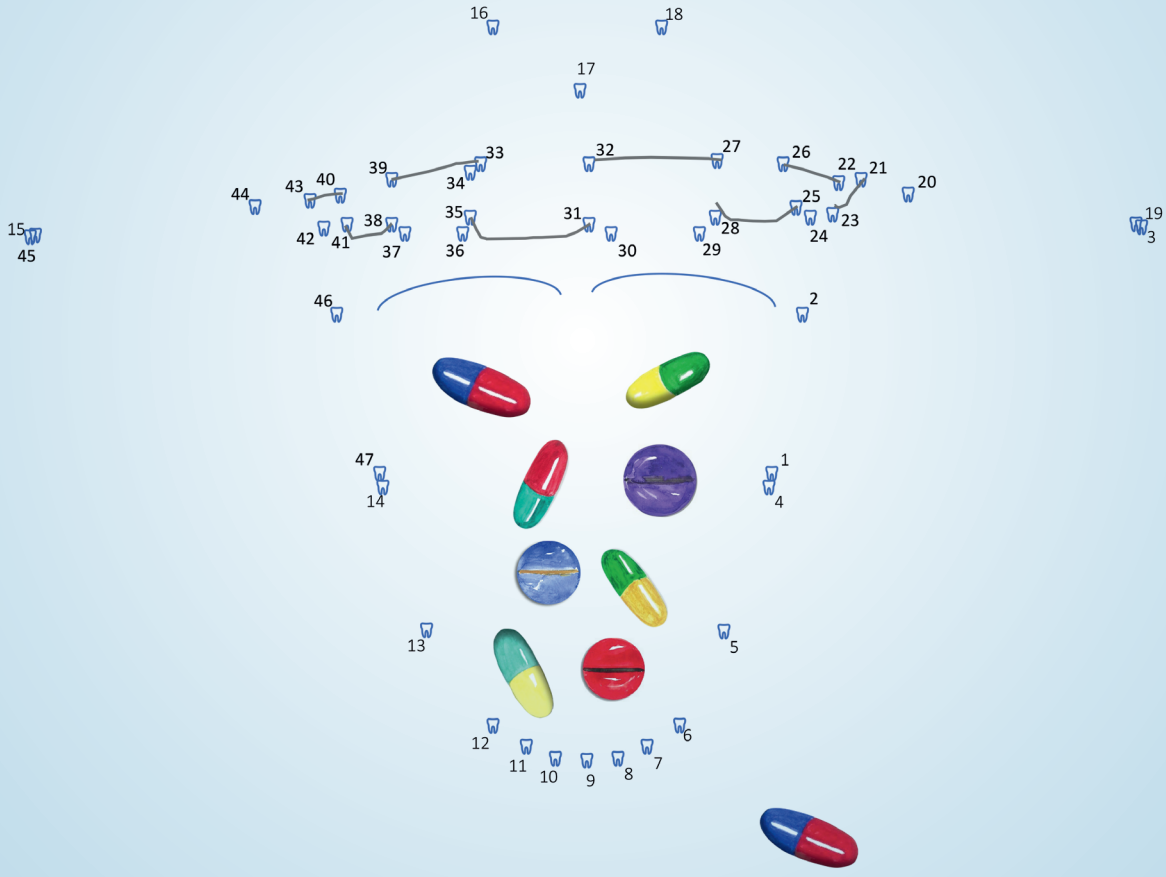
Implications of Medication Use for Oral Health and Oral Healthcare

Development of a Dental Clinical Decision Support System



Willem M.H. Rademacher

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Development of a Dental Clinical Decision Support System

Willem Maria Hubertus Rademacher

Amsterdam, 2023

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Implications of Medication Use for Oral Health and Oral Healthcare
Development of a Dental Clinical Decision Support System

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“Perpetuum mobile:
zodra verlangen vervuld is,
wordt het gemist.” – M. Egorie / opa

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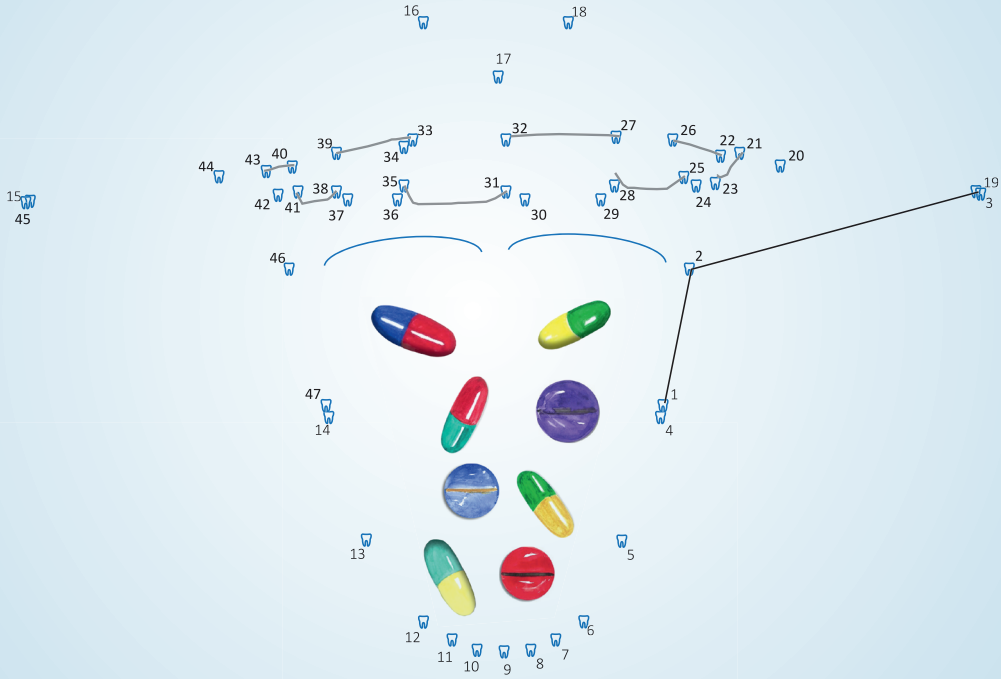
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1 General introduction

INTRODUCTION

Age distribution of the Dutch population has been changing for several decades. The average age of the population is increasing as the proportion of people of older age grows. In 1990, 9.9% of the Dutch population was 65 years of age and older. In two decades, this percentage has increased to 14.5% in 2019.[1]

In addition, the number of people over 80 years of age in the Netherlands is also increasing. These two trends together are called double aging. According to a forecast by the Central Bureau of Statistics (CBS) in the Netherlands, double aging has already started since 1950 and will continue until 2050.

Of the people over the age of 65, 70% is known to have one or more chronic medical conditions such as asthma, joint disorders and diabetes mellitus.[2-4] Such conditions are often treated (long-term) with one or more drugs. In the group of 65+, 75.9% uses at least one prescription drug and 25-50% are reported with polypharmacy, the use of five or more different medicines per day (Table 1).[5] Among those over 75 years of age, 20% consume more than nine prescription drugs on a daily basis.[6]

Table 1: Medication use in the Netherlands of patients 45 years and older.

	Prescribed drug	OTC* drug	Polypharmacy
	%	%	%
45 - 64 years	48.5	40.0	8.5
65 -74 years	75.9	36.6	25.2
>75 years	86.4	38.9	47.1

* over the counter

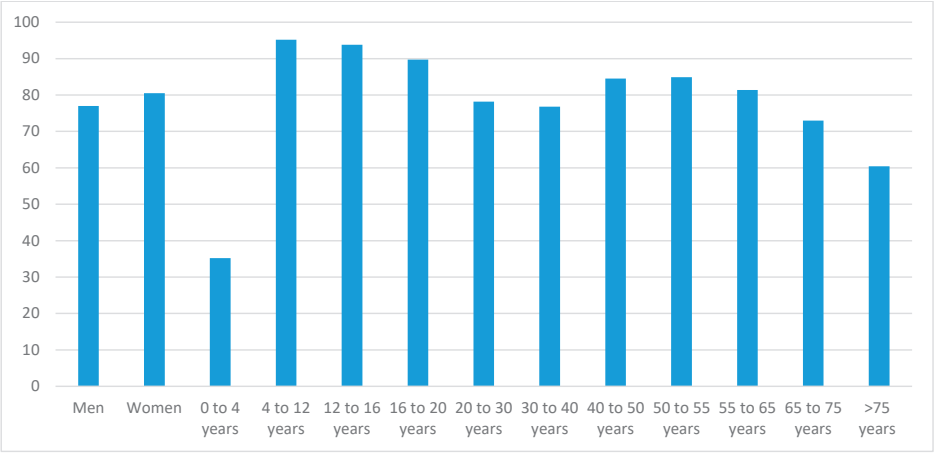
Double aging is resulting in increasing numbers of medically compromised patients also in dental practices. Medically compromised patients are generally considered to be those who have one or more somatic and/or psychological conditions. These patients are or have been treated with medications.

Previously, it was more common for people aged 65 and over to be edentulous.[7] In 1981, 75% of patients aged 65 years and over wore full dentures. Due to lack of own dentition invasive dental treatments were rarely indicated. These edentulous patients often did not visit the dentist for checkup or complaints. When (prosthetic) complaints occurred, they usually presented themselves to a dental technician or general practitioner.

Between 1981 and 2004, the percentage of Dutch people wearing full dentures halved from 32% to 14%.[7] As a result, together with the advent of new treatment options (e.g. implant-supported dentures), older people are visiting the dentist more regularly. Table 2 summarizes the percentage of Dutch people visiting the dentist at least once a year. Eighty percent of the 60-year-olds visit the dentist at least once a year and among the very elderly (>75years) this is still 61%.[3] Because of the longer preservation of one's own dentition, invasive treatments such as the placement of dental implants or tooth extractions are now part of daily practice among these patient groups.

Aforementioned phenomena lead oral healthcare professionals to be increasingly confronted with medically compromised patients who are taking one or more medicines.

Table 2: Persons (%) with at least 1 contact per year with the dentist according to age



MEDICALLY COMPROMISED PATIENTS IN ORAL HEALTHCARE

Increasing body of scientific research shows that both somatic conditions and the use of medications can have negative consequences for the oral health and/or the dental treatment.[8-13]

Somatic conditions, can manifest in and around the mouth, the orofacial region. The pathophysiology of these conditions varies widely.[14] A few examples are autoimmune diseases (e.g. m. Sjögren[15]), toxic-allergic diseases (e.g. erythema multiforme[16]) and infectious diseases (e.g. herpes viruses[17]). In addition, some somatic conditions have common risk factors for intraoral pathology. The association between diabetes

mellitus and periodontitis has been extensively described.[18-20] Furthermore, (medicated) treatment of somatic and/or psychological conditions can lead to complaints in the orofacial region. Patients who have been treated with radiotherapy in the head and neck region may remain at increased risk of osteoradionecrosis of the jaw for life when invasive dental treatment has to be performed.[21]

The potential oral health consequences of (daily) drug use can be divided into three categories:

First, a drug may produce adverse effects that manifest in the orofacial area. These adverse effects vary widely and range from visible lesions (e.g. oral lichenoid drug reactions[22] and aphthous ulcers[23]) to subjective complaints (e.g. taste alterations[24], tongue pain[25]). The use of multiple drugs simultaneously can also lead to adverse effects in the orofacial area. One such example is a decreased quantity and quality of saliva (xerostomia, hyposalivation) which increases the susceptibility to caries.[26]

Second, drugs commonly prescribed in oral healthcare may interact with drugs the patient is already using. In 2018, almost one million prescriptions were issued by 9000 dentists or dental specialists in the Netherlands (pop. 17.5mln). Almost half (420.000) involved antibiotics. Other commonly prescribed drugs were analgesics.[27] Both can cause interactions with other drugs like antithrombotic agents.

Third, some drugs pose a risk in invasive dental treatment. In order to treat safely, it is in some cases necessary to take preventive measures such as with antithrombotic drugs where the risk of postoperative bleeding after invasive treatment is increased.[28] Also, worth mentioning is medication-related osteonecrosis of the jaw (MRONJ). Invasive dental treatment of patients who use or have used certain antiresorptive agents (e.g. Bisphosphonates, Denosumab) or angiogenesis medications can result in impaired wound healing characterized by necrosis of the bone.[29, 30] In severe cases this can lead to the loss of large portions of the jaw.[31]

PROBLEM STATEMENT

To provide safe, adequate and effective dental care, it is important for oral healthcare providers to recognize and understand these somatic conditions and consequent medication use as etiological factors for certain complaints in the orofacial area.

In general, somatic conditions that pose an increased risk of a serious medical emergency (e.g. angina pectoralis, diabetes mellitus) are considered to be well known and recognized by oral healthcare professionals. This does not apply to diseases that do not pose a risk of medical catastrophe but may still affect the oral health. The available information on the latter conditions is huge, fragmented in literature and lacking user-friendly access channels. Therefore, it is impossible for oral healthcare professionals to determine all possible consequences of somatic conditions for each patient in daily practice. The same applies to the effects of drug use on the orofacial area. Here, too, often only the most common drugs (e.g. antithrombotics) or the most serious consequences (e.g. MRONJ) are generally recognized.

Fortunately, there are some supportive tools available. To screen patients for perioperative risks, the American Society of Anesthesiologist developed the "ASA physical status classification system". Using this questionnaire, based on 6 categories, an ASA score is created which can be used to roughly estimate the risk of perioperative complications in operations under general anesthesia. Inpijn et al. published a similar instrument for dental health providers. The European Medical Risk-Related History (EMRRH) questionnaire supports the oral healthcare professionals in conducting the medical history check.[32, 33] The outcome of the medical history check leads to an ASA score modified for dentistry (mASA). This score is used to prevent acute medical emergency resulting from dental treatment (myocardial infarction, epileptic seizure etc.) and indicates whether therapy modifications are required.

However, this frequently used questionnaire has some limitations. The mASA does not indicate what the consequences specifically entail or what precautions should be taken. Also no information is given on diseases which could cause intraoral symptoms or adverse effects of medications.. Furthermore, the EMRRH does not support dentists in prescribing medications. Such support is desirable since Brinkman et al. concluded from a questionnaire survey among a small sample of dentists, dental students, and dental specialists, that these groups on average possessed insufficient knowledge to adequately prescribe medications.[34] This can easily lead to incorrect prescribing behavior.[35]Innovative technology could support oral healthcare professionals in the aforementioned limitations. Software applications like clinical decision support systems (CDSS) are capable of making the scientific literature not only clinically available, but also patient-specific applicable. One example is an electronic prescription system with a built-in medication monitoring system (EPS/MMS). Such applications is being used in hospitals for several years to reduce the risk of prescribing errors.[36] When prescribing a new drug, the healthcare provider is presented with an overview of possible drug interactions, dosage errors and sometimes suggestions for an alterna-

tive drug. The Healthcare and Youth Inspectorate of The Netherlands and Royal Dutch Medical Association consider it no longer justifiable to prescribe medicines without using a EPS/MMS.[37] Nevertheless, such software is not yet used in oral care in the Netherlands.

To conclude, it is almost impossible due to the huge amount and fragmentation of available literature to oversee during daily dental practice the consequences of medical comorbidities for oral health.

GOALS OF THE THESIS

The goal of this thesis is to disclose and combine literature using innovative tools to support the oral healthcare professional in providing adequate, effective and safe care to medically compromised patients by:

1) Analysing medication-related risks during dental treatment and formulating appropriate therapeutic interventions;
2) Analysing adverse effects of drugs in the perioral region;
3) Development of a *Clinical Decision Support System (CDSS)*, which offers user-friendly, clinically applicable, science-based recommendations on the impact of medical co-morbidities and drug use on oral health and care.

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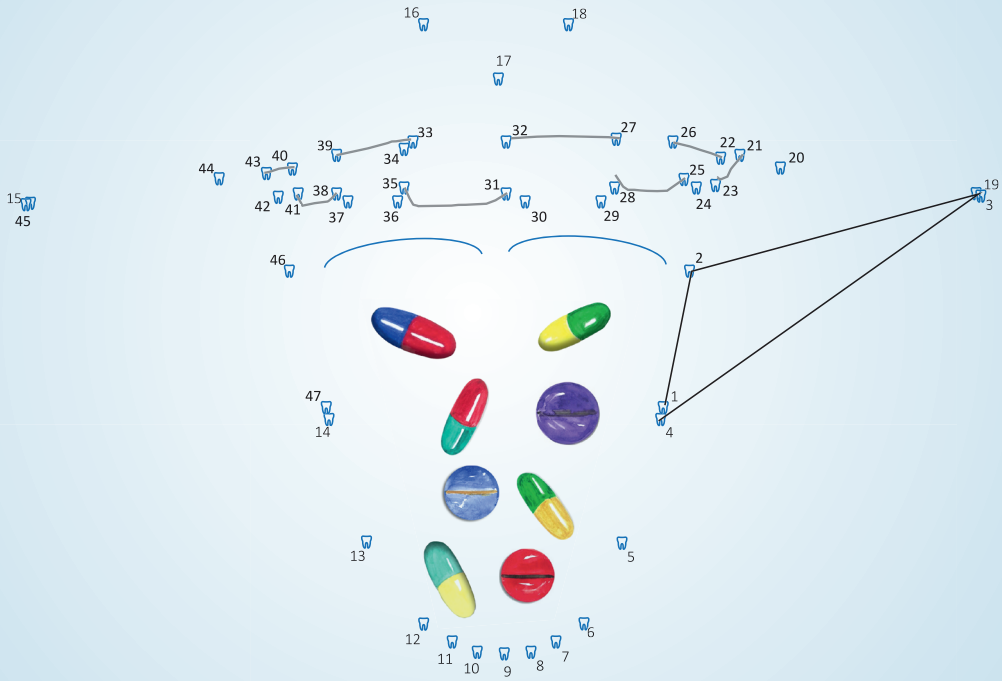
II Medication related questions in dentistry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2 Antibiotic prophylaxis is not indicated prior to dental procedures for prevention of periprosthetic joint infections: A systematic review and new guidelines of the Dutch Orthopaedic and Dental Societies

This chapter is based on the following publication:
Antibiotic prophylaxis is not indicated prior to dental procedures for prevention of periprosthetic joint infections: A systematic review and new guidelines of the Dutch Orthopaedic and Dental Societies

Willem M.H. Rademacher; Geert H.I.M. Walenkamp; Dirk Jan F. Moojen; Johannes G.E. Hendriks; Theo A Goedendorp and Frederik R. Rozema

Acta Orthop. 2017 Oct;88(5):568-574.
doi: 10.1080/17453674.2017.1340041. Epub 2017 Jun 22.

ABSTRACT

To minimize the risk of hematogenous periprosthetic joint infection (HPJI) international and Dutch guidelines recommended antibiotic prophylaxis prior to dental procedures. Unclear definitions and contradicting recommendations in these guidelines have led to unnecessary antibiotic prescriptions. To formulate new guidelines a joint committee of the Dutch Orthopaedic and Dental Societies conducted a systematic literature review to answer the following question: is antibiotic prophylaxis recommended in patients (with joint prostheses) undergoing dental procedures in order to prevent dental HPJI?

The Medline, Embase and Cochrane databases were searched for RCTs, reviews and observational studies until July 2015. Studies were included if they reported on patients with joint implants undergoing dental procedures, and either considered HPJI as an outcome measure or described a correlation between HPJI and prophylactic antibiotics. A guideline was formulated using the GRADE-method and AGREE II guidelines.

Nine studies were included in this systematic review. All were rated “very low quality of evidence”. Therefore, additional literature was consulted to address clinical questions that provide further insight into pathophysiology and risk factors. The 9 studies did not provide evidence that using antibiotic prophylaxis reduces the incidence of dental HPJI, and the additional literature supported the conclusion to discourage antibiotic prophylaxis in dental procedures.

Prophylactic antibiotics should not be prescribed in order to prevent dental HPJI to patients with a normal or an impaired immune system function. Patients are recommended to maintain good oral hygiene and visit the dentist regularly.

