazole and trimethoprim	J01EE01	Tongue discoloration	Frequency not known	Not given
DIRECT ACTING ANTIVIRALS		Darunavir	J05AE10	Tongue coated	Rare ($\geq 0.01\%$ and < 0.1%)	Not given
COMBINATION OF ANTIBACTERIALS		Combination of antibacterials	J01RA	Hairy tongue	Very rare (<0.01%)	In combination with amoxicillin
SULPHONAMIDES AND TRIMETHOPRIM		Sulphamethoxazole and trimethoprim	J01EE01	Hairy tongue	Frequency not known	Not given
ANTINEOPLASTIC IMMUNOMODULATING AND AGENTS		Peginterferon alfa-2a	L03AB11	Glossitis	Common (1-10%)	Not given
IMMUNOSTIMULANTS		Peginterferon alfa-2b	L03AB10	Glossitis	Common (1-10%)	Not given
OTHER ANTINEOPLASTIC AGENTS		Tivozanib	L01XE34	Glossitis	Common (1-10%)	Not given
ANTIMETABOLITES		Methotrexate	L01BA01	Glossitis	Frequency not known	Not given
IMMUNOSTIMULANTS		Peginterferon alfa-2b	L03AB10	Tongue discoloration	Rare ($\geq 0.01\%$ and < 0.1%)	Not given
CARDIOVASCULAR SYSTEM		Captopril	C09AA01	Glossitis	Rare ($\geq 0.01\%$ and < 0.1%)	Not given

(Continues)



TABLE 3 (Continued)

ATC level 1	ATC level 3	Generic name	ATC Code	LLT MedDRA*	Frequency	Specific type of administration
DERMATOLOGICALS	ACE INHIBITORS, PLAIN	Enalapril	C09AA02	Glossitis	Rare ($\geq 0.01\%$ and $< 0.1\%$)	Not given
	ACE INHIBITORS, PLAIN	Ramipril	C09AA05	Glossitis	Rare ($\geq 0.01\%$ and $< 0.1\%$)	Not given
	ACE INHIBITORS, PLAIN	Quinapril	C09AA06	Glossitis	Rare ($\geq 0.01\%$ and $< 0.1\%$)	Not given
DERMATOLOGICALS	ANTIADRENERGIC AGENTS, CENTRALLY ACTING	Methylidopa (levorotatory)	C02AB01	Tongue discoloration	Very rare ($< 0.01\%$)	Not given
	ANTIFUNGALS FOR TOPICAL USE	Ketoconazole	D01AC08	Tongue discoloration	Frequency not known	Not given
DERMATOLOGICALS	CHEMOTHERAPEUTICS FOR TOPICAL USE	Metronidazole	D06BX01	Tongue discoloration	Frequency not known	After cutaneous use
	CHEMOTHERAPEUTICS FOR TOPICAL USE	Metronidazole	D06BX01	Tongue discoloration	Very rare ($< 0.01\%$)	Not given
	PROTECTIVES AGAINST UV-RADIATION	Afamelanotide	D02BB02	Tongue discoloration	Uncommon (0.1-1%)	Not given
DERMATOLOGICALS	CHEMOTHERAPEUTICS FOR TOPICAL USE	Metronidazole	D06BX01	Tongue coated	Frequency not known	Not given
	CHEMOTHERAPEUTICS FOR TOPICAL USE	Metronidazole	D06BX01	Hairy tongue	Frequency not known	Not given
GENITOURINARY SYSTEM AND SEX HORMONES	OTHER GYNAECOLOGICALS	Fenoterol	G02CA03	Glossitis	Rare ($\geq 0.01\%$ and $< 0.1\%$)	In combination with ipratropium
MUSCULOSKELETAL SYSTEM	ANTI-INFLAMMATORY AND ANTIRHEUMATIC PRODUCTS, NON-STERIODS	Diclofenac	M01AB05	Glossitis	Rare ($\geq 0.01\%$ and $< 0.1\%$)	After systemic use
	DRUGS AFFECTING BONE STRUCTURE AND MINERALIZATION	Risedronic acid	M05BA07	Glossitis	Rare ($\geq 0.01\%$ and $< 0.1\%$)	Not given
NERVOUS SYSTEM	ANTIPILEPTICS	Carbamazepine	N03AF01	Glossitis	Rare ($\geq 0.01\%$ and $< 0.1\%$)	Not given
	ANTIDEPRESSANTS	Sertraline	N06AB06	Glossitis	Uncommon (0.1-1%)	Not given
	ANTIMIGRAINE PREPARATIONS	Eletriptan	N02CC06	Glossitis	Uncommon (0.1-1%)	Not given
PSYCHOSTIMULANTS, AGENTS USED FOR ADHD AND NOOTROPICS	PSYCHOSTIMULANTS, AGENTS USED FOR ADHD AND NOOTROPICS	Modafinil	N06BA07	Glossitis	Uncommon (0.1-1%)	Not given
	ANAESTHETICS, LOCAL	Mepivacaine	N01BB03	Glossitis	Very rare ($< 0.01\%$)	Not given
ANTIDEPRESSANTS	ANTIDEPRESSANTS	Amitriptyline	N06AA09	Tongue discoloration	Very rare ($< 0.01\%$)	Not given
	DRUGS USED IN ADDICTIVE DISORDERS	Varenicline	N07BA03	Tongue coated	Rare ($\geq 0.01\%$ and $< 0.1\%$)	Not given

(Continues)

TABLE 3 (Continued)

ATC level 1	ATC level 3	Generic name	ATC Code	LLT MedDRA*	Frequency	Specific type of administration
RESPIRATORY SYSTEM	OTHER DRUGS FOR OBSTRUCTIVE AIRWAY DISEASES, INHALANTS	Tiotropium bromide	R03BB04	Glossitis	Rare ($\geq 0.01\%$ and $< 0.1\%$)	Not given
SENSORY ORGANS	OPHTHALMOLOGICALS	Betaxolol	S01ED02	Glossitis	Very rare ($< 0.01\%$)	Not given
VARIOUS	ALLERGENS	Allergen extracts	V01AA	Glossitis	Common (1-10%)	After sublingual administration
			V01AA02			
	ALL OTHER THERAPEUTIC PRODUCTS	Sucroferric oxyhydroxide	V03AE05	Tongue discoloration	Uncommon (0.1-1%)	After oral or oromucosal administration

Definitions:

*Glossitis was defined as inflammation of the tongue with loss of filiform papillae, leading to pain, swelling and erythema.

*Tongue discoloration was defined as pigmentation of the tongue as a result of the drug or its metabolite deposition or by increasing the production of melanin.

*Hairy tongue is a transitory and harmless condition characterized by hypertrophy and prolongation of filiform papillae on the surface of the tongue.

*Coated tongue describes any area of the tongue with a coating on it.



FIGURE 4 ACE inhibitor-induced tongue oedema [Colour figure can be viewed at wileyonlinelibrary.com]

4 | DISCUSSION

Drug-induced tongue disorders were reported in 7.4% (121/1645) of the drugs used in the Netherlands. It was reported in all ATC level 1 drug categories except the drug category “antiparasitic products, insecticides and repellents.” We assume that many oral health-care providers are confronted with patients that suffer from drug-induced tongue disorders. Patients using drug from the categories “anti-infectives for systemic use” and “nervous system” are more likely to endure drug-induced tongue disorders.

As far as we know, this is the first article that gives a compendious overview of drug-induced tongue disorders. Most of the articles on this topic are case reports on one particular drug and adverse drug reaction. Till date, there is no study performed that gives a complete overview of drugs that cause tongue disorders. An important note is that the adverse effects reported in our study are not just derived from randomized controlled trials, which bears the hazard of underreporting, but from a mixture of clinical studies and case reports. Furthermore, the data on adverse effects are also extracted from scientific drug information, guidelines and summaries of product characteristics as well as that our study contains entries from LAREB. As the information on adverse drug effects originates from different sources, the hazard of underreporting and inaccurate reporting is minimized in this study.