INTRODUCTION

Worldwide, the number of patients with artificial joint prostheses has been increasing for decades. Prosthetic joint infections (PJIs) occur in approximately 0.3-2% of the patients and infection rates continue to rise.[1, 2] PJI is caused by bacterial contamination perioperatively or via hematogenous routes. Hematogenous PJIs (HPJIs) are responsible for about one third of the PJI cases and are thought to occur mainly as late PJI (>2 years post-implantation), but the proportion of HPJI in early PJI (<3 months post-implantation) is in fact unknown.[1, 3] Bacteria causing HPJI originate from distant anatomic sites such as the skin, urinary tract, and to a lesser extent the oral cavity (10% of all HPJI).[1,4] The hypothesis that transient bacteremia from the oral cavity can cause HPJIs in humans seems plausible but is mainly based on animal experiments and human studies in which bacteremia are used as a surrogate marker for the risk of HPJI.[5-7]

To reduce the risk of HPJI due to oral bacteremia, several national guidelines recommend antibiotic prophylaxis prior to dental procedures. Interestingly however, the literature is inconsistent with regard to the efficacy of antibiotic prophylaxis in reducing the incidence of HPJI of dental origin.[8, 9] Due to the lack of convincing supporting evidence, and possibly the fear of legal consequences, the AAOS/ADA guideline recommendations have been contradictory and confusing and resulted in defensive healthcare practices. European guidelines have often adopted AAOS/ADA guidelines, but tend to recommend antibiotic prophylaxis less frequently.

In the Netherlands, the 2010 guidelines advised antibiotic prophylaxis in cases involving dental procedures in “infected” oral pathology and in patients with “reduced immune capacity”.[10] These poorly defined indications were confusing. As a result, physicians formulated their own regional guidelines with varying indications for antibiotics which possibly lead to unnecessary antibiotic prescriptions.[11]

Therefore, the Dutch Orthopaedic and Dental Societies appointed a joint committee to formulate new and better defined guidelines for the prudent use of antibiotics for prophylaxis. This committee conducted a systematic literature review to answer the following question: is antibiotic prophylaxis recommended in patients (with joint prostheses) undergoing dental procedures in order to prevent dental HPJI?

MATERIAL AND METHODS

The committee consisted of orthopaedic surgeons (GW,JH,DM), a dental practitioner (TG), an oral maxillofacial surgeon (OMFS) (FR) and an OMFS resident (WR). The committee was supported by a medical literature specialist of the Knowledge Institute of Medical Specialists who: formulated the systematic literature searches, supported the literature quality assessment by the committee and ensured that the recommendations were formulated according to the AGREE II guidelines.

A systematic literature review was performed using the electronic Medline, Embase and Cochrane database. The search parameters were concentrated on literature published between 1980-2015 in English, German, French and Dutch. Only systematic reviews and original randomized controlled trials were eligible for full-text analysis, provided that they reported on patients with joint implants (e.g. knee, hip, shoulder) undergoing dental treatment, and either considered HPJI as 1 of the outcome measures or described a direct correlation between HPJI and antibiotic prophylaxis. The search strategy was conducted and results were analyzed according to criteria that were specified a priori.[12] All committee members individually screened the articles for title and abstract, and if eligible, read them full-text. Since this search provided just 1 eligible publication, a second similar search and analysis was performed, this time including observational studies. Finally, additional literature was found through the reference list of the selected publications. Two investigators (GW,WR) extracted information from the included trials on: 1) study characteristics (i.e. design, follow-up course) and inclusion and exclusion criteria; 2) overall participant demographics (e.g. prosthesis type, joint age); 3) methods of diagnosing dental HPJI (e.g. questionnaires, microbiological tests) and outcome measures (e.g. incidence of PJI and HPJI, type of dental treatment, use of prophylactic antibiotics). Relative risk reduction in dental HPJI due to antibiotics was the primary outcome measure. The final systematic literature searches were performed until July 2015.

The GRADE-method was used to determine the risk of bias of the included studies. In light of the limited quantitative and qualitative results presented by the systematic review, we formulated several additional questions that might provide further insight into the pathophysiology of dental HPJI, risk factors and risk procedures (Table 1). These questions were answered using literature from additional searches.

Table 1. Additional clinical considerations

1.	Which bacteria are able to cause a HPJI, in what numbers are they required and can antibiotic prophylaxis influence bacteremia?
2.	Is there an increased risk for HPJI in the first 2 postoperative years?
3.	Is bleeding during dental treatment an indicator of a higher risk of HPJI?
4.	Are prophylactic antibiotics indicated in patients with an impaired immune status?
5.	What are the risks and benefits of antibiotic prophylaxis for HPJI?
6.	Is antibiotic prophylaxis a cost-effective means of preventing HPJI?
7.	Is dental screening indicated before and/or after prosthesis placement?
8.	Is antibacterial mouthwash indicated before dental treatment?
9.	What are the international recommendations on antibiotic prophylaxis and dental HPJI?

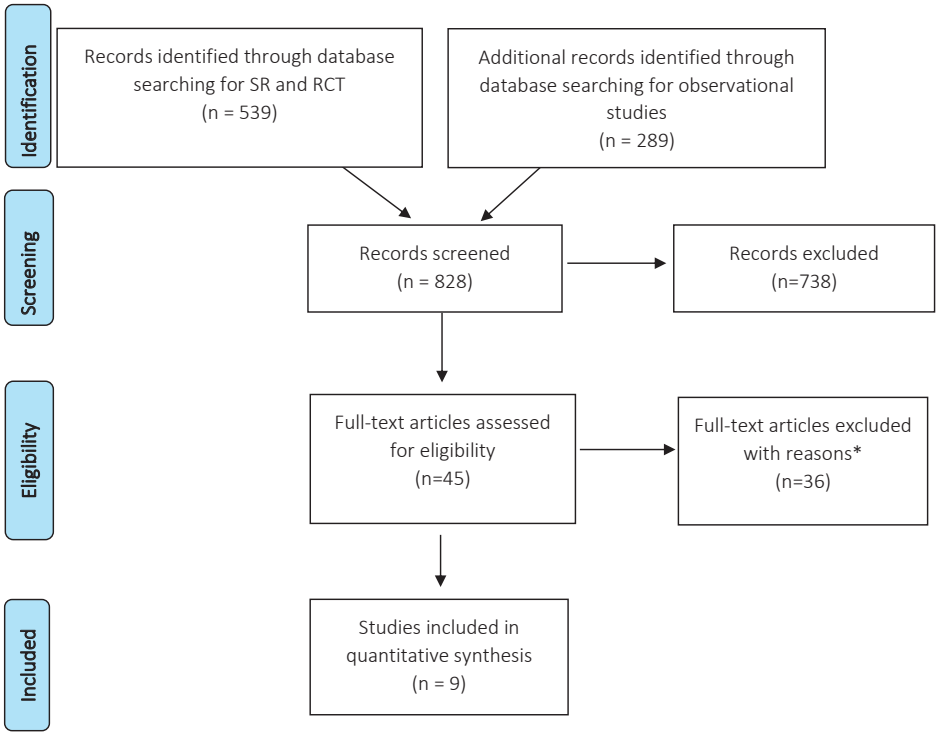
To increase the support of the guidelines and reduce potential bias, the draft guidelines were sent to 7 relevant Dutch medical societies. With help of their comments a definitive guideline was written and accepted by the Dutch Orthopaedic and Dental Societies in February 2016. Thereafter, more recent studies and reviews were included for the completeness of this manuscript.

RESULTS

In the systematic literature review, 828 studies were screened for title and abstract, of which 45 were selected for full-text critical appraisal. Following the exclusion of 36 full-text articles for systematic reasons (Table A2, see appendix), 9 eligible studies remained: 6 as a result of the systematic searches and 3 by checking the references of the included studies (Figure 1). Study characteristics are presented in Table 3. The incidence of PJI varied in these studies between 1.2-2.0% and the incidence of HPJI 0.1-1.7%. Based on indirect evidence, the incidences of dental HPJI ranged from 0.03-0.2%. None of the studies reported a significant reduction of dental HPJI associated with antibiotic prophylaxis.

Due to methodological limitations of the individual study designs, all studies were assigned an a priori ranking of “low quality of evidence” and finally downgraded to “very low quality of evidence” on the basis of inconsistency and indirectness of evidence (Table A4, see appendix). Because of this very low quality the risk of bias across studies was not assessed and no meta-analysis was performed.

Figure 1: Flow diagram presenting literature analysis



*The reasons for exclusion were various and are to be found in Table A2 in the appendix.

DISCUSSION

The purpose of this renewed guideline was to provide recommendations on the use of antibiotic prophylaxis in the prevention of dental HPJI. Based on this systematic review we conclude that there is *no* evidence that antibiotic prophylaxis has a positive or negative impact on the incidence of dental HPJI.

However, decisive studies are deemed unfeasible due to the low incidence of dental HPJI and difficulties of matching HPJI bacteria to the oral flora. Therefore, extra literature searches were performed on additional clinical questions that were necessary for the formulation of this guideline (Table 1):

1. Which bacteria are able to cause HPJI, in what numbers are they required and can prophylactic antibiotic prevent bacteremia?

PJIs were predominantly caused by *Staphylococcus Aureus* and *coagulase-negative species*. Oral bacteria like *Peptostreptococcus species*, *Actinomyces species* and

Table 3. Characteristics of included studies

Authors / year of publication	Study design	Joint type (number of patients)	Incidence DHPJI	Conclusion on effect of prophylactic antibiotics on HPJI
Jacobsen and Murray 1980	Retrospective observational	Hips (n=1885)	0.05%	The recommended prophylactic antibiotics should be based on drug sensitivity
Ainscow and Denham 1984	Prospective observational	Hips (n=885) Knees (n=115)	No significant influence of dental treatment on incidence of HPJI	Prophylactic antibiotics would not have prevented the HPJI cases
Waldman et al. 1997	Retrospective observational	Knees (n=3490)	0.2%	Indicated before extensive dental treatment in patients with systemic disease that compromises host defense mechanisms against infection
LaPorte et al. 1999	Retrospective observational	Hips (n=2973)	0.1%	Indicated before extensive dental treatment in patients with systemic disease that compromises host defense mechanisms against infections
Cook et al. 2007	Retrospective observational	Knees (n=3013)	0.03%	n.m.
Uçkay et al. 2009	Prospective observational	Hips (n=4002) Knees (n=2099)	No significant influence of dental treatment on incidence of HPJI	n.m.
Berbari et al. 2010	Prospective case-control	Hips (n= 328) Knees (n=350)	No significant influence of dental treatment on incidence of HPJI	Prophylactic antibiotics do not decrease the risk for DHPJI
Swan et al. 2011	Retrospective case-control	Knees (n=1641)	No significant influence of dental treatment on incidence of HPJI	n.m.
Skaar et al. 2011	Retrospective case-control	Hips (n=468) Knees (n=501) Other (n=31)	No significant influence of dental treatment on incidence of HPJI	Prophylactic antibiotics do not decrease the risk for DHPJI

DHPJI = dental treatment related hematogenous prosthetic joint infection; n.m. = not mentioned

beta-haemolytic streptococcus accounted for 10%.[16, 17] Animal studies showed that bacteremia could lead to HPJI, but the required number of bacteria (colony forming units (CFU)) was high (i.e. >1000 CFU/mL) and often resulted in sepsis.[5, 18, 19]

Based on the risk for subsequent bacteremia, dental procedures are often categorized into "low-risk" (e.g. dental filling, endodontic treatment) and "high-risk" (e.g. dental extraction, periodontal treatment).[17] However, everyday oral-activity leads to bacteremia as well; for example, the incidence of bacteremia after mastication and interdental flossing ranged between 8-51% and 20-58%, respectively.[20] Guntheroth (1984) calculated the 1-month cumulative exposure to bacteremia on the basis of incidence and duration of bacteremia after mastication, tooth brushing, and eventually dental extraction. Out of a total of 5376 minutes of bacteremia, only 6 minutes were attributable to the extraction. In 296 patients, the duration of bacteremia after tooth brushing or dental extraction was less than 20 minutes, and the serum concentration did not exceed 10^4 CFU/ml.[8] The beneficial effect of antibiotic prophylaxis prior to dental procedures on the incidence, duration and height of a bacteremia remains unclear. [8, 9, 21] The eventual clinical relevance will depend on the amount of reduction of these bacteremia parameters, but the literature indicates that there is an unknown risk reduction of an already very low risk for dental HPJI. Moreover, it must be realized that bacteremia is used as a surrogate marker for HPJI, but that there is little evidence that bacteremia truly directly relates to the incidence of dental HPJI.

2. Is there an increased risk for HPJI in the first 2 postoperative years?

In animal experiments, the susceptibility of prostheses for infections is the highest in the first postoperative weeks and decreases rapidly thereafter.[5, 6] Since the follow-up of these experiments is short they do not provide information on long term susceptibility. In 1993, Osmon et al. presented to the Musculo Skeletal Infection Society (MSIS), an incidence of HPJI in humans of 0.14 per 100 prosthesis years in the first 2 postoperative years, and 0.03 thereafter. This unpublished data was cited by Hanssen et al. (1996), and since then used in the consecutive AAOS guidelines, and copied by other authors. Deacon et al. (1996) confirmed that 50% of the HPJI occurred in the first 2 years. More recent studies in humans could not confirm the supposed higher risk in the first 2 years, but even found an increased susceptibility in higher joint ages of >2 or >5 years.[3, 17, 22, 23]

3. Is bleeding during dental treatment an indicator for a higher risk of HPJI?

For a long time, bleeding during dental treatment was considered a marker for the risk of bacteremia and therefore HPJI. This was first identified, though unsupported by literature, by a panel of experts from the American Heart Association.[24, 25] Indeed, in the event of generalized oral bleeding there was an 8-fold increased risk of bacteremia after tooth brushing in patients with higher dental plaque and calculus scores.[8] Roberts (1999) found that dental manipulations of the gingiva (including mastication) and subsequent alternating positive and negative pressure in the capillaries might lead to bacteremia, but that bleeding itself was not an independent predictor. The positive capillary pressure could possibly even prevent bacteria from entering the circulation.

4. Are prophylactic antibiotics indicated in patients with an impaired immune function?

Patients with an impaired immune system (e.g. rheumatoid arthritis, leukopenia) are thought to have an increased risk for HPJI.[23, 26, 27] However, in cases involving dental treatments and HPJI, these risk factors have never been confirmed so far.[17, 28] In our perception, patients with an impaired immune system will have comparable daily bacteremia analogous to healthy individuals as there is no evidence suggesting a higher incidence of HPJI in those patients.

5. What are the risks and benefits of antibiotic prophylaxis?

Only rough calculations were possible for the Dutch setting due to the lack of exact data. For example, we calculated a prevalence of patients with hip and knee prosthesis in the Netherlands ranging from 400,000-800,000, of which 300,000-600,000 would require antibiotics prophylaxis every year. Internationally reported variables had the same magnitude of uncertainties, these included: HPJI after dental procedures, the repercussions of HPJI (e.g. morbidity, mortality)[29], the efficacy of antibiotic prophylaxis[30], and risks associated with antibiotics (e.g. drug-interactions, bacterial resistance).[31, 32] Sendi et al. (2016) confirmed these uncertainties, but were able to calculate a number needed to treat of 625-1,250 patients. We could not calculate a reliable risk-benefit ratio.

6. Is antibiotic prophylaxis a cost-effective means of preventing HPJI?

Lockhart et al. (2013) concluded that the individual costs of antibiotic prophylaxis in relation to dental procedures were low, but the potential total costs for the American healthcare were high. In 1991, the costs for preventing one case of dental HPJI were

calculated at $480,000/year.[33] Several authors compared the cost-effectiveness for prophylaxis with penicillin versus no prophylaxis. They concluded that for the prevention of dental HPJI the regime of no prophylaxis was more cost-effective.[29, 30, 34, 35] Antibiotic prophylaxis was only cost-effective when the risk for HPJI after dental treatment was at least 1.2%[36], or when assuming an antibiotic prophylactic effectiveness of 100% in cases with evident oral infections.[37] However, these assumptions are unrealistic since the risk is probably lower and the 2 studies included did not show a prophylactic effectiveness of 100%.[15, 17]

7. Is dental screening indicated before and/or after prosthesis placement?

Over the last decades there has been an increasing awareness of the association between oral cavity diseases (e.g. gingivitis, periodontitis) and systemic diseases (e.g. rheumatoid arthritis, cardiovascular diseases). Some studies showed a higher incidence of bacteremia in patients with gingivitis or periodontitis after daily dental activities or dental treatment compared to healthy individuals.[38-40] Lockhart et al. (2009) could not confirm these results. It is plausible that the beneficial relation between a healthy oral condition and general health also applies to HPJI[28, 40-42], and in the absence of adverse effects it seems reasonable to recommend good oral hygiene and regular dental controls.

Similar to endocarditis prophylaxis, radiotherapy and intensive chemotherapy treatment, some authors suggested preoperative dental screening prior to orthopaedic implant placement. Interestingly, in 1 study chronic oral foci were left untreated in leukemic and autologous stem cell transplantation patients receiving intensive chemotherapy. The authors concluded that these foci did not increase infectious complications during intensive chemotherapy.[43] It is likely that these cancer patients would be more susceptible to infectious complications than patients planned for arthroplasty. Only 1 study reported on the efficacy of dental screenings before arthroplasty. Out of 100 patients 23 had untreated oral pathologies before arthroplasty. None of them developed PJI within 90 days after implant placement[44]; however, the study may have been underpowered to be conclusive.

8. Is antibacterial mouthwash indicated before dental treatments?

The antibacterial effect of chlorhexidine could reduce the oral bacterial load. Several randomized trials reported a significant reduction of incidence of bacteremia after using antibacterial mouthwash. The authors advised chlorhexidine 0.2% mouthwash before dental procedures.[45, 46] On the other hand, other reports found that chlorhexidine did not reduce the incidence of bacteremia.[21, 42] Given the cost implications and

limited but existing adverse effects (e.g. burning sensation, dental/lingual discoloration) associated with chlorhexidine mouthwash, more decisive studies are necessary before it can be recommended for routine use.

9. What are the international recommendations on antibiotic prophylaxis and dental HPJI?

Finally, we conducted an analysis of considerations and recommendations from international guidelines and expert-opinions on possible indications for antibiotic prophylaxis, dental treatment before arthroplasty and the need for good oral health in order to prevent HPJI. To be well-informed we focused especially on the arguments used in favor of antibiotic prophylaxis. In summary, other guidelines also tend towards recommending no antibiotic prophylaxis, but often include specific risk patients in whom prophylaxis may be justified (Table A5, see appendix).

CONCLUSION

In conclusion, we are convinced that HPJI can occur, and also after dental procedures. Nonetheless, the "very low level of evidence" found in our systematic literature review suggests that there is no convincing proof in the literature that antibiotic prophylaxis is helpful in preventing dental HPJI. At present, we cannot justify recommending antibiotic prophylaxis in so many prosthesis patients undergoing dental procedures, since their efficacy in preventing or reducing HPJI is insufficiently evident. This is supported by the answers (A) to the 9 additional questions:

A1: Bacteremia are common after dental treatment, but also very frequent in daily life. The effect of antibiotic prophylaxis on bacteremia and eventually dental HPJI remains unclear;

A2: The literature is indecisive on the duration of increased susceptibility. It is likely that there is a higher susceptibility for HPJI in a postoperative phase; however, it is unclear whether this phase last up to 2 years. Recent literature even shows an inversed relationship with more HPJI with increasing prosthesis age;

A3: Bleeding during a dental procedure is not correlated with an increased HPJI risk;

A4: Even in patients with an impaired immune system function, antibiotic prophylaxis before dental treatment for prevention of HPJI is not indicated;

A5: It was not possible to perform a reliable risk-benefit analysis with the available Dutch data and the international literature;

A6: Antibiotic prophylaxis for dental treatment in patients with a joint arthroplasty is not cost-effective;

A7: Preoperative dental screening before arthroplasty cannot be recommended on the basis of the literature. However, it is advised to inform patients on the effect of the oral health on systemic diseases and to prevent oral diseases by good daily oral hygiene and regular dental care;

A8: There is insufficient evidence to advise antibacterial mouthwash before dental treatment to prevent HPJI;

A9: Although prevailing opinions and guidelines increasingly tend to advise against the use of prophylactic antibiotics, they often offer exceptions on the basis of inconsistent literature.

The results of this extended literature search fail to deliver sufficient arguments in favor of antibiotic prophylaxis. They showed that risk factors such as joint age and bleeding during dental procedures, which are often presented in guidelines as reason for administering prophylactic antibiotics, appear to be unsupported by literature and are even illogical from a pathophysiological standpoint. Since there are increasing indications that the oral health affects aspects of the general health, we view regular dental control as beneficial; this might help to reduce even a minimal risk of dental HPJI and would have no serious adverse effects or increase in costs.