The drug-induced tongue disorders reported in the literature are often not well-defined or a wide range of terminology is used to describe a particular disorder and vice versa. For example, the term glossitis indicates a variety of tongue diseases. Depending upon the underlying cause and symptoms, it can refer to atrophic glossitis or median rhomboid glossitis or benign migratory glossitis or herpetic geometric glossitis, etc. Moreover, tongue conditions like candidiasis or tongue soreness caused by burning mouth syndrome can easily be labelled as glossitis due to their broadly similar clinical presentation and symptoms. As it is not possible to identify the exact definitions of the reported adverse drug reactions, we opted to describe tongue



TABLE 4 Increase in volume of the tongue (tongue oedema, hypertrophy of tongue papillae)

ATC level 1	ATC level 3	Generic name	ATC Code	LLT MedDRA*	Frequency	Specific type of administration
ALIMENTARY TRACT AND METABOLISM	OTHER ALIMENTARY TRACT AND METABOLISM PRODUCTS	Idursulfase	A16AB09	Tongue oedema	Common (1-10%)	Not given
ANTI-INFECTIVES FOR SYSTEMIC USE	OTHER BETA-LACTAM ANTIBIOTICS	Cefazolin	J01DB04	Tongue oedema	Rare ($\geq 0.01\%$ and $< 0.1\%$)	Not given
	ANTIMYCOTICS FOR SYSTEMIC USE	Voriconazole	J02AC03	Tongue oedema	Uncommon (0.1-1%)	Not given
	ANTIMYCOTICS FOR SYSTEMIC USE	Posaconazole	J02AC04	Tongue oedema	Rare ($\geq 0.01\%$ and $< 0.1\%$)	Not given
	CARBAPENEMS	Imipenem and cilastatin	J01DH51	Hypertrophy of tongue papillae	Rare ($\geq 0.01\%$ and $< 0.1\%$)	Not given
ANTINEOPLASTIC AND IMMUNOMODULATING AGENTS	HORMONE ANTAGONISTS AND RELATED AGENTS	Enzalutamide	L02BB04	Tongue oedema	Very rare ($< 0.01\%$)	Not given
BLOOD AND BLOOD-FORMING ORGANS	VITAMIN K AND OTHER HAEMOSTATICS	Eltrombopag	B02BX05	Tongue oedema	Common (1-10%)	In case of patients with immune thrombocytopenic purpura or aplastic anaemia
CARDIOVASCULAR SYSTEM	ACE INHIBITORS, PLAIN	Fosinopril	C09AA09	Tongue oedema	Very rare ($< 0.01\%$)	Not given
NERVOUS SYSTEM	ANTIDEPRESSANTS	Amitriptyline	N06AA09	Tongue oedema	Uncommon (0.1-1%)	Not given
	ANTIDEPRESSANTS	Doxepin	N06AA12	Tongue oedema	Rare ($\geq 0.01\%$ and $< 0.1\%$)	Not given
	ANTIDEPRESSANTS	Nortriptyline	N06AA10	Tongue oedema	Uncommon (0.1-1%)	Not given
	HYPNOTICS AND SEDATIVES	Melatonin	N05CH01	Tongue oedema	Very rare ($< 0.01\%$)	Not given
	ANTIMIGRAINE PREPARATIONS	Rizatriptan	N02CC04	Tongue oedema	Uncommon (0.1-1%)	Not given
	ANTIPILEPTICS	Pregabalin	N03AX16	Tongue oedema	Rare ($\geq 0.01\%$ and $< 0.1\%$)	Not given
	DOPAMINERGIC AGENTS	Rotigotine	N04BC09	Tongue oedema	Uncommon (0.1-1%)	In case of Parkinson's disease
	DOPAMINERGIC AGENTS	Rotigotine	N04BC09	Tongue oedema	Common (1-10%)	For restless legs
	ANTIPSYCHOTICS	Paliperidone	N05AX13	Tongue oedema	Uncommon (0.1-1%)	Not given
	ANAESTHETICS, LOCAL	Mepivacaine	N01BB03	Tongue oedema	Rare ($\geq 0.01\%$ and $< 0.1\%$)	Not given
RESPIRATORY SYSTEM	ADRENERGICS, INHALANTS	Indacaterol	R03AC18	Tongue oedema	Uncommon (0.1-1%)	Not given
SYSTEMIC HORMONAL PREPARATIONS, EXCL.	ANTIPTHYROID AGENTS	Calcitonin (salmon synthetic)	H05BA01	Tongue oedema	Rare ($\geq 0.01\%$ and $< 0.1\%$)	Not given
VARIOUS	MAGNETIC RESONANCE IMAGING CONTRAST MEDIA	Gadoteridol	V08CA04	Tongue oedema	Rare ($\geq 0.01\%$ and $< 0.1\%$)	Not given
	ALL OTHER THERAPEUTIC PRODUCTS	Palifermin	V03AF08	Tongue oedema	Very rare ($< 0.01\%$)	Not given
	ALLERGENS	Allergen extracts	V01AAV01AA02	Tongue oedema	Very rare ($< 0.01\%$)	After subcutaneous administration

*Definition: swelling of the tongue due to loss of vascular integrity causing extravasation of fluid into interstitial tissue.

TABLE 5 Alteration in sensitivity of the tongue (burning tongue, dysaesthesia of tongue, pruritus of tongue, glossodynia, tongue numbness)

ATC level 1	ATC level 3	Generic name	ATC Code	LLT MedDRA*	Frequency	Specific type of administration
ALIMENTARY TRACT AND METABOLISM	INTESTINAL ANTI-INFECTIVES	Colistin	A07AA10	Burning tongue	Very rare (<0.01%)	After inhalation
	ANTIPROPULSIVES	Loperamide	A07DA03	Burning tongue	Rare ($\geq 0.01\%$ and < 0.1%)	Not given
	STOMATOLOGICAL PREPARATIONS	Chlorhexidine	A01AB03	Burning tongue	Very rare (<0.01%)	Not given
	PROPULSIVES	Metoclopramide	A03FA01	Dysaesthesia of tongue	Frequency not known	Not given
ANTI-INFECTIVES FOR SYSTEMIC USE	BETA-LACTAM ANTIBACTERIALS, PENICILLINS	Pheneticillin	J01CE05	Glossodynia	Very rare (<0.01%)	Not given
	SULPHONAMIDES AND TRIMETHOPRIM	Trimethoprim	J01EA01	Glossodynia	Very rare (<0.01%)	Not given
ANTINEOPLASTIC AND IMMUNOMODULATING AGENTS	OTHER ANTINEOPLASTIC AGENTS	Cabozantinib	L01XE26	Burning tongue	Very common ($\geq 10\%$)	Not given
	OTHER ANTINEOPLASTIC AGENTS	Oxaliplatin	L01XA03	Dysaesthesia of tongue	Frequency not known	Not given
	OTHER ANTINEOPLASTIC AGENTS	Sorafenib	L01XE05	Glossodynia	Common (1-10%)	Not given
	OTHER ANTINEOPLASTIC AGENTS	Sunitinib	L01XE04	Glossodynia	Common (1-10%)	Not given
CARDIOVASCULAR SYSTEM	ANTIADRENERGIC AGENTS, CENTRALLY ACTING	Methyldopa (levorotatory)	C02AB01	Glossodynia	Very rare (<0.01%)	Not given
NERVOUS SYSTEM	ANTIMIGRAINE PREPARATIONS	Sumatriptan	N02CC01	Burning tongue	Common (1-10%)	Not given
	ANTIEPILEPTICS	Topiramate	N03AX11	Burning tongue	Uncommon (0.1-1%)	Not given
	ANAESTHETICS, LOCAL	Ropivacaine	N01BB09	Numbness of tongue	Uncommon (0.1-1%)	Not given
	ANAESTHETICS, LOCAL	Bupivacaine	N01BB01	Numbness of tongue	Uncommon (0.1-1%)	Not given
	ANAESTHETICS, LOCAL	Prilocaine	N01BB04	Numbness of tongue	Uncommon (0.1-1%)	Not given
RESPIRATORY SYSTEM	ADRENERGICS, INHALANTS	Salbutamol	R03AC02	Burning tongue	Common (1-10%)	After inhalation
	THROAT PREPARATIONS	Flurbiprofen	M01AE09	Burning tongue	Uncommon (0.1-1%)	Not given
VARIOUS	ALLERGENS	Allergen extracts	V01AAV01AA02	Burning tongue	Very rare (<0.01%)	After subcutaneous administration

(Continues)



TABLE 5 (Continued)

ATC level 1	ATC level 3	Generic name	ATC Code	LLT MedDRA*	Frequency	Specific type of administration
ALLERGENS	ALLERGENS	Allergen extracts	V01AAV01AA02	Burning tongue	Common (1-10%)	After sublingual administration
ALLERGENS	ALLERGENS	Allergen extracts	V01AA	Tongue pruritus	Common (1-10%)	After sublingual administration
ALLERGENS	ALLERGENS	Allergen extracts	V01AA	Glossodynia	Common (1-10%)	After sublingual administration

Definitions:

*Burning sensation of tongue caused by drugs.

*Dysaesthesia of the tongue is an abnormal unpleasant sensation of the tongue.