In other countries, guidelines also tend towards recommending no antibiotic prophylaxis, but often include specific risk patients in whom prophylaxis may be justified. However, daily bacteremia is frequent in both healthy and risk patients and dental treatment contributes only a small fraction to the overall bacteremia. It is also probable that bacteremia could cause dental HPJI only in septic patients. In septic patients, whether or not they have joint arthroplasty, the medical specialist may prescribe antibiotics for therapeutic rather than prophylactic reasons; this also includes patients with an impaired immune system. In a reverse case scenario involving oral infections (e.g. abscess or apical periodontitis), a dentist could indicate antibiotics for therapeutic rather than prophylactic purposes. Exceptions made in most guidelines on antibiotic prophylaxis are unnecessary and only lead to over defensive and

inconsistent healthcare, in which imprudent use of antibiotics has already yielded bacterial resistance throughout the world.

The strength of the current guideline is the combination of expertise and consensus from both orthopedic surgeons, dental practitioners and oral maxillofacial surgeons. Especially when evidence is lacking or the research is impossible to perform, expert consensus from the concerning professions is essential for guidelines to receive broad support and, in this case, for limiting clinicians in prescribing prophylactic antibiotics unnecessarily.

IN SUMMARY, THE GUIDELINE CONCLUDES:

1) There is *no* indication that antibiotic prophylaxis should be prescribed prior to dental procedures in order to prevent HPJI in patients with a joint implant;
2) Neither is there any indication for antibiotic prophylaxis in patients in whom an impaired immune system is supposed or confirmed;
3) Patients are advised to maintain good oral hygiene and to visit the dentist regularly.

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APPENDIX

Table A2: Reasons for exclusion after full-text analysis

Authors	Reason for exclusion
Primary search: systematic reviews and randomized controlled trials	
Aminoshariae & Kulild 2010	Review, no primary research
Brennan et al. 2007	Subject: bacteremia after tooth extraction in children
de Andrade et al. 2012	Subject: effect Chlorhexidine mouth wash on biofilm in dental prosthesis
Deacon et al. 1996	Review, no primary research
Dinsbach 2012	Review, no primary research
Drangsholt 1998	Commentary letter to the editor, no primary research
Esposito et al. 2003	Subject: antibiotic prophylaxis during dental implant placement
George 1995	Subject: questionnaire amongst dermatologists
Jones et al. 1997	Subject: hematogenous infections in vascular prosthesis
Krijnen et al. 2001	Subject: cost and effectiveness in patients with rheumatoid arthritis and orthopedic prosthesis
Kuong et al. 2009	Review, no primary research
Lauber et al. 2007	Subject: questionnaire on antibiotic prophylaxis prescriptions in Canada
Legout et al. 2012	Review, no primary research
Little et al. 2010	Authors opinion on AAOS 2009 guideline, no primary research
Little 1994	Review, no primary research
Marculescu & Osmon 2005	Review, no primary research
Pineiro et al. 2010	Subject: effect of chlorhexidine mouthwash on bacteremia after dental implant placement
Rosengren & Dixon 2010	Subject: review on dermatological infection and antibiotic prophylaxis
Salvi et al. 2008	Subject: review on effect of Diabetes Mellitus II on periodontitis and dental peri-implantitis
Schwartz & Larson 2007	Review, no primary research
Seymour et al. 2003	Review, no primary research
Shurman & Benedetto 2010	Subject: review on antibiotic prophylaxis in dermatology
Strom et al. 2000	Subject: risk factors for endocarditis
Sziegoleit et al. 1999	Subject: analysis of oral microbiome
Tong & Theis 2008	Subject: questionnaire in New Zeeland, no primary research
Tornos et al. 2005	Subject: review on endocarditis
Treister & Glick. 1999	Subject: review on oral health care and rheumatoid arthritis
Uçkay et al. 2008	Review, no primary research
Uyemura 1995	Review, no primary research
Van der Bruggen & Mudrikova 2007	Review, no primary research
Watters et al. 2013	Review of AAOS/ADA guideline ‘12, no primary research

Table A2: Reasons for exclusion after full-text analysis (*continued*)

Authors	Reason for exclusion
Wijngaarden & Kruize 2007	Review, no primary research
Secondary search: observational studies	
Hamilton & Jamieson 2008	Subject: prospective study on PJI, but no description of dental treatment related HPJI
Lacassin et al. 1995	Subject: study on endocarditis risk factors
Meer (van der) et al. 1992	Subject: endocarditis
Meijndert et al. 2010	Subject: oral microbiome
Powell et al. 2005	Subject: periodontal treatment
Wicht et al. 2004	Subject: effect of Chlorhexidine mouthwash on caries prevention
Young et al. 2014	Review, no primary research

Table A4. Bias assessment of included studies according to the GRADE-method

Study reference	Bias due to a non-representative or ill-defined sample of patients?[1]	Bias due to insufficiently long, or incomplete follow-up, or differences in follow-up between treatment groups?[2]	Bias due to ill-defined or inadequately measured outcome?[3]	Bias due to inadequate adjustment for all important prognostic factors?[4]
Ainscow and Denham 1984	unlikely	likely	unclear	likely
Berbari et al. 2010	likely	unclear	unlikely	unlikely
Cook et al. 2007	unlikely	unclear	unlikely	likely
Jacobsen and Murray 1980	unlikely	unclear	unclear	likely
LaPorte et al. 1999	unlikely	unclear	likely	likely
Skaar et al. 2011	unlikely	unclear	likely	unlikely
Swan et al. 2011	likely	unlikely	likely	unlikely
Uçkay et al. 2009	unlikely	unclear	unlikely	unlikely
Waldman et al. 1997	unlikely	unclear	unlikely	unlikely

[1]Failure to develop and apply appropriate eligibility criteria: a) case-control study: under- or over-matching in case-control studies; b) cohort study: selection of exposed and unexposed from different populations.
[2]Bias is likely if: the percentage of patients lost to follow-up is large; or differs between treatment groups; or the reasons for loss to follow-up differ between treatment groups; or length of follow-up differs between treatment groups or is too short. The risk of bias is un-clear if: the number of patients lost to follow-up; or the reasons why, are not reported.
[3]Flawed measurement or differences in measurement of outcome in treatment and control group; bias may also result from a lack of blinding of those assessing outcomes (detection or information bias).
[4]Failure to adequately measure all known prognostic factors and/or failure to adequately adjust for these factors in multivariate statistical analysis.

Table A5. An overview of international recommendations

Country	Year	Reference	Society / profession	AB-prophylaxis should be considered				Recommendations for good oral health	Recommendations for chlorhexidine mouthwash	Dental screening before implant placement	Type of recommendation
				Always	In patients with risk factors	In specific dental procedures with an increased risk	Postoperative risk period				
USA	1997	American Dental Association and American Academy of Orthopaedic Surgeons 1997	ADA + AAOS	no	yes	yes	2 years	yes	n.m.	yes	Advisory statement
	2003	American Dental Association and American Academy of Orthopaedic Surgeons 2003	ADA + AAOS	no	yes	yes	2 years	yes	n.m.	yes	Advisory statement
	2009	American Academy of Orthopaedic Surgeons 2009	AAOS	yes	yes	yes	n.m.	yes	n.m.	n.m.	Information statement
	2012	American Academy of Orthopaedic Surgeons and American Dental Association 2012	ADA + AAOS	no	yes	n.m.	n.m.	yes	indecisive	n.m.	Evidence based guideline
	2014	Chen et al. 2014	AAOS	no	yes	n.m.	Life-time for high-risk patients	n.m.	n.m.	n.m.	International expert consensus
	2015	Sollecito et al. 2015	ADA	no	yes	n.m.	n.m.	n.m.	n.m.	n.m.	Evidence based guideline

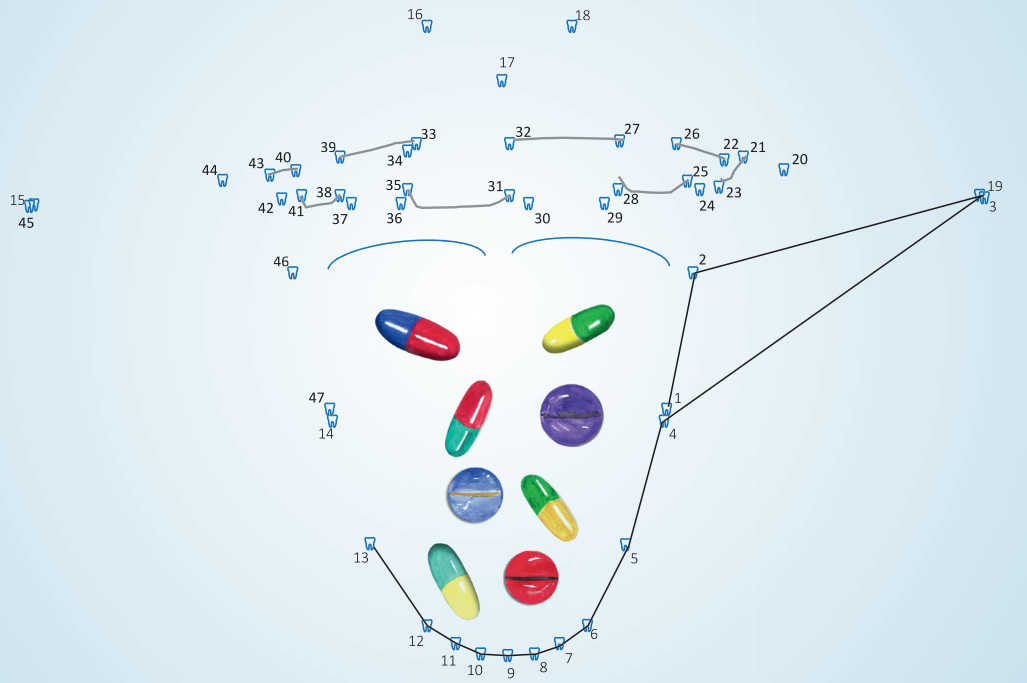
Table A5. An overview of international recommendations (*continued*)

Country	Year	Reference	Society / profession	AB-prophylaxis should be considered				Recommendations for good oral health	Recommendations for chlorhexidine mouthwash	Dental screening before implant placement	Type of recommendation
				Always	In patients with risk factors	In specific dental procedures with an increased risk	Postoperative risk period				
UK	1992	Simmons et al. 1992	BSAC	no	no	n.m.	n.m.	n.m.	n.m.	n.m.	Expert opinion
	2003	Seymour et al. 2003	BOA + BDA	no	yes	n.m.	n.m.	yes	yes	yes	Expert opinion
Australia	2005	Scott et al. 2005	OS + OMFS	no	yes	yes	n.m.	yes	n.m.	yes	Expert opinion
New Zealand	2003	New Zealand Dental Association 2003	NZDA	no	yes	yes	n.m.	yes	n.m.	yes	Code of practice
	2013	New Zealand Dental Association 2013	NZDA	no	yes	n.m.	n.m.	yes	n.m.	yes	Code of practice
Canada	2016	Canadian Agency for Drugs and Technologies in Health 2016	CADTH	no	no	n.m.	n.m.	n.m.	n.m.	n.m.	Conclusion of review
South-Afrika	2009	Kotzé 2009	OMFS	no	yes	yes	n.m.	yes	n.m.	yes	Conclusion of review
France	2012	Legout et al. 2012	AFSSAPS + ANSM	no	no	no	no	yes	n.m.	yes	Evidence based guideline
Switzerland	2005	Rossi et al. 2005	SGINF	no	yes	yes	n.m.	n.m.	n.m.	n.m.	Conclusion of review and expert opinion

Table A5. An overview of international recommendations (*continued*)

Country	Year	Reference	Society / profession	AB-prophylaxis should be considered				Recommendations for good oral health	Recommendations for chlorhexidine mouthwash	Dental screening before implant placement	Type of recommendation
				Always	In patients with risk factors	In specific dental procedures with an increased risk	Postoperative risk period				
	2010	Uçkay et al. 2010	OS	no	yes	no	n.m.	yes	n.m.	n.m.	Conclusion of review
	2016	Sendi et al. 2016	OS + I	no	no	yes	n.m.	yes	yes	yes	Conclusion of review
Italy	2009	Termine et al. 2009	D	no	yes	n.m.	n.m.	n.m.	n.m.	n.m.	Conclusion of review
Norway	2010	Olsen et al. 2010	OS + MI	no	n.m.	n.m.	n.m.	yes	n.m.	n.m.	Conclusion of review
Sweden	2012	Swedish Guideline 2012	OS	no	yes	n.m.	<3 months	yes	n.m.	yes	Evidence based guideline
the Netherlands	2011	Swierstra et al. 2011	OS	no	yes	yes	n.m.	n.m.	n.m.	n.m.	Evidence based guideline

AAOS = American Academy of Orthopaedic Surgeons; ADA = American Dental Association; AFSSAPS/ANSM = French health authorities; BASC = British Society for Antimicrobial Chemotherapy; BOA =British Orthopaedic Association; DE = dentists; IN = infectiologists; n.m. = not mentioned; NZDA = New Zealand Dental Association; MI = microbiologists; OMFS = oral and maxillofacial surgeons; OS = orthopaedic surgeons; SGINF = Swiss Society for Infectious Diseases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3 Predictors of oral cavity bleeding and clinical outcome after dental procedures in patients on vitamin K antagonists: A cohort study

This chapter is based on the following publication:
Predictors of oral cavity bleeding and clinical outcome after dental procedures in patients on vitamin K antagonists A cohort study

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ABSTRACT

Patients on vitamin K antagonists (VKA) often undergo invasive dental procedures. International guidelines consider all dental procedures as low-risk procedures, while bleeding risk may differ between standard low-risk (e.g. extraction 1–3 elements) and extensive high-risk (e.g. extraction of >3 elements) procedures. Therefore current guidelines may need refinement.

In this cohort study, we identified predictors of oral cavity bleeding (OCB) and evaluated clinical outcome after low-risk and high-risk dental procedures in patients on VKA. Perioperative management strategy, procedure risk, and 30-day outcomes were assessed for each procedure.

We identified 1845 patients undergoing 2004 low-risk and 325 high-risk procedures between 2013 and 2015. OCB occurred after 67/2004 (3.3%) low-risk and 21/325 (6.5%) high-risk procedures (p=0.006). In low-risk procedures, VKA continuation with tranexamic acid mouthwash was associated with a lower OCB risk compared to continuation without mouthwash [OR=0.41, 95%CI 0.23–0.73] or interruption with bridging [OR=0.49, 95%CI 0.24–1.00], and a similar risk as interruption without bridging [OR=1.44, 95%CI 0.62–3.64]. In high-risk procedures, VKA continuation was associated with an increased OCB risk compared to interruption [OR=3.08, 95%CI 1.05–9.04]. Multivariate analyses revealed bridging, antiplatelet therapy, and a supratherapeutic or unobjectified INR before the procedure as strongest predictors of OCB. Non-oral cavity bleeding (NOCB) and thromboembolic event (TE) rates were 2.1% and 0.2%. Bridging therapy was associated with a twofold increased risk of NOCB [OR=1.93, 95%CI 1.03–3.60], but not with lower TE rates.

In conclusion, predictors of OCB were mostly related to perioperative management and differed between low-risk and high-risk procedures. Perioperative management should be differentiated accordingly.

INTRODUCTION

Due to the high prevalence of cardiovascular disease worldwide, millions of people currently receive oral anticoagulants such as vitamin K antagonists (VKA). Patients on VKA often require invasive dental procedures for which they require periprocedural VKA management. The bleeding risk after dental procedures in these patients is higher than in individuals without VKA therapy.[1] Various studies have compared different management strategies in order to minimize the risk of oral cavity bleeding after dental procedures, without increasing the risk of thromboembolic complications.[2-4] However, most of these studies included only small numbers of patients and were underpowered to detect differences in bleeding rates between different management strategies. Current guidelines and guidance documents have suggested that VKA therapy can safely be continued with co-administration of a local prohemostatic agent (e.g. tranexamic acid (TXA) mouthwash) during low bleeding risk dental procedures.[5-8] However, these guidelines do not differentiate between low and high bleeding risk dental procedures in their recommendations on VKA-management. Differentiating into these categories may lead to clearer and safer perioperative strategies. The use of preoperative international normalized ratio (INR) values in these guidelines and standardized VKA management probably makes the bleeding risk in patients on warfarin similar to that of patients on acenocoumarol or phenprocoumon and vice versa.

The goals of the present study were to evaluate, in a real world setting, VKA management and clinical outcome after low-risk and high-risk dental procedures in patients on VKA, and to identify predictors of oral cavity bleeding for both categories.

MATERIAL AND METHODS

Study design and setting

We used data from the anticoagulation clinic of the Star Medical Diagnostic Centre (Rotterdam, the Netherlands). All registered dental procedures in patients on VKA between January 1, 2013 and January 1, 2015 were retrieved from the clinic's medical database. These procedures were either reported beforehand by the patients or treating physicians or in retrospect by the patients during subsequent visits to the clinic. We collected information regarding patient and dental procedure characteristics, periprocedural VKA-management. A waiver for informed consent was granted on behalf of the ethics committee of the Erasmus University Medical Centre based on the observational nature of our study.

Periprocedural VKA management

In the Netherlands, patients are treated with acenocoumarol or phenprocoumon and are monitored by anticoagulation clinics. Dental practitioners consult these clinics for advice regarding periprocedural VKA management. For standard low-risk procedures (e.g. extraction or implantation 1–3 elements), VKA management is based on the guideline from the Academic Centre for Dentistry Amsterdam (ACTA).[5] This guideline classifies dental procedures as low or high bleeding risk, and states that low-risk procedures can be safely performed under VKA continuation, provided that the INR is ≤ 3.5, the wound is sutured, and a local prohemostatic agent (TXA-mouthwash 5.0%, 10 ml 4dd for 5 days) is prescribed.[5] In order to follow this protocol, the patients must report the planned dental procedure to the anticoagulation clinic at least 24 h in advance. This guideline, however, does not provide guidance on perioperative management for high-risk procedures (e.g. extraction or implantation >3 elements and orthognatic surgery). For these high-risk procedures, anticoagulant therapy is usually interrupted without routine TXA prescription, and bridged with LMWH if required, in line with international recommendations. Regardless of the bleeding risk of the elective dental procedure, when VKA therapy is interrupted, the INR is not routinely measured at the clinic prior to the procedure as discontinuation for several days in patients treated with the short acting acenocoumarol is sufficient to ensure adequately low INR levels.

Candidate predictors for oral cavity bleeding

Candidate predictors for oral cavity bleeding were selected beforehand based on literature and presumed clinical relevance.[1, 6] The following patient characteristics were analyzed: age, sex, intensity of VKA treatment, type of VKA, and quality of anticoagulation control prior to the procedure defined as percentage of time in therapeutic range (TTR in%). The TTR was calculated using the Rosendaal method for each patient from three months until one week prior to the procedure.[9] Potential predictors related to periprocedural management were: concomitant exposure to antiplatelet agents (thrombocyte aggregation inhibitors, non-steroidal anti-inflammatory drugs (NSAIDs), and selective serotonin reuptake inhibitors (SSRIs)), whether VKA treatment was interrupted, whether the last INR result at the clinic was ≤3.5, whether the procedure was reported at least 24 h in advance, and whether a valid INR-measurement was performed at the anticoagulation clinic within 72 h before the procedure. Since patients are differently managed depending on the classification as low-risk or high-risk procedure, we identified the predictors for bleeding separately according to the ACTA classification.

Study outcomes

Our primary outcome was clinically relevant oral cavity bleeding (OCB) within 30 days after the procedure. Bleedings were considered clinically relevant if these: 1) were spontaneously reported by the patient to the anticoagulation clinic apart from planned visits, 2) required a second intervention or alteration in medication, or 3) caused hospitalization or death. Minor bleedings such as small hematomas reported only during routine visits were not considered clinically relevant. Since patients at our thrombosis service are instructed at each visit to proactively report serious bleeding complications between appointments, we considered this definition an adequate cutoff for clinically relevant bleeding with a low chance of missing these bleedings.

Secondary outcomes were: clinically relevant non-oral cavity bleedings (NOCB) (using the previously mentioned definition for clinical relevance), objectified thromboembolic complications (transient ischemic attack, ischemic stroke, myocardial infarction or venous thrombosis), hospitalization (any), and all-cause mortality within 30 days. Two different investigators (JB, WR) independently classified all procedures as low-risk or high-risk and evaluated periprocedural management for each procedure. All outcome events were independently classified by physicians of the anticoagulation clinic as part of routine care and reviewed by both investigators.