*Pruritus of tongue is as an itchy sensation of the tongue.

*Glossodynia is a burning sensation of the tongue.

*Numbness of the tongue is a loss of sensation in the tongue.

TABLE 6 Defect of surface of the tongue (tongue ulceration)

ATC level 1	ATC level 3	Generic name	ATC Code	LLT MedDRA*	Frequency	Specific type of administration
ANTINEOPLASTIC IMMUNOMODULATING AND AGENTS	IMMUNOSUPPRESSANTS	alemtuzumab	L04AA34	Tongue ulceration	Frequency not known	In case of patients with B-cell chronic lymphocytic leukaemia
CARDIOVASCULAR SYSTEM	VASODILATORS USED IN CARDIAC DISEASES	Nicorandil	C01DX16	Tongue ulceration	Rare ($\geq 0.01\%$ and $< 0.1\%$)	Not given
NERVOUS SYSTEM	HYPNOTICS AND SEDATIVES	Melatonin	N05CH01	Tongue ulceration	Rare ($\geq 0.01\%$ and $< 0.1\%$)	Not given
	ANTIDEPRESSANTS	Sertraline	N06AB06	Tongue ulceration	Rare ($\geq 0.01\%$ and $< 0.1\%$)	Not given

TABLE 7 Other tongue disorders (tongue irritation, tongue disorders NOS)

ATC level 1	ATC level 3	Generic name	ATC Code	LLT MedDRA*	Frequency	Specific type of administration
ANTI-INFECTIVES FOR SYSTEMIC USE	SULPHONAMIDES AND TRIMETHOPRIM	Sulphamethoxazole and trimethoprim	J01EE01	Tongue disorder NOS	Frequency not known	Not given
ANTINEOPLASTIC AND IMMUNOMODULATING AGENTS	HORMONES AND RELATED AGENTS	Leuprorelin	L02AE02	Tongue disorder NOS	Common (1-10%)	Not given
BLOOD AND BLOOD-FORMING ORGANS	ANTITHROMBOTIC AGENTS	Iloprost	B01AC11	Tongue irritation	Common (1-10%)	After inhalation
CARDIOVASCULAR SYSTEM	LIPID MODIFYING AGENTS, PLAIN	Cholestyramine	C10AC01	Tongue irritation	Very rare (<0.01%)	Not given
NERVOUS SYSTEM	ANTIDEPRESSANTS	Imipramine	N06AA02	Tongue disorder NOS	Frequency not known	Not given
VARIOUS	ANTIDEPRESSANTS	Sertraline	N06AB06	Tongue disorder NOS	Uncommon (0.1-1%)	Not given
	ALLERGENS	Allergen extracts	V01AA	Tongue disorder NOS	Uncommon (0.1-1%)	After sublingual administration

*Tongue disorder NOS: tongue disorder not otherwise specified.

disorders using the most common definitions. Furthermore, to assure data uniformity we standardized the data by using the ATC and MedDRA classification. The use of ATC and MedDRA classification makes our data internationally applicable. As mentioned in the first article of this series, it is recommended to use MedDRA classification for homogenous data collection. We assume that it will improve recording of adverse drug reactions in the future. As discussed in the first article, there will be drugs that are not mentioned in this paper due to difference in local law and regulations on drug per country. But most of the drugs mentioned in this study are available in European countries.

In the recent years, several studies have reported cases of drug-induced tongue disorders. Drugs like angiotensin-converting enzyme (ACE) inhibitors (Leung et al., 2012; Stallone et al., 2004), non-steroidal anti-inflammatory drugs (NSAIDs) aspirin and certain antibiotics are reported to cause angioedema of the lips, tongue and face. About 25%-40% of angioedema in orofacial region are induced by ACE inhibitors. Perindopril is one of the ACE inhibitors that is often associated with angioedema of the lips and tongue. The underlying mechanism for ACE inhibitor-induced angioedema is the enzymatic inhibition of bradykinin degradation (Alharbi et al., 2018). Early recognition of drug-induced tongue oedema is important as it can be a life-threatening condition. In this study, tongue oedema was reported in 22 drugs, mainly in the drug category "nervous systems" (45.5%). Fosinopril was the only ACE inhibitor that was reported to cause tongue oedema. Contrary to expectations, the frequency of fosinopril-induced tongue oedema was very rare (<0.01%). This discrepancy could be explained by the fact that other studies report on all cases of ACE inhibitor-induced angioedema in the orofacial region. They do not subdivide the orofacial angioedema into different categories. In this study, however, the focus lied solely on the tongue oedema.