Statistical analysis

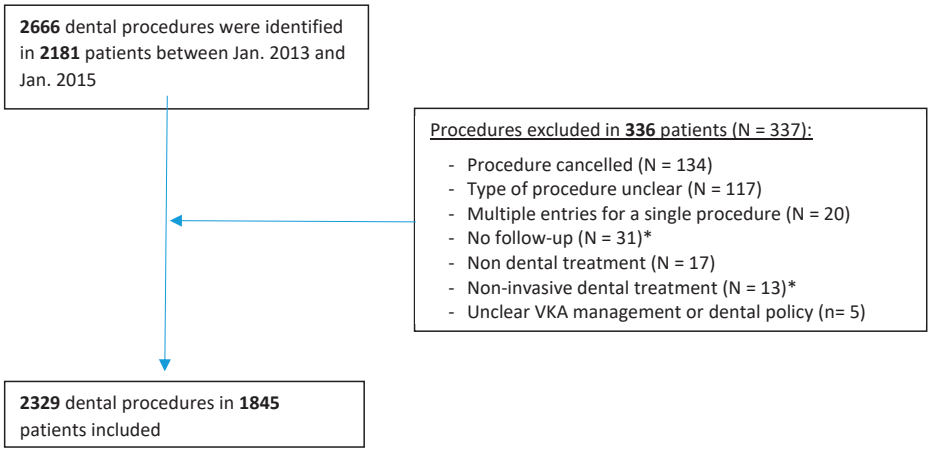
Standard descriptive statistics were performed to assess differences regarding patient characteristics, procedure characteristics, and clinical outcomes. Continuous covariates were compared between groups by Student's t-test in case of a normal distribution and by Mann Whitney-U test for non-normally distributed covariates. Proportions were compared by Chi-square test. For all clinical outcomes, 30-day event rates with 95% confidence intervals (CI) were calculated in line with recommendations for reporting procedure related outcomes.[10] Univariate logistic regression analysis and multivariate backward conditional logistic regression analysis were used to identify predictors of oral cavity bleeding after low-risk and high-risk procedures. Odds ratios (OR) with 95%CI were calculated and compared between different management strategies regarding the risk of oral cavity bleeding. We performed a sensitivity analysis including only the first procedure of each patient during the study period. If the second intervention was a re-intervention, it is conceivable that this could also affect the risk of bleeding and therefore influence the results. P-value for model inclusion in the backward logistic regression models was set at p=0.10. Statistics were performed using SPSS version 23.0 (IBM Corp., Armonk, NY, USA).

RESULTS

Study population

In total, 2666 dental procedures were identified, performed in 2181 patients between January 2013 and January 2015. Of these, 337 (14.1%) procedures performed in 336 patients were excluded for analysis for various reasons (Figure 1). After exclusion, 2329 procedures performed in 1845 patients were included for final analysis. Of these, 2004 (86.0%) were low-risk procedures and 325 (14.0%) high-risk procedures. Most patients (n=1457, 79.0%) underwent one procedure during the study period. Procedure and patient characteristics, overall and by procedure risk, are shown in Table 1.

Figure 1: Study flow chart



* E.g. annual check-up, prosthesis adjustments, radiographic imaging. n= number of procedures.

Low bleeding risk procedures

Of the 2004 low-risk procedures, 1540 (77.8%) were reported to the clinic at least 24 h in advance. In 1083/2004 (54.0%) procedures, a valid INR measurement was performed at the anticoagulation clinic within 72 h before the procedure. Treatment with VKA was continued in 1350/2004 (67.4%) procedures, of which 900/1350 (66.7%) with TXA mouthwash and 450/1350 (33.3%) without. Treatment with VKA was interrupted in 654/2004 procedures (32.6%), of which 246/654 (37.6%) were bridged with LMWH. Clinically relevant oral cavity bleeding within 30 days occurred in 67/2004 low-risk procedures (3.3%, 95%CI 2.6–4.2). Oral cavity bleeding rates, ordered by procedure risk and management strategy, are shown in Table 2. Oral cavity bleeding occurred significantly more often in patients using antiplatelet therapy (16/237, 6.8%), compared to non-users (51/1767, 2.9%) [P=0.002]. Overall, the bleeding risk

Table 1: Patient and procedure characteristics by procedure risk

	No. (%)			
	Overall	Low-risk	High-risk	P Value
Characteristic	**(n=2329)**	**(n=2004)**	**(n=325)**	**(low vs. High)**
Patient				
Age, median [IQR], years	73.0 [64.0-81.0]	73.0 [64.0-81.0]	73.0 [65.0-81.0]	0.254
Male sex	1297 (55.7)	1092 (54.5)	205 (63.1)	0.004
VKA treatment duration, median [IQR], years	4.4 [1.3-10.2]	4.4 [1.3-10.2]	4.5 [1.3-10.6]	0.537
VKA type				
Acenocoumarol	2156 (93.1)	1853 (92.5)	303 (93.2)	0.829
Phenprocoumon	173 (6.9)	151 (7.5)	22 (6.8)	
Treatment indication				
Atrial fibrillation	1442 (61.9)	1235 (61.6)	207 (63.7)	<0.001
Venous thrombosis	301 (12.9)	270 (13.5)	31 (9.5)	
Heart valve replacement	154 (6.6)	146 (7.3)	8 (2.5)	
Arterial thrombosis	418 (17.9)	341 (17.0)	77 (23.7)	
Prophylaxis	14 (0.6)	12 (0.6)	2 (0.6)	
Therapeutic INR range				
2.0-3.5	1855 (79.6)	1598 (79.7)	257 (79.1)	0.963
2.5-4.0	404 (17.3)	346 (17.3)	58 (17.8)	
Other	70 (3.0)	60 (3.0)	10 (3.1)	
TTR [IQR]	82.0 [60.6-100.0]	82.9 [61.5-100.0]	77.4 [53.8-95.7]	0.004
Procedure				
Type				
Tooth extraction of 1-3 elements	1403 (60.2)	1403 (70.0)	-	
Endodontic therapy	68 (2.9)	68 (3.4)	-	
Abscess incision	16 (0.7)	16 (0.8)	-	
Dental implant placement of 1-3 implants	118 (5.1)	118 (5.9)	-	
Scaling or root planning	259 (11.1)	259 (12.9)	-	
Tooth restoration	42 (1.8)	42 (2.1)	-	
Apex resection	16 (0.7)	16 (0.8)	-	
Wisdom tooth extraction	28 (1.2)	28 (1.4)	-	
Periodontal flap surgery	17 (0.7)	17 (0.8)	-	
Dental crown or bridge work	37 (1.6)	37 (1.8)	-	
Tooth extraction of >3 elements	296 (12.8)	-	296 (91.1)	
Dental implant placement of >3 implants	13 (0.6)	-	13 (4.0)	
Orthognathic surgery	16 (0.7)	-	16 (4.9)	

Table 1: Patient and procedure characteristics by procedure risk (*continued*)

	No. (%)			
	Overall	**Low-risk**	**High-risk**	**P Value**
Reported at least 24h in advance	1834 (78.7)	1540 (76.8)	294 (90.5)	<0.001
VKA interrupted for procedure	946 (40.6)	654 (32.6)	292 (89.8)	<0.001
Bridging with LMWH	397 (17.0)	246 (12.3)	151 (46.5)	<0.001
Tranexamic acid mouthwash prescribed	967 (41.5)	947 (47.3)	20 (6.2)	<0.001
Valid INR at clinic within 72h before procedure	1144 (49.1)	1083 (54.0)	61 (18.8)	<0.001
Last INR at clinic ≤ 3.5	1942 (83.4)	1658 (82.7)	284 (87.4)	0.037
Periprocedural exposure to antiplatelet drugs				
Platelet aggregation inhibitors (any)	282 (12.1)	237 (11.8)	45 (13.8)	0.300
Ascal	170 (7.3)	141 (7.0)	29 (8.9)	0.546
Clopidogrel	80 (3.4)	69 (3.4)	11 (3.4)	-
Dipyridamol	26 (1.1)	21 (1.0)	5 (1.5)	-
Prasugrel	6 (0.3)	6 (0.3)	-	-
NSAID	268 (11.5)	232 (11.6)	36 (11.1)	0.793
SSRI	141 (6.1)	122 (6.1)	19 (5.8)	0.865

IQR=Interquartile range, VKA=Vitamin K Antagonist, INR=International Normalized Ratio, TTR=Time in Therapeutic Range, LMWH=Low-Molecular-Weight Heparin, NSAID=Non-Steroid Anti-Inflammatory Drug, SSRI=Selective Serotonin Reuptake Inhibitor.

after continuation of VKA with TXA mouthwash was similar to VKA interruption without bridging [OR 1.44, 95%CI 0.62–3.64]. Continuation of VKA with TXA mouthwash was, however, associated with a lower bleeding risk compared to VKA continuation without TXA mouthwash [OR=0.41, 95%CI 0.23–0.73] or VKA interruption with bridging [OR=0.49, 95%CI 0.24–1.00]. When VKA therapy was interrupted (n=654), bridging was associated with an increased bleeding risk compared to forgoing bridging [OR=2.94, 95%CI 1.14–7.57] (Table 2). Sensitivity analysis revealed similar results (Table 2).

Backward conditional modelling revealed that bridging therapy [OR 3.19, 95%CI 1.22–8.35], a missing [OR 1.90, 95%CI 1.10–3.28] or supra-therapeutic INR [OR 1.75, 95%CI 0.98–3.12] before the procedure, procedures that were not reported to the clinic in advance [OR 2.60, 95%CI 1.52–4.46] and concomitant exposure to thrombocyte aggregation inhibitors [OR 2.40, 95%CI 1.33–4.32] were the factors most strongly associated with an increased risk of oral cavity bleeding (Table 3).

High bleeding risk procedures

Of the 325 high-risk procedures, 294 (90.5%) were reported to the clinic at least 24 h in advance. Most high-risk procedures (n=296, 91.1%) were extractions of more than three elements (Table 1). VKA therapy was interrupted in 292/325 (89.8%) of these procedures, of which 151/292 (51.7%) were bridged with LMWH. Clinically relevant oral cavity bleeding within 30 days occurred in 21/325 (6.5%, 95%CI 4.27–9.68) of these procedures (Table 2). Oral cavity bleeding rates were significantly higher in patients using NSAIDs (6/36, 16.7%) compared to non-users (15/289, 5.2%) [p=0.008].

Overall, VKA continuation was associated with a significantly higher bleeding risk compared to VKA interruption [OR 3.08, 95%CI 1.05–9.04]. When VKA was interrupted, bridging with LMWH was not associated with a significantly higher bleeding risk compared to forgoing bridging [OR 1.60, 95%CI 0.56–4.51]. Sensitivity analysis revealed similar results (Table 2). Backward conditional modelling revealed that exposure to NSAIDs [OR 4.10, 95%CI 1.38–12.20] and a missing INR before the procedure [OR 5.25, 95%CI 0.92–30.11] were associated with an increased risk of bleeding for high-risk procedures, while VKA interruption strongly lowered the risk of bleeding [OR 0.14, 95%CI 0.03–0.58] (Table 3).

Table 2. Oral cavity bleeding within 30 days by procedure risk and management strategy

	No. of bleeding / Total No. (%)					
	VKA continuation			VKA interruption		
	Without TXA	With TXA	OR (95%CI)	Without Bridging	With Bridging	OR (95%CI)
All procedures						
Low-Risk (n=2004)	26/450 (5.8%)	22/900 (2.4%)	0.41 (0.23-0.73)	7/408 (1.7%)	12/246 (4.9%)	2.94 (1.14-7.57)
High-Risk (n=325)	4/23 (17.4%)	1/10 (10.0%)	0.53 (0.05-5.43)	6/141 (4.3%)	10/151 (6.6%)	1.60 (0.56-4.51)
Overall (n=2329)	30/473 (6.3%)	23/910 (2.5%)	0.38 (0.22-0.67)	13/549 (2.4%)	22/397 (5.5%)	2.42 (1.20-4.86)
Sensitivity analysis [a]						
Low-Risk (n=1597)	21/365 (5.8%)	15/729 (2.1%)	0.34 (0.18-0.68)	5/315 (1.6%)	9/188 (4.8%)	3.12 (1.03-9.45)
High-Risk (n=248)	4/20 (20.0%)	0/7 (0.0%)	-	4/106 (3.8%)	9/115 (7.8%)	2.17 (0.65-7.25)
Overall (n=1845)	25/385 (6.3%)	15/736 (2.5%)	0.30 (0.16-0.58)	9/421 (2.1%)	18/303 (5.9%)	2.89 (1.28-6.53)

VKA=Vitamin K Antagonist, TXA=Tranexamic acid mouthwash, LMWH=Low-Molecular-Weight Heparin, OR=Odds Ratio, CI=Confidence Interval

[a] First procedure from each patient

Table 3. Predictors of oral cavity bleeding by procedure risk

	Beta	*OR (95%CI)*
Low-risk (n=2004)		
Bridging with LMWH	1.159	3.19 (1.22 - 8.35)
Exposure to platelet aggregation inhibitor	0.874	2.40 (1.33 - 4.32)
No valid INR before procedure	0.641	1.90 (1.10 - 3.28)
Last INR at clinic >3.5	0.557	1.75 (0.98 - 3.12)
Procedure not reported in advance	0.956	2.60 (1.52 - 4.46)
VKA interruption	-0.880	0.42 (0.18 - 0.96)
Time in therapeutic range (per percent increase)	0.010	1.01 (1.00 - 1.02)
High-risk (n=325)		
Exposure to NSAID	1.411	4.10 (1.38 - 12.20)
VKA interruption	-1.992	0.14 (0.03 - 0.58)
No valid INR before procedure	1.658	5.25 (0.92 - 30.11)
Age at procedure (per year increase)	0.046	1.05 (1.00 - 1.09)
Time in therapeutic range (per percent increase)	-0.018	0.98 (0.97 - 1.00)

Backward conditional logistic regression model. OR=Odds Ratio, INR=International Normalized Ratio; NSAID=Non-Steroidal Anti-Inflammatory Drug; LMWH=Low-Molecular-Weight Heparin, VKA= Vitamin K Antagonist

Secondary clinical outcomes

Clinically relevant non-oral cavity bleeding within 30 days occurred in 50/2329 procedures (2.1%, 95%CI 1.6–2.8%). Of these bleedings, one was an intracranial bleeding (2%), four were gastrointestinal bleedings (8%), three patients reported hematuria (6%), three bleedings were of vaginal origin (6%). All other bleedings were cutaneous bleedings (30/50, 60%) or nose bleedings (9/50, 18%).

The bleeding rates after low-risk (41/2004, 2.0%) and high-risk (9/325, 2.8%) procedures were similar [p=0.40]. Non-oral cavity bleeding occurred more often after procedures that were bridged with LMWH (14/397, 3.5%) compared to those where VKA therapy was continued or interrupted without bridging (36/1932, 1.9%) [p=0.04]. Bridging therapy was associated with an almost two-fold increased risk of non-oral cavity bleeding compared to VKA continuation or interruption without bridging [OR 1.93, 95%CI 1.03–3.60]. After correction for age, sex, treatment intensity, indication, TTR percentage, treatment duration and use of antiplatelet drugs, perioperative bridging remained significantly associated with an increased non-oral cavity bleeding risk [OR 2.18, 95%CI 1.14–4.16].

A thromboembolic event within 30 days occurred in 5/2329 procedures (0.2%, 95%CI 0.1–0.5%). Of these thromboembolic events, three occurred after a low-risk (3/2004, 0.1%) and two after a high-risk procedure (2/325, 0.6%) [p=0.09]. Three occurred after VKA continuation (3/1383, 0.2%) and two after a procedure for which VKA therapy was interrupted (2/946, 0.2%) [p=0.98]. Of the latter two events, one occurred in the non-bridging group (1/549, 0.2%) and the other in the bridging group (1/397, 0.3%) [p=0.82].

Hospitalization within 30 days occurred in 100/2329 procedures (4.3%, 95%CI 3.5–5.2). Reasons for hospitalization were: intracranial bleeding (1/100), ischemic event (6/100), post-dental treatment hemorrhage (8/100), and 85/100 were unrelated to dental treatment or perioperative management. A fatal event within 30 days occurred in 5/2329 procedures (0.2%, 95%CI 0.1–0.5). None of these were related to the dental procedure or management.

DISCUSSION

We evaluated the periprocedural management and clinical outcome after dental procedures in patients on VKA, in a real-world setting, and identified predictors for post-procedural oral cavity bleeding. Depending on the procedure risk, we observed an oral cavity bleeding rate of 3% after low-risk procedures and 6% after high-risk procedures. These rates are in accordance with previously reported bleeding rates.[1, 3, 11] In contrast to international guidelines, the ACTA guideline incorporates the number of teeth involved in the procedure as a factor for bleeding risk. A previous study in 439 patients on VKA showed that for every extra extracted tooth the risk of bleeding increased by 28%.[12] We also observed differences in bleeding rates after low-risk and high-risk procedures, which suggest that it is justifiable to categorize dental procedures accordingly. The specification of the number of teeth (1–3 low-risk, >3 high-risk) makes it easier for the dental practitioner and anticoagulation clinics to assess the bleeding risk of the procedure, which should be incorporated in decision making regarding periprocedural VKA management.[5, 7]

In our study, patient-related factors associated with an increased risk of bleeding were: increasing age (high-risk procedures) and concomitant exposure to antiplatelet therapy (low-risk procedures) or NSAIDs (high-risk procedures), which have also been reported in previous studies.[1, 13] Therapeutic quality control (e.g. lower TTR %) was not associated with an increased bleeding risk in our multivariate models, irrespective of the procedure risk, making it unlikely that TTR differences could explain the dif-

ference in bleeding risk between high-risk and low-risk procedures. Despite the well-known increased risk of bleeding associated with NSAID use[14], dental practitioners often prescribe these drugs for management of dental pain and swelling. Based on guideline recommendations[15] and our own findings, we discourage the use of NSAIDs for pain relief after invasive dental treatment, especially after high-risk procedures, in patients using VKA.

Considering periprocedural VKA management, like prior studies[16-18], our results indicate that VKA can be continued safely in low-risk procedures, in combination with a local prohemostatic agent, provided that the INR is at a therapeutic level before the procedure, since a supra-therapeutic INR before the procedure (INR>3.5) or absence of an objectified INR from the clinic within 72 h before the procedure, were independent predictors for bleeding. Furthermore, our data clearly indicates a risk reduction (approximately 50%) of bleeding when TXA mouthwash is prescribed during VKA continuation. The exact effect of TXA has been a point of discussion. Some studies[18, 19], reported a lower bleeding rate when used after dental procedures, while another[20], found no differences in bleeding between exposure groups. Most of these studies were relatively small though, with heterogeneous periprocedural management and with very few bleeding complications, thus likely to be underpowered to find differences in outcomes between exposures if present.

In low-risk procedures, the risk of oral cavity bleeding was lower in patients who continued VKA treatment in combination with TXA compared to those bridged with LMWH, but similar compared to patients in whom VKA therapy was interrupted without bridging therapy. In one-third of the low-risk procedures, VKA therapy was temporarily interrupted where it should have been continued according to the guidelines. The most likely explanation for this finding is that anticoagulation clinics interrupt VKA therapy if deemed necessary by the dental practitioner. Assuming that the anticoagulation clinic will guard the thromboembolic safety of the patient, the dental practitioner often advocates an INR as low as possible before invasive treatment to prevent bleeding.[21] On the other hand, anticoagulation clinics assume that the low INR is necessary to prevent bleeding and try to meet the request of clinicians by interrupting VKA therapy. On a population level, this causes heterogeneous VKA-management, and in the end exposes a part of the patients to a higher bleeding risk if bridging therapy is initiated. Clear communication between dental practitioners and anticoagulation clinics is therefore required before deviating from management guidelines.

For high-risk procedures, we advise to interrupt VKA treatment and to avoid the use of NSAIDs as analgesics. The beneficial effect of TXA mouthwash was not statistically

significant in high-risk procedures, likely due to a lack of power. We suggest that, in line with low-risk procedures, its use may lower the bleeding risk and should be considered regardless of management strategy.

Another important observation is that where VKA therapy was interrupted, bridging therapy was initiated by the anticoagulation clinic in a substantial proportion of both the low-risk (~1/3) and high-risk (~1/2) procedures. A previous study, evaluating both dental and other surgical procedures (n=222), showed that in daily practice adherence to bridging guidelines at anticoagulation clinics is suboptimal and LMWH therapy is frequently initiated without a proper indication.[22] Furthermore, these authors even concluded that the decision for bridging was often not based on the thromboembolic risk of the patient or the bleeding risk of the procedure, despite the increased bleeding risk associated with bridging.[22] We also found an increased risk of clinically relevant oral and non-oral bleeding associated with bridging therapy, and very low thromboembolic event rates, irrespective of the procedure risk or chosen management strategy. Since it has been shown that perioperative bridging therapy is associated with an increased risk of bleeding without lowering the risk of thromboembolic events[23-25], we advise that bridging should be kept to a minimum and only used in patients at the highest risk of thromboembolic complications during VKA interruption, such as recent stroke or venous thromboembolism, mechanical mitral valves and isolated atrial fibrillation with CHA_2DS_2-Vasc >7), in accordance with the Dutch guideline.[26]

It is expected that direct oral anticoagulants will increasingly replace VKA for the majority of patients requiring anticoagulation therapy. Due to their predictable pharmacokinetics, rapid onset of action, and short half-lives, these drugs can be interrupted for a shorter time than VKA and require no bridging with LMWH during interruption, irrespective of the patient's thrombotic risk.[26] Although this simplifies perioperative management, dental surgeons and dentists should be aware of direct oral anticoagulants (DOAC) use by their patients and take adequate precautions to prevent bleeding in case of DOAC continuation.

Strengths and limitations

An important strength of our study is the large number of included dental procedures, which allowed us to compare clinical outcomes after different management strategies in both low and high bleeding risk procedures. The fact that these procedures were not performed in a trial setting enhances the generalizability of our findings. It is estimated that one in every six patients on chronic anticoagulant therapy is annually

assessed for periprocedural VKA management for an elective procedure, which illustrates the importance of our findings beyond only dental procedures.[6]

A few limitations of our study should be mentioned. First, we had no data on local dental influences that may affect the risk of oral cavity bleeding, such as the condition of the extracted teeth, the state of the surrounding gums, and local prohemostatic measures undertaken by the dentist or oral surgeon to prevent bleeding (e.g. proper sutures).[1] This impaired us to correct our models for these potential confounding factors. However, these factors are usually not communicated between dental practitioners and anticoagulation clinics, and it is safe to assume that dental practitioners always try to achieve primary hemostasis during treatment, making our results representative for daily practice. To specifically relate these local factors to clinical outcome, in combination with the perioperative management strategy, a prospective study should be conducted in which both anticoagulation clinics, dentists and oral surgeons provide the required information. Second, given the retrospective study design and use of administrative data, we cannot definitively exclude the possibility of omission or misclassification of procedures and outcomes. We minimized the risk of misclassification by manually checking individual patient files independently by two investigators and by excluding procedures if these were inadequately described. In case of omission of bleeding events, it is unlikely that these bleedings are systemically related to a specific dental procedure or management strategy. Therefore we deem the chance of significant bias of our results due to the omission of bleeding events as low.

CONCLUSIONS

Most predictors of oral cavity bleeding were specifically related to periprocedural management and differed between low-risk and high-risk dental procedures, justifying different bleeding risk categories. Our observations emphasize the importance of adherence to VKA management guidelines, in which dental procedures should be categorized into low-risk and high-risk, each with specific perioperative management strategies. Overall, the concomitant use of NSAIDs during dental treatment as analgesics should be avoided. VKAs can safely be continued in low-risk dental procedures in combination with tranexamic acid mouthwash provided that the INR≤3.5. In high-risk procedures, VKA should be interrupted and combined with tranexamic acid mouthwash. Bridging should only be applied in patients at highest risk of thromboembolic complications.

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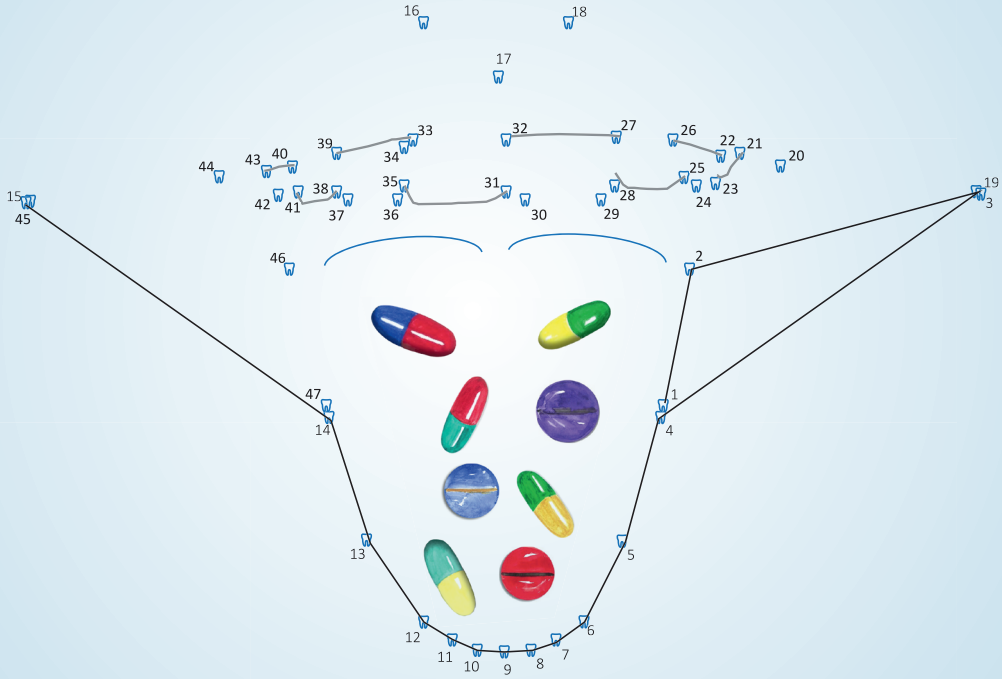
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4 Bleeding risk after third molar removal in healthy patients; a multi-center prospective observational clinical trial

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Submitted

ABSTRACT

Third molar removal in healthy patients is considered as a procedure with a low bleeding risk. However, studies on the incidence of postoperative bleeding after (surgical) third molar removal in healthy patients are heterogeneous. Therefore, an observational multicenter trial was conducted to assess the postoperative bleeding risk and associated risk factors.

Our study cohort included 1877 patients, of which 1035 with a complete follow-up. Of these, 329 patients (31.8%) reported a postoperative bleeding but did not consult the practitioner. Only 15 patients (1.5%) were advised to visit the hospital for clinical examination of which eight patients (0.8%) required minimal invasive treatment (e.g. suturing). No patients required hospital admission. An increased age was associated with a slightly decreased risk of any type of postoperative bleeding [OR 0.97, 95%CI 0.95-0.99]. Surgical removal was associated with an increased risk for any type of postoperative bleeding [OR 1.68, 95%CI 1.13-2.52].

There was a clear difference between the incidence of bleeding reported by patients and bleeding that required clinical examination and/or treatment. Patients should therefore receive detailed information on benign symptoms after third molar removal in order to reduce this difference. Overall, the incidence of postoperative bleeding was low.

INTRODUCTION

The removal of a third molar (M3) is a treatment performed by both dentists and Oral Maxillofacial Surgeons (OMS), and is commonly indicated for symptomatic M3s.[1] Prophylactic M3 removal is often indicated in order to prevent associated pathology, such as pericoronitis, decay in the second molar or cysts formation.[2, 3] Consequently, approximately ten million M3 removals are performed every year in the United States alone.[4] The most frequently reported short term adverse effects of M3 removal are pain, swelling, alveolar osteitis, infection, nerve damage and postoperative bleeding.[5]

A number of studies describe incidences of postoperative bleeding after M3 removal in healthy patients, with incidences ranging from 0 to 61.3%.[6-19] This wide range is mainly due to differences in study design and differences in the definition of postoperative bleeding. A lower incidence (0-0.97%) of postoperative bleeding was reported when the bleeding was diagnosed by a healthcare professional after clinical examination.[6, 11, 14, 18, 19] Incidences of self-reported postoperative bleeding by patients alone ranged between 4.2 - 61.3%.[7, 12, 14, 17] However, none of these studies were primarily designed to assess postoperative bleeding incidences after M3 removal, thereby making them unsuitable to accurately determine postoperative bleeding incidence. Furthermore, most of the studies did not include a sufficient number of patients to provide the statistical power needed to reliably report postoperative bleeding incidences.

A reliable incidence rate of postoperative bleeding is necessary when informing patients prior to dental treatment, especially if the treatment is considered prophylactic, as is often the case in M3 removal. Accurate incidence rates of postoperative bleeding in healthy patients are also essential in the development of guidelines on reducing postoperative bleeding complications in patients with risk factors, for example in patients using antithrombotic drugs, as this incidence serves as the baseline of postoperative bleeding.

Therefore, the aim of this study was to provide accurate data on the incidence of both patient reported postoperative bleeding and clinically examined postoperative bleeding after third molar removal in healthy patients. Furthermore, we investigated whether any risk factors for postoperative bleeding after M3 removal could be identified.

MATERIALS AND METHODS

Between 2016 and 2018, a multicenter prospective observational trial was conducted at the Departments of Oral and Maxillofacial Surgery of one teaching-hospital (Amsterdam Medical Center) and four non-teaching hospitals in the Netherlands. The trial was registered in the Dutch trial register (NL5730/NTR5917).[20] The medical ethical review board of the Free University Medical Center in Amsterdam provided a waiver.

Selection of patients

The indication for M3 removal was based on the Dutch clinical guideline 'The third molar'.[21] This guideline recommends removing symptomatic M3s in all patients and removing asymptomatic M3s that are partially erupted due to angulation (horizontal, mesioangular or distoangular) in patients between 25-30 years of age. Healthy patients of all ages were eligible for inclusion. Patients were considered healthy if they: 1) did not use any prescribed medication, 2) were not diagnosed with a systemic disease, and 3) had not taken any medication that could affect hemostasis in the 10 days prior to treatment (i.e. non-steroidal anti-inflammatory drugs; NSAIDs). Patients were excluded if they: 1) were pregnant, 2) could not give informed consent, 3) were unable to read and write in Dutch, 4) were treated under sedation or general anesthesia, or 5) had teeth other than the third molars removed during the same procedure.

Treatment procedures

All procedures were conducted in outpatient surgery units and carried out under local anesthesia (articaine/epinephrine 1:100.000) by an OMS or an OMS resident. The M3s could either be removed non-surgically using a dental elevator and/or forceps, or surgically by mucoperiostal flap elevation, alveolectomy or sectioning of the molar. Either primary wound closure using local hemostatic measures (e.g. Spongostan®, Surgicel®) and/or suturing, or secondary wound closure was performed (without suturing). Postoperative measures included gauze compression for 30 minutes and the prescription of analgesics and/or antibacterial mouth rinse. The OMS or OMS resident based the choice of treatment on the individual situation of the patient.

Study design and variables

After inclusion patients underwent M3 removal. Immediately thereafter, the first questionnaire (Q1), with questions about the details of the performed procedure was filled in by the OMS or OMS resident. One week after M3 removal, patients were sent an e-mail asking them to complete a questionnaire (Q2) with questions about the postoperative period. If the patient did not reply, a reminder was sent 10 and 13 days after the initial treatment. If no reply followed after two reminders the patient was

considered lost to follow-up and excluded. If Q1 was missing, the patient was also excluded.

When the patient contacted the hospital by phone during the period between Q1 and Q2 because of bleeding complications, the OMS or OMS resident determined if clinical examination at the outpatient clinic was indicated. If so, the OMS and OMS residents were instructed to fill in a third questionnaire (Q3) which was designed to objectify the severity of the postoperative bleeding. In case of missing data on Q3, medical records were analyzed retrospectively.

Primary outcome variables were the incidence of patient reported postoperative bleeding, clinically examined postoperative bleeding, and treatment required to stop the bleeding. Secondary outcome variables were patient characteristics (e.g. demographics and intraoral health status), treatment characteristics (e.g. surgical procedure and postoperative hemostatic measures), and postoperative treatment and instructions (e.g. use and type of analgesics or antiseptic mouth rinse).

To categorize the degree of postoperative bleeding a classification of postoperative bleeding was developed (Table 1). The classification is based on the measures taken by the patient to stop the bleeding, the effectiveness of these measures and, if necessary, the treatment carried out by the OMS or OMS resident to stop the bleeding.

Table 1. Classification of postoperative bleeding

Type of bleeding	Definition
Type I (patient reported)	Patient retrospectively self-reported postoperative bleeding, but did not consult a healthcare professional at the time of the postoperative bleeding.
Type II (patient reported)	Consultation with and instructions of a healthcare professional by phone/e-consult was sufficient to treat the postoperative bleeding. No clinical examination or treatment by a healthcare professional was required.
Type III (clinically examined)	Consultation with a healthcare professional by phone/e-consult was **not** sufficient to treat the postoperative bleeding. Clinical examination by a healthcare professional was required. However, after clinical examination **no** treatment [a] by a healthcare professional to achieve hemostasis was required.
Type IV (clinically examined)	Consultation with a healthcare professional by phone/e-consult was **not** sufficient. Clinical examination and treatment [a] by a healthcare professional to achieve hemostasis was required.
Type V (clinically examined)	Hospital admission was required for the treatment of the postoperative bleeding
a (re)suturing of the wound, with or without local hemostatic material, and/or application or prescribing of tranexamic acid 5% was sufficient to achieve hemostasis on clinical examination.	

Statistical methods

Our power analysis was based on the results of the study by Haug et al.[6], which reported an incidence of <0.1% for postoperative bleeding after M3 removal in healthy patients. It was assumed that a minimum of 1000 patients with a full follow-up (Q1+Q2) was sufficient to investigate the primary outcome variables.

Standard descriptive statistics were performed to analyze information on procedure characteristics, patient characteristics and clinical outcomes. Univariate binary regression analysis was used to assess the association between each predictor and outcome. If the P-value was <0.05 the predictor was included in a subsequent multivariate binary logistic regression analysis with backward selection (entrance P<0.05 and removal P>0.10). Statistics were performed using SPSS version 26.0 (IBM Corp., Armonk, NY, USA). Complete-case analysis was used for all the analyses.

RESULTS

A total of 1877 patients were included in this study. In 842 patients (44.9%) only Q1 was collected. Table 2 shows the treatment characteristics of all patients with at least Q1. Complete follow-up (Q1 and Q2) was achieved in 1035 patients (55.1%). Table 3 presents the demographic and treatment characteristics of these patients.

Of the 1035 patients, a postoperative bleeding of any type (type I, II, III, IV or V) was reported in 386 patients (37.3%; Table 3). 329 patients (31.8%) reported a postoperative bleeding but did not consult a healthcare professional (type I), 42 patients (4.0%) consulted an OMS or OMS resident but were not required to visit the hospital for clinical examination (type II). In total, 15 patients (1.5%) were advised to visit the hospital for clinical examination. In 7 patients (0.7%) counseling and gauze applications were sufficient to stop the bleeding (type III). Only 8 patients (0.8%) required additional invasive treatment (type IV). One patient was treated with a hemostasis promoting wound dressing (Surgicel®) and received a prescription for tranexamic acid 5% oral rinse, three patients were treated only with a hemostasis promoting wound dressing (Surgicel®), one patient required suturing and received a prescription for tranexamic acid 5% oral rinse, one patient required only suturing, and two patients only received a prescription for tranexamic acid 5% oral rinse. No patients were admitted to the hospital for treatment (type V).

In 250 of the 386 patients (64.8%), the bleeding occurred on the same day of the procedure, in 61 patients (15.8%) the bleeding occurred the day after treatment, in

Table 2. Characteristics of procedure in all patients based on Q1 questionnaires

	N	%
Total number of patients with at least a Q1 questionnaire	1877	100%
Procedure performed by:		
- Oral Maxillofacial Surgeon	1277	68.0%
- Senior resident	377	20.1%
- Junior resident	146	7.8%
- Intern	29	1.5%
- Unknown	48	2.6%
Element(s) removed		
- 18	73	3.9%
- 28	85	4.5%
- 38	316	16.8%
- 48	356	19.0%
- 18 and 28	48	2.6%
- 28 and 38	443	23.6%
- 38 and 48	10	0.5%
- 18 and 38	2	0.1%
- 28 and 48	13	0.7%
- 18 and 48	437	23.3%
- 18, 28 and 38	23	1.2%
- 28, 38 and 48	2	0.1%
- 18, 38 and 48	1	0.1%
- 18, 28 and 48	18	1.0%
- 18, 28, 38 and 48	1	0.1%
Surgical removal[a]	1457	77.6%
Time of procedure in minutes (SD, range)	7.90 (5.58, 1 – 45)	
Bleeding perioperatively more than usual (reported by OMF)	106	5.6%
Pericoronitis of removed element(s)	537	28.6%
Poor oral hygiene	138	7.4%
Complications during procedure leading to extra bleeding	23	1.2%
Postoperative gauze compression	1801	96.0%
Additional measures undertaken to improve hemostasis	1570	83.6%
- Suturing	1557	83.0%
- Spongostan®	29	1.5%
- Surgicel®	4	0.2%
- HemCon®	0	
- Electrocoagulation	1	0.1%
Hospital		
- University hospital	510	27.2%
- Non-university hospital	1367	72.8%

SD = Standard Deviation; [a] If either incision, creation of mucoperiosteal flap, alveotomy, dividing, and/or decapitating was required to remove a molar, the procedure was considered a surgical removal; if this was not required, the procedure was considered a non-surgical extraction

27 patients (7.0%) two days after treatment and in 39 patients (10.1%) three days or more after treatment, of which 9 patients (2.3%) reported that the bleeding occurred after 7 days. Nine patients could not recall how many days after treatment the bleeding occurred. In 171 patients (44.3%) the bleeding occurred spontaneously, in 38 patients (9.8%) during eating or drinking, in 33 patients (8.5%) during tooth brushing and in 24 patients (6.2%) during mouth rinsing. Ten patients (2.6%) reported that the bleeding had simply never stopped after M3 removal. 110 patients (28.6%) reported other causes (e.g. sporting, smoking). On average, patients reported that the postoperative bleeding stopped after 3.19 hours (standard deviation ± 8.07, range 0.02 – 72 hours). Five patients reported a postoperative bleeding that was active for more than 24 hours.

Overall, in 14 of the 1877 patients (0.7%) who underwent M3 removal a complication occurred during treatment. The complications were: tooth fracture of adjacent tooth (n=3), rupture of a connected odontogenic cyst (n=1), rupture of the mucous tissue (n=1), fracture of the maxillary tuberosity (n=1), a visible inferior alveolar nerve after extraction (n=3) and the presence of an oroantral communication after extraction (n=5).

Due to the small number of patients per type of bleeding the postoperative bleedings were combined into the categories “no bleeding” (type 0) and “any type of bleeding” (type I-V) for the purpose of regression analysis. Table 4 presents the results of the univariate binary logistical regression analysis. Multivariate binary regression analysis with backward selection revealed a statistically significant decrease in risk of postoperative bleeding with increasing age (OR = 0.969, 95%CI [0.951 – 0.987], p = .001) and a statistically significant increased risk of postoperative bleeding when M3s were surgically removed (OR = 1.686, 95%CI [1.130 – 2.515], p = .01).

DISCUSSION

The main goal of this study was to provide a baseline incidence of postoperative bleeding after M3 removal in healthy patients. We found an incidence of postoperative bleeding of 37.3%. Most of these postoperative bleedings (31.8%) were self-reported and did not require contact with or treatment by an OMS or OMS resident. Only 0.8% of the patients required a minimally invasive intervention. None required hospital admission.