Drugs such as tetracycline, penicillins, anticholinergics and linezolid are reported to cause black hairy tongue (Balaji et al., 2014; Braggio et al., 2018; Gurvits & Tan, 2014; Reamy et al., 2010). Beside the colour black, hairy tongue can also be yellow, green, blue, brown or even colourless. Generally, no treatment is necessary for this condition as it is predominantly asymptomatic. The pathophysiology of drug-induced black hairy tongue is still unknown. In this study, hairy tongue as an adverse effect was reported for 4 drugs: metronidazole, hydrogen peroxide, antibiotics in combination with amoxicillin and sulphamethoxazole and trimethoprim. On the other hand, 21 drugs were associated with the development of tongue discoloration as an adverse drug reaction. As expected, most of the drugs were antibiotics. The difference is likely due to categorizing the tongue disorders by using the MedDRA classification and ATC codes. In order to collect homogenous data on adverse drug reactions, MedDRA classification is recommended to be used.

The occurrence of severe glossitis after administration of sulphanilamide and sulphathiazole has been reported in the literature. The underlying mechanism for glossitis in those cases was avitaminoses without apparent cause (Brown, 1949). In the

present study, glossitis was one of the most frequent adverse effects of drugs. The drug categories “anti-infectives for systemic use” and “nervous systems” contained most of the medications that can induce glossitis. Nonetheless, both medications are not mentioned in the drug category “anti-infectives for systemic use.” The reason could be difference in local law and regulations on drug per country. Both antibiotics are not registered in the “farmacotherapeutisch Kompas.” Farmacotherapeutisch Kompas is an online database in Dutch (FK, 2019) which consist all the medications registered with the Medicines Evaluation Board of the Netherlands. In addition, it also consists drugs that are registered in European Medicines Agency.

Antirheumatic drugs such as leflunomide are reported to cause ulcers in the tongue (Kalogirou et al., 2017). Tongue ulcers are also associated with nicorandil use. The pathophysiology of nicorandil-induced tongue ulcers is still unclear (Healy et al., 2004). These ulcers usually heal after the discontinuation of the drugs. In the present study, four drugs were reported to cause ulceration of the tongue: alemtuzumab, nicorandil, melatonin and sertraline. Contrary to the literature, tongue ulceration was not reported for leflunomide. Our study might underreport some adverse drug reactions compared to another studies which are not based on MedDRA classification. The LLT term used to categorize the drug-induced tongue disorders is very specific. According to the farmacotherapeutisch Kompas, an adverse effect of leflunomide is ulcers in the mouth which is unspecific compared to tongue ulceration.

5 | CONCLUSION

The growing use of drugs is accompanied by a more frequent observation of tongue disorders that may have been induced by the use of drugs. As mentioned before, a wide variety of, partly overlapping, terminology is found in the literature to describe a particular tongue disorder related to the use of a drug and vice versa. The terminology used in this paper might help to bring the terminology used in pharmacology and oral medicine more in line. The overview of drugs reported in this paper helps oral healthcare workers in the recognition, diagnosis and eventual treatment of drug-induced tongue disorders.

AUTHOR CONTRIBUTIONS

Yalda Aziz: Data curation; Validation; Visualization; Writing-original draft; Writing-review & editing. **Willem Rademacher:** Data curation; Investigation; Methodology; Validation. **Atty Hielema:** Methodology; Resources. **Scott Bradley Patton Wishaw:** Methodology; Resources. **Denise van Diermen:** Supervision. **Jan de Lange:** Supervision. **Arjan Vissink:** Supervision, Writing-review & editing. **Frederik Rozema:** Conceptualization, Methodology, Supervision, Writing-review & editing.

ACKNOWLEDGEMENTS

The authors would like to acknowledge the Royal Dutch Pharmacist Association for providing access to Informatorium Medicamentorum.

PEER REVIEW

The peer review history for this article is available at <https://publons.com/publon/10.1111/odi.13680>.

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How to cite this article: Aziz Y, Rademacher WMH, Hielema A, et al. Oral adverse effects: drug-induced tongue disorders. *Oral Dis*. 2021;27:1528–1541. <https://doi.org/10.1111/odi.13680>