Table 3. Characteristics of patients with complete follow-up (Q1 and Q2)

	No bleeding		Type I		Type II		Type III		Type IV		Type V		Total	
Number of patients with at least Q1 and Q2	649	62.7%	329	31.8%	42	4.0%	7	0.7%	8	0.8%	0	0.0%	1035	100.0%
Gender														
Male	257	39.6%	141	42.9%	12	28.6%	3	42.9%	7	87.5%	0		420	40.6%
Female	392	60.4%	188	57.1%	30	71.4%	4	57.1%	1	12.5%	0		615	59.4%
Age in years: mean (SD, range)	27.1 (8.87, 10 - 69)		24.6 (7.80, 12 - 75)		24.8 (8.20; 17 - 54)		23.0 (2.77, 19 - 28)		25.4 (6.52, 18 - 40)				26.2 (8.55, 10 - 75)	
Ethnicity														
Dutch	573	88.3%	288	87.5%	34	81.0%	6	85.7%	7	87.5%	0		908	87.7%
Surinam	30	4.6%	12	3.6%	3	7.1%	0		0		0		45	4.3%
Moroccan	5	0.8%	2	0.6%	1	2.4%	0		0		0		8	0.8%
Turkish	3	0.5%	2	0.6%	1	2.4%	0		0		0		6	0.6%
Indonesian	3	0.5%	1	0.3%	0		0		0		0		4	0.4%
Antillean	10	1.5%	3	0.9%	0		0		1	12.5%	0		14	1.4%
Chinese	3	0.5%	2	0.6%	1	2.4%	0		0		0		6	0.6%
Other, non-Western	13	2.0%	14	4.3%	1	2.4%	1	14.3%	0		0		29	2.8%
Other, Western	9	1.4%	5	1.5%	1	2.4%	0		0		0		15	1.4%
Tabacco smoking	114	17.6%	63	19.1%	11	26.2%	2	28.6%	4	50.0%	0		194	18.7%
If smoking, average number of cigarettes per day (SD, range)	8.9 (5.87, 1 - 25)		8.6 (5.70, 1 - 23)		11.0 (9.25, 1 - 25)		7.5 (3.54, 5 - 10)		6.5 (4.04, 3 - 10)				8.8 (5.98, 1 - 25)	
M3 removal by														
OMS	441	68.0%	213	64.7%	25	59.5%	6	85.7%	6	75.0%	0		691	66.8%
Senior resident	133	20.5%	73	22.2%	12	28.6%	1	14.3%	2	25.0%	0		221	21.4%
Junior resident	52	8.0%	36	10.9%	3	7.1%	0		0		0		91	8.8%
Intern	6	0.9%	4	1.2%	1	2.4%	0		0		0		11	1.1%

Table 3. Characteristics of patients with complete follow-up (Q1 and Q2) (*continued*)

	No bleeding		Type I		Type II		Type III		Type IV		Type V	Total	
Unknown	17	2.6%	3	0.9%	1	2.4%	0		0		0	21	2.0%
Element(s) removed													
18	34	5.2%	11	3.3%	1	2.4%	0		0		0	45	4.4%
28	42	6.5%	7	2.1%	0		0		0		0	49	4.7%
38	104	6.5%	59	17.9%	6	14.3%	0		2	25.0%	0	171	16.5%
48	128	16.0%	48	14.6%	6	14.3%	1	14.3%	1	12.5%	0	184	17.8%
18 and 28	20	3.1%	9	2.7%	0		0		0		0	29	2.8%
28 and 38	143	22.0%	86	26.1%	10	23.8%	2	28.6%	3	37.5%	0	224	23.6%
38 and 48	3	0.5%	4	1.2%	0		0		0		0	7	0.7%
18 and 38	0		1	0.3%	0		0		0		0	1	0.1%
28 and 48	4	0.6%	4	1.2%	2	4.8%	0		0		0	10	1.0%
18 and 48	141	21.7%	91	27.7%	15	35.7%	4	57.1%	2	25.0%	0	253	24.4%
18, 28 and 38	8	1.2%	2	0.6%	0		0		0		0	10	1.0%
28, 38 and 48	0		0		0		0		0		0	0	
18, 38 and 48	1	0.2%	0		0		0		0		0	1	0.1%
18, 28 and 48	6	0.9%	3	0.9%	1	2.4%	0		0		0	10	1.0%
18, 28, 38 and 48	0		1	0.3%	0		0		0		0	1	0.1%
Surgical removal	494	76.1%	283	86.0%	36	85.7%	6	85.7%	8	100.0%	0	827	79.9%
Mean time of procedure in minutes (SD, range)	7.57 (5.9, 1 - 45)		8.69 (5.7, 1 - 45)		9.83 (5.0, 2 - 25)		8.00 (4.0, 3 - 15)		10.00 (6.6, 4 - 25)			8.04 (5.9, 1 - 45)	
Bleeding perioperatively more than usual (reported by healthcare professional)	36	5.5%	22	6.7%	2	4.8%	0		1	12.5%	0	61	5.9%
Pericoronitis of removed element(s)	182	28.0%	95	28.9%	6	14.3%	5	71.4%	4	50.0%	0	292	28.2%
Poor oral hygiene	47	7.2%	15	4.6%	2	4.8%	0		0		0	64	6.2%

Table 3. Characteristics of patients with complete follow-up (Q1 and Q2) (*continued*)

	No bleeding		Type I		Type II		Type III		Type IV		Type V	Total	
Complications possibly leading to extra bleeding	9	1.4%	2	0.6%	3	7.1%	0		0		0	14	1.4%
Postoperative gauze compression	621	95.7%	319	97.0%	41	97.6%	7	100.0%	8	100.0%	0	996	96.2%
Additional measures undertaken to improve hemostasis	523	80.6%	295	89.7%	38	90.5%	6	85.7%	6	75.0%	0	868	83.9%
Suturing	519	80.0%	293	89.1%	36	85.7%	6	85.7%	4	50.0%	0	858	82.9%
Spongostan®	8	1.2%	6	1.8%	2	4.8%	0		1	12.5%	0	17	1.6%
Surgicel®	0		2	0.6%	0		0		1	12.5%	0	3	0.3%
HemCon®	0		0		0		0		0		0	0	
Electrocoagulation	1	0.2%	0		0		0		0		0	1	0.1%
Use of analgesics postoperatively	560	86.3%	293	89.1%	41	97.6%	6	85.7%	8	100.0%	0	908	87.7%
Paracetamol	150	23.1%	62	18.8%	7	16.7%	1	14.3%	0		0	220	21.3%
NSAIDs	363	55.9%	199	60.5%	26	61.9%	4	57.1%	6	75.0%	0	598	57.8%
Opiates/opioids	5	0.8%	4	1.2%	1	2.4%	0				0	10	1.0%
Paracetamol and NSAIDs	39	6.0%	26	7.9%	6	14.3%	1	14.3%	1	12.5%	0	73	7.1%
Paracetamol and opiates/opioids	2	0.3%	0		0		0		0		0	2	0.2%
Paracetamol, NSAIDs and opiates/opioids	0		1	0.3%	1	2.4%	0		0		0	2	0.2%
NSAIDs and opiates/opioids	0		0		0		0		1	12.5%	0	1	0.1%
Smoking cannabis	0		1	0.3%	0		0		0		0	1	0.1%
Unknown	90	13.9%	36	10.9%	1	2.4%	1	14.3%	0		0	128	12.4%
Use of antiseptic mouth rinse in days after treatment	367	56.5%	226	68.7%	26	61.9%	5	71.4%	5	62.5%	0	629	60.8%
Cooling of cheek in days after treatment	329	50.7%	188	57.1	31	73.8%	3	42.9%	4	50.0%	0	555	53.6%
Treatment center													
Teaching hospital	179	27.6%	103	31.3%	15	35.7%	2	28.6%	2	25.0%	0	301	29.1%

Table 3. Characteristics of patients with complete follow-up (Q1 and Q2) (*continued*)

	No bleeding		Type I		Type II		Type III		Type IV		Type V	Total	
Non- teaching hospital	470	72.4%	226	68.7%	27	64.3%	5	71.4%	6	75.0%	0	734	70.9%

OMS = Oral Maxillofacial Surgeon; SD = Standard Deviation; NSAID = Non-Steroid Anti-Inflammatory Drug; a If either incision, creation of mucoperiosteal flap, alveotomy, dividing, and/or decapitating was required to remove a molar, the procedure was considered a surgical removal; if this was not required, the procedure was considered a non-surgical extraction

Table 4. Univariate binary regression analysis for predictors of "any type of bleeding" (type I-V)

		95% C.I. for OR	P-value
	OR	Lower - Upper	
Male gender	1.115	0.863 - 1.440	0.405
Dutch ethnicity	0.871	0.596 - 1.273	0.477
Age in years	0.962	0.946 - 0.978	0.001*
Poor intra oral hygiene	1.698	0.960 - 3.004	0.069
Smoking	1.227	0.892 - 1.687	0.208
Removal of 2 M3s or less	0.770	0,311 - 1.907	0.573
Surgical removal	1.971	1.401 - 2.774	0.001*
Additional measures undertaken to improve hemostasis	1.908	1.282 - 2.839	0.001*
Remarkable amount of blood loss during treatment	1.174	0.693 - 1.989	0.550
Postoperative use of NSAIDs	1.398	1.021 - 1.914	0.037*
Complications possibly leading to extra bleeding	0.930	0.309 - 2.796	0.897
OR = Odds Ratio; M3s = Third molars; NSAID = Non-Steroid Anti-Inflammatory Drug; *statistically significant			

The results of our study are comparable to the results of previous studies. We report similar incidences of clinically examined postoperative bleedings (1.5% vs. 0-0.97%[11, 14, 18, 19]) and patient-reported postoperative bleedings (35.8% vs. 4.2- 61.3%[7, 12, 14, 17]) as described in the literature. However, the results should be compared with caution, as none of the previous studies were specifically designed to assess postoperative bleeding incidences, and study settings were different from the setting in our study.

One study with a comparable clinical setting is a Dutch case-control study, which compared the postoperative bleeding risk after dentoalveolar surgery and non-surgical teeth extraction in patients on antithrombotic drugs to healthy patients.[22] A mild postoperative bleeding was reported in 2 out of 101 healthy patients, which is roughly similar to the incidence in our study. However, despite its comparable clinical setting, the results should be compared with caution, as the sample size was too small to accurately determine postoperative bleeding incidences in healthy patients.

The second goal of our study was to investigate the association between patient and treatment characteristics, and the risk of postoperative bleeding. It should be emphasized that all types of postoperative bleeding were combined into one group of postoperative bleeding for the purpose of logistic regression analysis. By doing so, type I and II postoperative bleedings, which constituted the majority of the postoperative bleedings, had the most weight in the analysis. Consequently, the analysis does not solely explore the associations for clinically significant bleedings (i.e. type

IV and V), but rather explores the associations for normal postoperative symptoms or mild oozing symptoms (i.e. type I and II bleedings). In our study an increasing age was associated with a decreased risk of postoperative bleeding. It is possible that older patients were simply more willing to accept their symptoms as normal postoperative symptoms, compared to younger patients. Surgical removal was associated with an increased risk for postoperative bleeding. It is likely that the presence of blood in saliva for several days is more prevalent after surgical removal of a third molar compared to non-surgical removal, due to a larger surgical wound. However, these statistically significant findings might not be clinically relevant since only few patients required treatment for postoperative bleeding.

The use of NSAIDs after M3 removal was associated with an increased risk of postoperative bleedings in univariate logistic regression. However, the multivariate logistic regression analysis showed no statistically significant association. It has been suggested that NSAIDs increase the risk of postoperative bleedings in patients using antithrombotic drugs.[23] However, it is unknown whether this also applies to healthy patients. Our study did not provide evidence in support of this theory. Biedermann et al.[23] only found an increased odds ratio for patients using NSAIDs and vitamin K antagonists undergoing high-risk dental procedures (e.g. removal of more than 3 elements), but found no increased risk in patients undergoing low-risk dental procedures.

Treatment by more experienced surgeons (OMF) did not result in a significant lower bleeding incidences compared to less experienced residents or interns. Other variables that were statistically significant in univariate logistic regression analysis (i.e. pericoronitis, poor oral hygiene, or the number of teeth removed) were also not significantly associated with postoperative bleeding in the multivariate analysis.

Some general study limitations of our study should be addressed. First of all, not all eligible patients were willing to participate in the present study. The response rate for Q2 was 55.1%. It is unknown why 44.9% of the patients were lost during follow-up. Postoperative bleedings could have occurred in these patients, which would result in an underreporting of the postoperative bleeding incidence. However, we assume it to be more likely that patients experiencing postoperative bleeding would be more willing to reply and complete the follow-up. If so, the described postoperative bleeding incidence would be an overestimation, rather than an underestimation.

Secondly, we did not differentiate between postoperative oozing and postoperative bleeding, as suggested by Kumbargere Nagraj et al.[24] It is likely that patients with postoperative symptoms, such as a pink discoloration of the saliva, classified this

as postoperative bleeding, whereas a healthcare professional would classify this as normal postoperative symptoms. Postoperative oozing for 12-24 hours after tooth removal is considered normal.[25] If any oozing persists after 24 hours, clinical examination is warranted, as an underlying medical condition may cause a prolonged clotting time.[26] The average bleeding time was a little more than three hours, with only 5 patients reporting active bleeding for longer than 24 hours. The majority (80.6%) of patients in our study who experienced postoperative bleeding reported that the bleeding occurred on the day of the procedure or the day after. When also considering that 96.1% of all reported postoperative bleedings constituted type I and II postoperative bleedings, it seems likely that a significant proportion of patients were actually experiencing what can be considered as normal postoperative symptoms. These findings emphasize that patients should receive detailed information on benign symptoms after teeth removal. This includes the possibility of pink discoloration of saliva, and presence of blood in saliva for several days.

Thirdly, the patients in this study were all referred by a dentist to an OMS department for third molar removal. It is therefore possible that more complicated cases were included. Consequently, these patients might require relatively more invasive treatment and might therefore be more prone to bleeding complications. This would result in an overestimation of the incidence of postoperative bleeding when compared with M3 removal carried out by a dentist in a general dental practice.

CONCLUSION

Taking these limitations into account, we conclude that the risk of clinically significant bleeding complications is very low after removal of third molars in healthy patients. In the rare case that a clinically significant postoperative bleedings occurs, it can be treated with minimally invasive measures. We emphasize the need for properly informing patients about the normal postoperative course after M3 removal, as well as instructing them when to contact their healthcare provider, as our results show a large discrepancy between patient reported postoperative bleedings and the number of patients with a clinically significant bleeding.

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CONFLICTS OF INTEREST

No conflicts of interest are reported.

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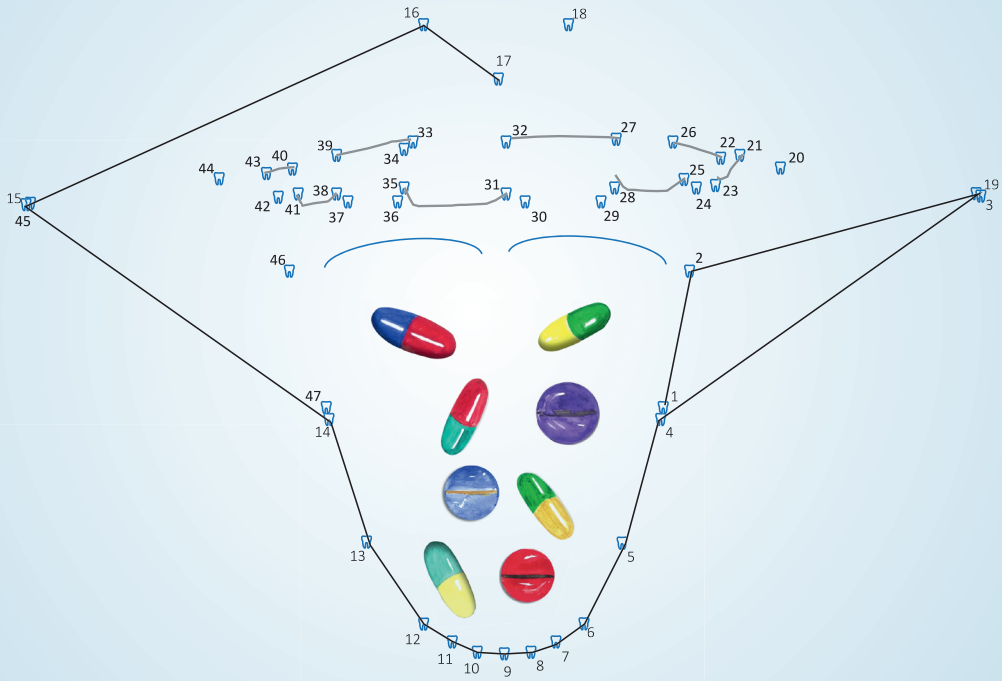
III Medication related adverse effects in dentistry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5 Oral adverse effects of drugs: taste disorders

This chapter is based on the following publication:
Oral adverse effects of drugs: taste disorders

Willem M.H. Rademacher; Yalda Aziz; Atty Hielema; Ka-Chun Cheung; Jan de Lange; Arjan Vissink and Frederik R. Rozema

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ABSTRACT

Oral healthcare professionals are frequently confronted with patients using drugs on a daily basis. These drugs can cause taste disorders as adverse effect. The literature that discusses drug-induced taste disorders is fragmented. This article aims to support oral healthcare professionals in their decision making whether a taste disorder can be due to use of drugs by providing a comprehensive overview of drugs with taste disorders as an adverse effect.

The national drug information database for Dutch pharmacists, based on scientific drug information, guidelines and summaries of product characteristics, was analyzed for drug-induced taste disorders. “MedDRA classification” and “Anatomic Therapeutical Chemical codes” were used to categorize the results.

Of the 1645 drugs registered in the database, 282 (17%) were documented with “dysgeusia” and 61 (3.7%) with “hypogeusia”. Drug-induced taste disorders are reported in all drug categories, but predominantly in “antineoplastic and immunomodulating agents”, “antiinfectives for systemic use” and “nervous system”. In ~45% “dry mouth” coincided as adverse effect with taste disorders.

Healthcare professionals are frequently confronted with drugs reported to cause taste disorders. This article provides an overview of these drugs to support clinicians in their awareness, diagnosis and treatment of drug-induced taste disorders.

INTRODUCTION

The global consumption of drugs to treat acute and chronic diseases continues to increase.[1] Inevitably, healthcare professionals are frequently confronted with patients using one or more drugs on a daily basis. These drugs can cause adverse effects in the oral region such as xerostomia, hyposalivation, mucositis and taste disorders.

Due to the large number of different 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 will publish a series of articles discussing the most frequent adverse effects of drugs in the oral region. The first paper in this series discusses drug-induced taste disorders (DITD).

Fark et al. (2013) divided taste disorders into quantitative taste disorders and qualitative taste disorders. Quantitative taste disorders include hypergeusia (an abnormally heightened sense of taste), normageusia (a normal sense of taste), hypogeusia (an abnormally lowered sense of taste) and ageusia (a lacking sense of taste). Qualitative taste disorders are dysgeusia (a distortion in sense taste) and phantogeusia (a taste perception without a stimulus).[2] Although disturbances in taste seem harmless, they can interfere with a patients' social behavior by avoiding dinners, or lead to a change in diet which can, amongst others, cause weight-loss, nutrient deficiencies or overweight due to excessive use of salt and sugar to compensate bad flavors.[3] As such, taste disorders can lead to a significant reduction in the quality of life.[4] Therefore, it is important that oral healthcare professionals are aware of the possible causes and treatment modalities of taste disorders. Adverse effects of drugs account for 9%-22% of the taste disorders.[2, 5] This article aims to support oral healthcare professionals in their decision making whether a taste disorder can be due to use of drugs by providing a comprehensive overview of drugs documented with taste disorders as an adverse effect.

MATERIAL AND METHODS

Data source

The Informatorium Medicamentorum (IM) of the Royal Dutch Pharmacists Association (KNMP) is the leading national drug information database and reference work for pharmacists in the Netherlands. This database is based on scientific drug information,

guidelines and summaries of product characteristics (SmPC's).[6] The IM is updated every two weeks with the latest available information from scientific publications, warnings of authorities and SmPC's of the European Medicines Agency and Medicines Evaluation Board in the Netherlands.

The IM was last searched on August, 1 2018 and all data regarding adverse effects available that time were included in this study. Of each drug, the category "adverse effects" from the IM was searched for taste disorders and synonyms (e.g. dysgeusia).

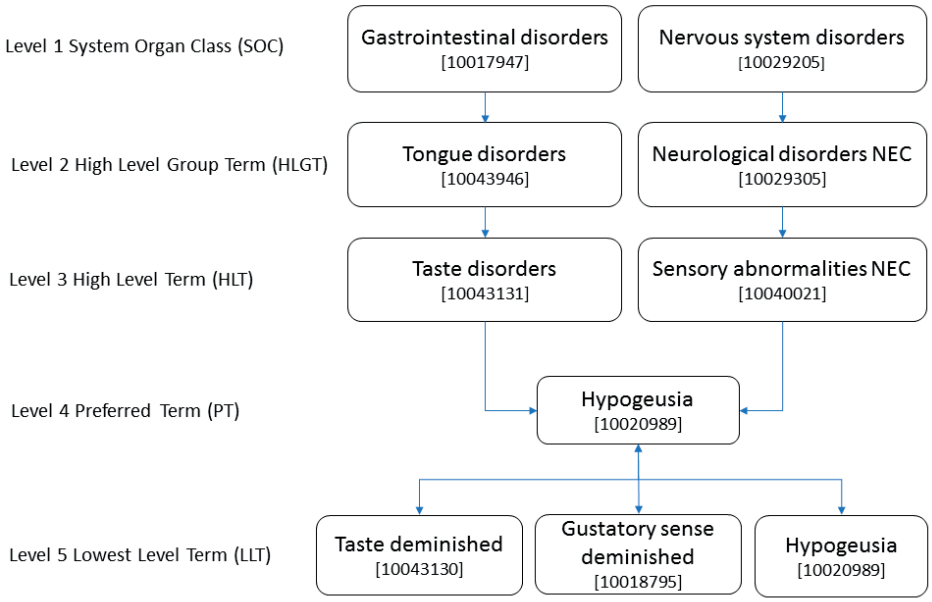
The following characteristics of drugs causing DITD were registered: generic name of the drug, term of the adverse effect, incidence of the adverse effect and Anatomic Therapeutical Chemical (ATC) codes of the drug. The ATC classification was developed by the World Health Organization and categorizes all active substances in drugs according to a hierarchy with five levels. It serves as a tool for exchanging data on drug use on a national and international level.[7] It is worth noting that one active substance can be used in different drugs with different treatment goals. Therefore, it is possible that one active substance (e.g. Miconazol) has several ATC-codes (Figure 1).

Figure 1: Hierarchy of ATC-codes for Miconazol

ATC-level	
1:	**A** Alimentary tract and metabolism
2:	**A07** Antidiarrheal, intestinal anti-inflammatory/infective agents
3:	**A07A** Intestinal antiinfectives
4:	**A07AC** Imidazole derivatives
5:	**A07AC01** Miconazole oral gel
1:	**G** Genito urinary system and sex hormones
2:	**G01** Gynecological antiinfectives an antiseptics
3:	**G01A** Antiinfectives and antiseptics, excl. combinations with corticosteroids
4:	**G01AF** Imidazole derivatives
5:	**G01AF04** Miconazole vaginal gel
1:	**D** Dermatologicals
2:	**D01** Antifungals for dermatological use
3:	**D01A** Antifungals for topical use
4:	**D01AC** Imidazole and triazole derivatives
5:	**D01AC02** Miconazole (cutaneous)
1:	**S** Sensory organs
2:	**S02** Otologicals
3:	**S02A** Antiinfectives
4:	**S02AA** Antiinfectives
5:	**S02AA13** Miconazole ear drops

Originally, the terms used to describe one adverse effect (e.g. taste disorders) in the SmPC's varied between drugs and throughout the years. In order to create a standardized structured database, the MedDRA classification was manually applied after the selection of drugs causing DITD. The MedDRA classification is developed by the International Council for Harmonization of Technical Requirements for Pharmaceuticals for Human and endeavors to standardize all international medical terminology, including terms for adverse effects.[8] The MedDRA classification is a hierarchical system that distinguishes five levels in the categorization of medical terminology. The most specific level is the "Lowest Level Term (LLT)" and the next level is called the "Preferred Term (PT)". Each LLT is directly linked to only one PT. Each PT is linked to at least one LLT (itself) and sometimes several synonyms of the LLT. In Figure 2 the PT "Hypogeusia" is presented with its LLT's. After the selection of drugs related to DITD from the IM, the adverse effect terms were first matched in accordance with the support document[9], with the most applicable LLT in Dutch. Terms were then translated into English by using the LLT-codes and the English version of MedDRA. The English LLT were automatically matched with the English PT level according to the MedDRA hierarchy. Microsoft® Excel (version 16.16.1) was used to create the database with the acquired information on DITD and to perform descriptive statistics.

Figure 2: Hierarchy for "Hypogeusia" in MedDRA



NEC: Not Elsewhere Classified

RESULTS

In total, 1645 drugs (active substances) were registered in the IM. Each drug can cause multiple adverse effects resulting in approximately 65,000 unique combinations between a drug and an adverse effect in the IM. Of these 65,000 combinations, 2335 (3.5%) were defined by the authors as relevant for the oral healthcare provider and 343 (0.5%) concerned taste disorders. Of the 1645 drugs, 314 (19%) could cause DITD. As IM discriminates different administration forms per drug, the number of drugs (314) and number of combinations (343) causing taste disorders differ. For example, "Budesonide", which can be administered rectally, nasally and by inhalation is registered three times with dysgeusia as a potential adverse effect with three different incidences. Table 1 presents the different LLTs and PTs used in the IM for taste disorders and the number drugs which can potentially cause them. Taste disturbance as an adverse effect was reported in all level 1 categories of the ATC-classification (Table 2). "Normogeusia", "hypergeusia", "ageusia" and " phantogeusia" were not reported in the IM.

Table 1. LLTs and PT for taste disorders in IM analysis.

Adverse effect term	No. drugs
Dysgeusia (PT)	**282**
Dysgeusia (LLT)	15
Taste bitter (LLT)	9
Taste disturbance (LLT)	245
Taste garlic (LLT)	1
Taste metallic (LLT)	12
Hypogeusia (PT)	**61**
Hypogeusia (LLT)	61
Total	**343**

Table 2. Number of drugs causing dysgeusia or hypogeusia per ATC level 1 category.

ATC level 1 Category	Dysgeusia (%)	Hypogeusia (%)	Total
Alimentary tract and metabolism	24 (8.5)	2 (3.1)	26
Antiinfectives for systemic use	44(15.6)	7 (11.0)	51
Antineoplastic and immunomodulating agents	53 (18.8)	22 (39.0)	75
Antiparasitic products, insecticides and repellents	5 (1.7)	-	5
Blood and blood forming organs	13 (4.6)	1 (1.4)	14
Cardiovascular system	23 (8.1)	5 (7.8)	28
Dermatologicals	13 (4.6)	2 (3.2)	15
Genito urinary system and sex hormones	5 (1.7)	3 (4.7)	8
Musculo-skeletal system	12 (4.3)	2 (3.1)	14
Nervous system	39 (13.8)	12 (19.0)	51
Respiratory system	16 (5.7)	-	16
Sensory organs	10 (3.5)	1 (1.5)	10
Systemic hormonal preparations, excl.	7 (2.5)	2 (3.1)	9
Various	18 (6.3)	2 (3.1)	20
Total:	**282**	**61**	**343**

Dysgeusia

Dysgeusia (PT) as an adverse effect was reported 282 times (17.1% of 1645 drugs) (Table 1). The drug categories "antineoplastic and immunomodulating agents" (18.8%), "antiinfectives for systemic use" (15.6%) and "nervous system" (13.8%) account for almost half of the drug-induced dysgeusia (Table 2). Hypergeusia, ageusia and phantogeusia were not reported.

Table 3 presents a selection of the drugs that could cause dysgeusia (PT) and comprises only the category "Alimentary tract and metabolism". The frequencies of the adverse effect and whether a drug also causes the adverse effects "parosmia", "anosmia", "dry mouth" or "hyposalivation" are presented as well, since these adverse effects are closely related to taste disorders. In some drugs, dysgeusia is only caused when the drug is administered through a specific route or under certain circumstances. The full table of all the 282 drugs causing dysgeusia is presented in Table A1 of the appendix. In these 282 drugs, the frequency of dysgeusia was "very common" in 7.1%, "common" in 31.2%, "uncommon" in 32.7% and "rare or very rare" in 9.9% of the drugs. In 19.1% of the drugs the "frequency was not known", which means that in the IM the frequency could not be estimated based on the available data. Dysgeusia coincided in 114/282 drugs (40.4%) with "dry mouth" as an adverse effect, in 5/282 drugs (1.7%) with "anosmia", in 2/282 drugs (0.7%) with "parosmia", in 6/282 drugs (2.1%) with "dry mouth and anosmia", and in 3/282 drugs (1.0%) with "dry mouth and parosmia". None of these drugs were reported to cause "hyposalivation".

Tables A2 and A3 in the appendix present drugs that cause a bitter taste (LLT) or metallic taste (LLT), respectively. Disulfiram (N07BB01), a drug used to treat patients with alcohol abuses, was the only drug reported to cause a garlic taste (LLT).

Hypogeusia

Drug-induced hypogeusia was reported in 61 drugs (3.7% of 1645). Hypogeusia was predominantly reported in the drug categories "Antineoplastic and immunomodulating agents" (39.0%) and "Nervous system" (19%). Hypogeusia did not occur in the drug categories "Respiratory system" and "Antiparasitic products, insecticides and repellents" (Table 2). Table 4 presents all drugs in the IM that are reported to cause hypogeusia. In these 61 drugs, the frequency of hypogeusia was "very common" in 9.5%, "common" in 31.7%, "uncommon" in 25.4%, "rare or very rare" in 15.9% of the drugs. In 17.5% of the drugs the "frequency was not known". Hypogeusia coincided in 28/61 drugs (45.9%) with "dry mouth", in 1/61 drugs (1.6%) with "anosmia", and in 2/61 drugs (3.2%) with "dry mouth/anosmia". None of these drugs were reported to cause "hyposalivation".

Table 3. Drug-induced dysgeusia (PT) in level 1 ATC category: Alimentary tract and metabolism.

ATC level 1	ATC level 3	Generic name	ATC Code	LLT MedDRA	Frequency	Specific type of administration	Coinciding adverse effects
ALIMENTARY TRACT AND METABOLISM	Antiemetics And Antinauseants	Aprepitant	A04AD12	Taste disturbance	Frequency not known	-	D
		Rolapitant	A04AD14	Taste disturbance	Uncommon (0 1-1%)	-	-
	Antipropulsives	Loperamide	A07DA03	Taste disturbance	Frequency not known	-	D
	Blood Glucose Lowering Drugs Excl. Insulins	Exenatide	A10BJ01 A10BJ01	Taste disturbance	Uncommon (0 1-1%)	-	-
		Glimepiride	A10BB12	Taste disturbance	Frequency not known	-	-
		Liraglutide	A10BJ02	Taste disturbance	Common (1-10%)	-	D
		Metformine	A10BA02	Taste disturbance	Common (1-10%)	-	-
	Drugs For Peptic Ulcer And Gastro-Oesophageal Reflux Disease (GORD)	Esomeprazol	A02BC05	Taste disturbance	Frequency not known	After intravenous administration	D
		Famotidine	A02BA03	Taste disturbance	Uncommon (0 1-1%)	-	D
		Lansoprazol	A02BC03	Taste disturbance	Frequency not known	-	D
		Rabeprazol	A02BC04	Taste disturbance	Frequency not known	-	D
	Intestinal Antiinfectives	Fidaxomicine	A07AA12	Taste disturbance	Uncommon (0 1-1%)	-	D
		Miconazol	A07AC01 D01AC02 G01AF04 S02AA13	Dysgeusia	Common (1-10%)	After oral administration	D
		Miconazol	A07AC01 D01AC02 G01AF04 S02AA13	Taste disturbance	Uncommon (0 1-1%)	After oral administration	D
	Intestinal Antiinflammatory Agents	Budesonide	A07EA06 R01AD05 R03BA02	Taste disturbance	Uncommon (0 1-1%)	After rectal administration	D,P
		Budesonide	A07EA06 R01AD05 R03BA02	Taste disturbance	Common (1-10%)	After inhalation	D,P
		Budesonide	A07EA06 R01AD05 R03BA02	Taste disturbance	Frequency not known	After nasal administration	D,P

Table 3. Drug-induced dysgeusia (PT) in level 1 ATC category: Alimentary tract and metabolism. (*continued*)

ATC level 1	ATC level 3	Generic name	ATC Code	LLT MedDRA	Frequency	Specific type of administration	Coinciding adverse effects
ALIMENTARY TRACT AND METABOLISM		Cromoglicic acid	A07EB01 R01AC01 R03BC01 S01GX01	Dysgeusia	Uncommon (0 1-1%)		-
		Sulfasalazine	A07EC01	Taste disturbance	Common (1-10%)	-	A
	Other Alimentary Tract And Metabolism Products	Agalsidase alfa	A16AB03	Taste disturbance	Common (1-10%)	-	A
		Sodium phenylbutyrate	A16AX03	Taste disturbance	Common (1-10%)	-	-
	Stomatological Preparations	Chlorhexidine	A01AB03 B05CA02 D08AC02 D09AA12 S01AX09	Taste disturbance	Rare or very rare (<0 1%)	-	-
		Triamcinolone	A01AC01 D07AB09 H02AB08 R01AD11 S01BA05 S02BA	Taste disturbance	Rare or very rare (<0 1%)	After nasal administration	-
		Hydrogen peroxide	A01AB02	Dysgeusia	Frequency not known	-	-

ATC= Anatomic Therapeutical Chemical; LLT= lowest level term; D= dry mouth; A= Ansomia; P= Parosmia

Table 4. Drug-induced hypogeusia (PT) in all ATC level 1 categories.

ATC level 1	ATC level 3	Generic name	ATC Code	LLT MedDRA	Frequency	Specific type of administration	Coinciding adverse effects
ALIMENTARY TRACT AND METABOLISM	Belladonna And Derivatives, Plain	Atropine	A03BA01 S01FA01	Hypogeusia	Frequency not known	-	D
	Intestinal Antiinfectives	Colistine	A07AA10 J01XB01	Hypogeusia	Rare or very rare (<0,1%)	After inhalation	-
ANTIINFECTIVES FOR SYSTEMIC USE	Antimycotics For Systemic Use	Micafungine	J02AX05	Hypogeusia	Uncommon (0,1-1%)	-	-
	Direct Acting Antivirals	Darunavir	J05AE10	Hypogeusia	Frequency not known	-	D
	Drugs For Treatment Of Tuberculosis	Rifabutine	J04AB04	Hypogeusia	Rare or very rare (<0,1%)	-	-
	Macrolides, Lincosamides And Streptogramins	Claritromycine	J01FA09	Hypogeusia	Rare or very rare (<0,1%)	-	D
	Other Antibacterials	Methenamine	J01XX05	Hypogeusia	Rare or very rare (<0,1%)	-	-
	Quinolone Antibacterials	Levofloxacine	J01MA12	Hypogeusia	Rare or very rare (<0,1%)	After oral and intravenous administration	-
		Ofloxacine	J01MA01 S01AE01 S02AA16	Hypogeusia	Rare or very rare (<0,1%)	After oral administration	D,A

Table 4. Drug-induced hypogeusia (PT) in all ATC level 1 categories. (*continued*)

ATC level 1	ATC level 3	Generic name	ATC Code	LLT MedDRA	Frequency	Specific type of administration	Coinciding adverse effects
ANTINEOPLASTIC AND IMMUNOMODULATING AGENTS	Antimetabolites	Capecitabine	L01BC06	Hypogeusia	Common (1-10%)	-	D
		Tegafur	L01BC03	Hypogeusia	Common (1-10%)	-	D
	Hormone Antagonists And Related Agents	Anastrozol	L02BG03	Hypogeusia	Common (1-10%)	-	-
	Immunostimulants	Aldesleukine	L03AC01	Hypogeusia	Common (1-10%)	-	-
	Other Antineoplastic Agents	Afatinib	L01XE13	Hypogeusia	Common (1-10%)	-	-
		Axitinib	L01XE17	Hypogeusia	Very common (>10%)	-	-
		Bosutinib	L01XE14	Hypogeusia	Common (1-10%)	-	-
		Cabozantinib	L01XE26	Hypogeusia	Common (1-10%)	-	-
		Cisplatine	L01XA01	Hypogeusia	Frequency not known	-	-
		Crizotinib	L01XE16	Hypogeusia	Very common (>10%)	-	-
		Dasatinib	L01XE06	Hypogeusia	Common (1-10%)	-	-
		Everolimus	L01XE10 L04AA18	Hypogeusia	Common (1-10%)	In case of oncologic treatment	D
		Necitumumab	L01XC22	Hypogeusia	Common (1-10%)	-	-
		Nilotinib	L01XE08	Hypogeusia	Common (1-10%)	-	-
		Palbociclib	L01XE33	Hypogeusia	Common (1-10%)	-	-
		Panobinostat	L01XX42	Hypogeusia	Common (1-10%)	-	D
		Sorafenib	L01XE05	Hypogeusia	Common (1-10%)	-	D
		Temsirolimus	L01XE09	Hypogeusia	Common (1-10%)	-	-
		Trastuzumab	L01XC03	Hypogeusia	Very common (>10%)	-	D
		Trastuzumab emtansine	L01XC14	Hypogeusia	Common (1-10%)	-	D
		Vandetanib	L01XE12	Hypogeusia	Common (1-10%)	-	D
		Vismodegib	L01XX43	Hypogeusia	Common (1-10%)	-	-

Table 4. Drug-induced hypogeusia (PT) in all ATC level 1 categories. (*continued*)

ATC level 1	ATC level 3	Generic name	ATC Code	LLT MedDRA	Frequency	Specific type of administration	Coinciding adverse effects
BLOOD AND BLOOD FORMING ORGANS	Iron, Parenteral Preparations	Ferricarboxymaltose	B03AC	Hypogeusia	Uncommon (0,1-1%)	-	-
CARDIOVASCULAR SYSTEM	Ace Inhibitors, Plain	Captopril	C09AA01	Hypogeusia	Common (1-10%)	-	D
		Enalapril	C09AA02	Hypogeusia	Frequency not known	-	D
		Ramipril	C09AA05	Hypogeusia	Uncommon (0,1-1%)	-	D,A
	Beta Blocking Agents	Esmolol	C07AB09	Hypogeusia	Uncommon (0,1-1%)	-	D
	Lipid Modifying Agents, Plain	Atorvastatine	C10AA05	Hypogeusia	Uncommon (0,1-1%)	-	-
DERMATOLOGICALS	Antifungals For Topical Use	Terbinafine	D01AE15 D01BA02	Hypogeusia	Uncommon (0,1-1%)	-	-
	Other Dermatological Preparations	Tacrolimus	D11AH01 L04AD02 S01XA	Hypogeusia	Frequency not known	After intravenous administration	-
GENITO URINARY SYSTEM AND SEX HORMONES	Hormonal Contraceptives For Systemic Use	Ulipristal	G03AD02 G03XB02	Hypogeusia	Frequency not known	When used as emergency anticonceptive	D
	Other Urologicals, Incl. Antispasmodics	Solifenacine	G04BD08	Hypogeusia	Uncommon (0,1-1%)	-	D
		Tiopronine	G04BX16	Hypogeusia	Uncommon (0,1-1%)	-	-
MUSCULOSKELETAL SYSTEM	Muscle Relaxants, Centrally Acting Agents	Baclofen	M03BX01	Hypogeusia	Uncommon (0,1-1%)	-	D
	Specific Antirheumatic Agents	Penicillamine	M01CC01	Hypogeusia	Common (1-10%)	-	-

Table 4. Drug-induced hypogeusia (PT) in all ATC level 1 categories. (*continued*)

ATC level 1	ATC level 3	Generic name	ATC Code	LLT MedDRA	Frequency	Specific type of administration	Coinciding adverse effects
NERVOUS SYSTEM	Anesthetics, Local	Articaine	N01BB08	Hypogeusia	Frequency not known	-	-
		Cocaine	N01BC01 S01HA01	Hypogeusia	Frequency not known	-	A
		Mepivacaine	N01BB03	Hypogeusia	Frequency not known	-	-
	Antidepressants	Duloxetine	N06AX21	Hypogeusia	Uncommon (0,1-1%)	-	D
		Maprotiline	N06AA21	Hypogeusia	Frequency not known	-	D
	Antiepileptics	Pregabaline	N03AX16	Hypogeusia	Uncommon (0,1-1%)	-	D
	Antimigraine Preparations	Rizatriptan	N02CC04	Hypogeusia	Uncommon (0,1-1%)	-	D
	Antipsychotics	Paliperidon	N05AX13	Hypogeusia	Uncommon (0,1-1%)	-	D
	Dopaminergic Agents	Opicapon	N04BX04	Hypogeusia	Uncommon (0,1-1%)	-	D
	Drugs Used In Addictive Disorders	Varenicline	N07BA03	Hypogeusia	Frequency not known	-	D
	Opioids	Hydromorfon	N02AA03	Hypogeusia	Uncommon (0,1-1%)	After oral administration	D
	Psychostimulants, Agents Used For ADHD And Nootropics	Dexamfetamine	N06BA02	Hypogeusia	Rare or very rare (<0,1%)	-	D
SENSORY ORGANS	Antiglaucoma Preparations And Miotics	Brinzolamide	S01EC04	Hypogeusia	Rare or very rare (<0,1%)	After systemic administration	D
SYSTEMIC HORMONAL PREPARATIONS, EXCL.	Antithyroid Preparations	Carbimazol	H03BB01	Hypogeusia	Frequency not known	-	-
		Propylthiouracil	H03BA02	Hypogeusia	Rare or very rare (<0,1%)	-	-

Table 4. Drug-induced hypogeusia (PT) in all ATC level 1 categories. (*continued*)

ATC level 1	ATC level 3	Generic name	ATC Code	LLT MedDRA	Frequency	Specific type of administration	Coinciding adverse effects
VARIOUS	Allergens	Grass pollen	V01AA02 V01AA	Hypogeusia	Rare or very rare (<0,1%)	After subcutaneous administration	D
	Magnetic Resonance Imaging Contrast Media	Gadoteric acid	V08CA02	Hypogeusia	Uncommon (0,1-1%)	After intravenous administration	-

ATC= Anatomic Therapeutical Chemical; LLT= lowest level term; D= dry mouth; A= Ansomia

DISCUSSION

In total, 20% (343/1645) of the drugs used in the Netherlands has been reported to potentially cause DITD (dysgeusia and hypogeusia). DITD was reported in all ATC level 1 categories, suggesting that all healthcare professionals may frequently encounter the adverse effects of these drugs. Healthcare professionals that treat patients using antineoplastic drugs are most likely to be confronted with DITD. Despite the recorded percentage of our search, the exact incidence of DITD is unclear due to a lack of systematic well controlled clinical trials.[10]

To the best of our knowledge, this study is the first comprehensive overview of DITD based on the analysis of a national drug information database which includes adverse effects. The available literature that discusses DITD is fragmented, since previous articles usually report on a specific type of patients with DITD (e.g. cancer) [11-13], specific drug categories causing DITD (e.g. cardiovascular drugs) [14, 15] or summarize the literature instead of providing an overall analysis of what registered drugs are linked to DITD.[10, 16, 17] In addition, the ATC classification is not always applied, making it difficult to compare the results of the various studies.

Our data source contains predominantly PT level terms. Although this is in accordance with the MedDRA guidelines, it is likely that specific LLT terms like “bitter taste” and “metallic taste” might therefore be underreported compared to previous studies which do not use the MedDRA. It also has to be mentioned that the terms and incidences used in the database (e.g. “dysgeusia”, “hypoguesia”) are based on patient-reported adverse effects during pharmacological developing studies or post-marketing studies. This subjective reporting by patients might lead to a reporting bias or inaccuracy in terminology. The difference between objective and subjective adverse effects measuring is a common point of discussion when reporting on adverse effects and one without a clear solution. When considering taste disorders, there are no commonly used test available for objectifying taste disorders. Which makes it impossible to report solely objective data. In order to make future studies on oral adverse effects more comparable it is recommended that the MedDRA terminology and hierarchy and, if available, objective tests are used during data collection and describing the results. Homogenous reporting of results, on for instance incidences, will lead to clinically more applicable data.

Due to differences in local and regional laws and regulations on drug admission, registered drugs differ per country. Thus, there will be drugs that are reported in the current study that are not available in some countries and reverse. However, with

regard to the European countries, most of the reported drugs will be available in all countries. By applying the ATC and MedDRA classification, the data is internationally applicable and could serve as a guidance for future reports on DITD.

The exact mechanisms underlying DITD are still unclear and may vary between individuals. Individual variations may be caused by polypharmacy (drug interactions), dosage differences and patient-specific variables (e.g. genetics, age and medical conditions).[10] Schiffman (2018) describes several presumed mechanisms behind DITD. Some drugs have sensory properties that cause a bitter or metallic taste. These drugs interact with the taste buds: 1) after oral application, 2) by diffusion into the saliva after absorption in the gut or intravenous administration, or 3) by accumulation in the taste buds when used chronically. The latter might explain why DITD can occur months or years after the initial usage (e.g. lithium carbonate). Other drugs distort taste and smell signals for sweet or salt, causing a bitter or sour taste perception of food and beverages. The garlic like taste caused by disulfiram is due to exhalation of carbon disulfide. Drug-drug interactions can lead to elevated blood-plasma levels beyond therapeutic concentrations and therefore cause DITD, which particularly could occur in polypharmacy patients.

Saliva could also play a role in the underlying mechanism of DITD. Saliva protects the external environment of the taste receptor cells, and acts as a solvent and transportation medium for taste substances.[18] Many drugs are known to cause quantitative or qualitative changes in saliva.[19] Almost 45% of the drugs known to potentially cause DITD coincided with dry mouth as an adverse effect, suggesting that there is at least some correlation. However, the exact correlation is difficult to assess since both MedDRA and the data that underlies the IM do not clearly discriminate between subjective "xerostomia" and objective "hyposalivation". The term "dry mouth" is presumably used for both.

A healthcare professional confronted with a patient with DITD should assess which drug, or drug combination, is presumably responsible for the DITD. This can be done by comparing the temporal onset of DITD with the alterations in the drug usage (e.g. dosage, new drugs). However, as stated before, it is possible that DITD occurs months or years after the initial usage, complicating the assessment of a temporal relationship. Another possibility is to consult pharmaceutical databases and overviews like the approach used in the present study.

Cessation of the drug responsible for DITD will most likely result in a decrease and eventually even recovery of DITD, but this (partial) recovery could take months.

If cessation and alterations are not possible, other treatment modalities could be considered to relieve the symptoms. The evidence behind these modalities is scarce and based on research on taste disorders with other causes than DITD. Proposed treatment modalities include improving oral hygiene, suppletion of zinc, stimulation food flavors, saliva substitutes and administration of alpha lipoic acid.[10, 20-22]

CONCLUSION

Healthcare professionals are frequently confronted with drugs that are documented with DITD. The exact incidences of DITD remain unclear. This overview supports clinicians in their awareness, diagnosis and possible treatment of DITD, and could serve as a reference for future research reporting on DITD

CONFLICT OF INTEREST

None.

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APPENDIX

Table A1. Drug induced dysgeusia (PT) in all level 1 ATC categories

ATC level 1	ATC level 3	Generic name	ATC Code	LLT MedDRA	Frequency	Specific type of administration	Coinciding adverse effects
ALIMENTARY TRACT AND METABOLISM	Antiemetics And Antinauseants	Aprepitant	A04AD12	Taste disturbance	Frequency not known	-	D
		Rolapitant	A04AD14	Taste disturbance	Uncommon (0 1-1%)	-	-
	Antipropulsives	Loperamide	A07DA03	Taste disturbance	Frequency not known	-	D
	Blood Glucose Lowering Drugs Excl. Insulins	Exenatide	A10BJ01	Taste disturbance	Uncommon (0 1-1%)	-	-
		Glimepiride	A10BB12	Taste disturbance	Frequency not known	-	-
		Liraglutide	A10BJ02	Taste disturbance	Common (1-10%)	-	D
		Metformine	A10BA02	Taste disturbance	Common (1-10%)	-	-
	Drugs For Peptic Ulcer And Gastro-Oesophageal Reflux Disease (GORD)	Esomeprazol	A02BC05	Taste disturbance	Frequency not known	After intravenous administration	D
		Famotidine	A02BA03	Taste disturbance	Uncommon (0 1-1%)	-	D
		Lansoprazol	A02BC03	Taste disturbance	Frequency not known	-	D
		Rabeprazol	A02BC04	Taste disturbance	Frequency not known	-	D
	Intestinal Antiinfectives	Fidaxomicine	A07AA12	Taste disturbance	Uncommon (0 1-1%)	-	D
		Miconazol	A07AC01 D01AC02 G01AF04 S02AA13	Dysgeusia	Common (1-10%)	After oral administration	D
		Miconazol	A07AC01 D01AC02 G01AF04 S02AA13	Taste disturbance	Uncommon (0 1-1%)	After oral administration	D
	Intestinal Antiinflammatory Agents	Budesonide	A07EA06 R01AD05 R03BA02	Taste disturbance	Uncommon (0 1-1%)	After rectal administration	D,P
		Budesonide	A07EA06 R01AD05 R03BA02	Taste disturbance	Common (1-10%)	After inhalation	D,P

Table A1. Drug induced dysgeusia (PT) in all level 1 ATC categories (*continued*)

ATC level 1	ATC level 3	Generic name	ATC Code	LLT MedDRA	Frequency	Specific type of administration	Coinciding adverse effects
ALIMENTARY TRACT AND METABOLISM		Budesonide	A07EA06 R01AD05 R03BA02	Taste disturbance	Frequency not known	After nasal administration	D,P
		Cromoglicic Acid	A07EB01 R01AC01 R03BC01 S01GX01	Dysgeusia	Uncommon (0 1-1%)		-
		Sulfasalazine	A07EC01	Taste disturbance	Common (1-10%)	-	A
	Other Alimentary Tract And Metabolism Products	Agalsidase Alfa	A16AB03	Taste disturbance	Common (1-10%)	-	A
		Sodium Phenylbutyrate	A16AX03	Taste disturbance	Common (1-10%)	-	-
	Stomatological Preparations	Chlorhexidine	A01AB03 B05CA02 D08AC02 D09AA12 S01AX09	Taste disturbance	Rare or very rare (<0 1%)	-	-
		Triamcinolone	A01AC01 D07AB09 H02AB08 R01AD11 S01BA05 S02BA	Taste disturbance	Rare or very rare (<0 1%)	After nasal administration	-
		Hydrogen Peroxide	A01AB02	Dysgeusia	Frequency not known	-	-
ANTIINFECTIVES FOR SYSTEMIC USE	Aminoglycoside Antibacterials	Tobramycine	J01GB01 J01GB01 S01AA12	Taste disturbance	Common (1-10%)	After inhalation	-
		Tobramycine	J01GB01 J01GB01 S01AA12	Taste disturbance	Rare or very rare (<0 1%)	After nebulization	-
	Amphenicols	Chloramphenicol	J01BA01 S01AA01	Taste bitter	Frequency not known	After ocular administration	-
	Antimycotics For Systemic Use	Caspofungin	J02AX04	Taste disturbance	Uncommon (0 1-1%)	-	-
		Fluconazol	J02AC01	Taste disturbance	Uncommon (0 1-1%)	-	D

Table A1. Drug induced dysgeusia (PT) in all level 1 ATC categories (*continued*)

ATC level 1	ATC level 3	Generic name	ATC Code	LLT MedDRA	Frequency	Specific type of administration	Coinciding adverse effects
ANTIINFECTIVES FOR SYSTEMIC USE		Isavuconazol	J02AC05	Taste disturbance	Uncommon (0 1-1%)	-	-
		Itraconazol	J02AC02	Taste disturbance	Common (1-10%)	-	-
		Voriconazol	J02AC03 S01AX	Taste disturbance	Uncommon (0 1-1%)	-	-
	Beta-Lactam Antibacterials Penicillins	Amoxicillin	J01CA04 V04CL	Taste disturbance	Common (1-10%)	-	-
	Direct Acting Antivirals	Atazanavir	J05AE08	Taste disturbance	Uncommon (0 1-1%)	-	D
		Darunavir	J05AE10	Taste disturbance	Uncommon (0 1-1%)	-	D
		Ganciclovir	J05AB06	Taste disturbance	Common (1-10%)	-	-
		Indinavir	J05AE02	Taste disturbance	Very common (>10%)	-	D
		Lopinavir	J05AR10	Taste disturbance	Uncommon (0 1-1%)	-	D
		Raltegravir	J05AX08	Taste disturbance	Uncommon (0 1-1%)	-	D
		Ribavirine	J05AP01	Taste disturbance	Common (1-10%)	-	D
		Ritonavir	J05AE03	Taste disturbance	Very common (>10%)	-	D
		Saquinavir	J05AE01	Taste disturbance	Common (1-10%)	-	-
		Telbivudine	J05AF11	Taste disturbance	Uncommon (0 1-1%)	-	-
		Valganciclovir	J05AB14	Taste disturbance	Common (1-10%)	-	-
		Zidovudine	J05AF01	Taste disturbance	Frequency not known	-	D
	Drugs For Treatment Of Lepra	Clofazimine	J04BA01	Taste disturbance	Frequency not known	-	-
	Immunoglobulins	Immunoglobulins, Normal Human, For Intravascular Adm.	J05AF01 J06BA02	Taste disturbance	Uncommon (0 1-1%)	After intravenous administration	-
	Macrolides Lincosamides And Streptogramins	Azitromycin	J01FA10 S01AA26	Taste disturbance	Rare or very rare (<0 1%)	After intravenous administration	A

Table A1. Drug induced dysgeusia (PT) in all level 1 ATC categories (*continued*)

ATC level 1	ATC level 3	Generic name	ATC Code	LLT MedDRA	Frequency	Specific type of administration	Coinciding adverse effects
ANTIINFECTIVES FOR SYSTEMIC USE		Claritromycin	J01FA09	Taste disturbance	Common (1-10%)	-	-
		Roxitromycin	J01FA06	Taste disturbance	Rare or very rare (<0 1%)	-	-
	Other Antibacterials	Dalbavancin	J01XA04	Taste disturbance	Uncommon (0 1-1%)	-	-
		Daptomycin	J01XX09	Taste disturbance	Uncommon (0 1-1%)	-	-
		Daptomycin	J01XX09	Taste metallic	Rare or very rare (<0 1%)	-	-
		Fosfomycin	J01XX01	Taste disturbance	Uncommon (0 1-1%)	After parenteral administration	-
		Linezolid	J01XX08	Taste metallic	Common (1-10%)	-	D
		Tedizolid	J01XX11	Taste disturbance	Uncommon (0 1-1%)	-	D
	Other Beta-Lactam Antibacterials	Ceftazidim	J01DD02 S01AA	Dysgeusia	Rare or very rare (<0 1%)	-	-
		Ertapenem	J01DH03	Taste disturbance	Uncommon (0 1-1%)	-	D
		Imipenem	J01DH51	Taste disturbance	Frequency not known	-	-
	Quinolone Antibacterials	Ciprofloxacine	J01MA02 V04CL	Taste disturbance	Uncommon (0 1-1%)	-	A
		Levofloxacin	J01MA12	Taste disturbance	Uncommon (0 1-1%)	After oral and intravenous administration	-
		Levofloxacin	J01MA12	Taste disturbance	Very common (>10%)	After inhalation	-
		Moxifloxacin	J01MA14 S01AE07	Taste disturbance	Uncommon (0 1-1%)	After oral and intravenous administration	-
		Moxifloxacin	J01MA14 S01AE07	Taste disturbance	Common (1-10%)	After ocular administration	-

Table A1. Drug induced dysgeusia (PT) in all level 1 ATC categories (*continued*)

ATC level 1	ATC level 3	Generic name	ATC Code	LLT MedDRA	Frequency	Specific type of administration	Coinciding adverse effects
ANTIINFECTIVES FOR SYSTEMIC USE		Ofloxacin	J01MA01 S01AE01 S02AA16	Taste disturbance	Common (1-10%)	After auricular administration	-
		Ofloxacin	J01MA01 S01AE01 S02AA16	Taste disturbance	Frequency not known	After oral administration	-
	Sulfonamides And Trimethoprim	Cotrimoxazol	J01EE01	Taste metallic	Frequency not known	-	-
	Viral Vaccines	Encephalitis, Japanese, Inactivated, Whole Virus	J07BA02	Taste disturbance	Frequency not known	-	-
ANTINEOPLASTIC AND IMMUNOMODULATING AGENTS	Alkylating Agents	Bendamustine	L01AA09	Taste disturbance	Frequency not known	-	-
		Chloormethine	L01AA05	Taste metallic	Rare or very rare (<0 1%)	After intravenous administration	-
		Temozolomide	L01AX03	Taste disturbance	Common (1-10%)	-	D
	Antimetabolites	Methotrexate	L01BA01 L04AX03 S01XA	Taste metallic	Frequency not known	-	-
		Nelarabine	L01BB07	Taste disturbance	Common (1-10%)	-	-
		Tegafur	L01BC03	Taste disturbance	Common (1-10%)	-	D
	Cytotoxic Antibiotics And Related Substances	Mitoxantron	L01DB07	Taste disturbance	Uncommon (0 1-1%)	-	-
		Pixantron	L01DB11	Taste disturbance	Common (1-10%)	-	D
	Hormone Antagonists And Related Agents	Anastrozol	L02BG03	Taste disturbance	Common (1-10%)	-	-
		Letrozol	L02BG04	Taste disturbance	Uncommon (0 1-1%)	-	D

Table A1. Drug induced dysgeusia (PT) in all level 1 ATC categories (*continued*)

ATC level 1	ATC level 3	Generic name	ATC Code	LLT MedDRA	Frequency	Specific type of administration	Coinciding adverse effects
ANTINEOPLASTIC AND IMMUNOMODULATING AGENTS	Hormones And Related Agents	Busereline	L02AE01	Taste disturbance	Frequency not known	After nasal administration	P
		Leuproreline	L02AE02	Taste disturbance	Common (1-10%)	-	D
		Triptoreline	L02AE04	Taste disturbance	Frequency not known	-	D
	Immunostimulants	Glatiramer Acetate	L03AX13	Taste disturbance	Common (1-10%)	-	-
		Histamin	L03AX14 V04CG03 V04CX	Taste metallic	Frequency not known	After nasal administration	-
		Interferon Alfa 2A	L03AB04	Taste disturbance	Common (1-10%)	-	D
		Interferon Alfa 2B	L03AB05	Taste disturbance	Common (1-10%)	-	D
		Peginterferon Alfa 2A	L03AB11	Taste disturbance	Common (1-10%)	-	D
		Peginterferon Alfa 2B	L03AB10	Taste disturbance	Common (1-10%)	-	D
	Immunosuppressants	Alemtuzumab	L04AA34	Taste disturbance	Common (1-10%)	-	D
		Eculizumab	L04AA25	Taste disturbance	Common (1-10%)	-	-
		Golimumab	L04AB06	Taste disturbance	Frequency not known	-	-
		Leflunomide	L04AA13	Taste disturbance	Uncommon (0 1-1%)	-	-
		Lenalidomide	L04AX04	Taste disturbance	Very common (>10%)	-	D
		Mycofenolzuur	L04AA06	Taste disturbance	Common (1-10%)	-	-
		Pirfenidon	L04AX05	Taste disturbance	Common (1-10%)	-	-
	Other Antineoplastic Agents	Bevacizumab	L01XC07 S01LA	Taste disturbance	Very common (>10%)	-	-
		Bortezomib	L01XX32	Taste disturbance	Common (1-10%)	-	-
		Cabozantinib	L01XE26	Taste disturbance	Very common (>10%)	-	-

Table A1. Drug induced dysgeusia (PT) in all level 1 ATC categories (*continued*)

ATC level 1	ATC level 3	Generic name	ATC Code	LLT MedDRA	Frequency	Specific type of administration	Coinciding adverse effects
ANTINEOPLASTIC AND IMMUNOMODULATING AGENTS		Carboplatine	L01XA02	Taste disturbance	Common (1-10%)	-	-
		Eribuline	L01XX41	Taste disturbance	Common (1-10%)	-	D
		Everolimus	L01XE10 L04AA18	Taste disturbance	Very common (>10%)	In case of oncologic treatment	D
		Imatinib	L01XE01	Taste disturbance	Common (1-10%)	-	D
		Lenvatinib	L01XE29	Taste disturbance	Very common (>10%)	-	D
		Mitotaan	L01XX23	Taste disturbance	Rare or very rare (<0 1%)	-	-
		Olaparib	L01XX46	Taste disturbance	Very common (>10%)	-	-
		Oxaliplatine	L01XA03	Taste disturbance	Very common (>10%)	-	-
		Pazopanib	L01XE11	Taste disturbance	Very common (>10%)	-	D
		Pembrolizumab	L01XC18	Taste disturbance	Common (1-10%)	-	D
		Regorafenib	L01XE21	Taste disturbance	Common (1-10%)	-	D
		Ribociclib	L01XE42	Taste disturbance	Common (1-10%)	-	-
		Rituximab	L01XC02	Taste disturbance	Uncommon (0 1-1%)	When used to treat lymphoma's	-
		Sonidegib	L01XX48	Taste disturbance	Very common (>10%)	-	-
		Sunitinib	L01XE04	Taste disturbance	Very common (>10%)	-	D
		Trastuzumab	L01XC03	Taste disturbance	Common (1-10%)	-	D
		Vemurafenib	L01XE15	Taste disturbance	Very common (>10%)	-	-
		Vismodegib	L01XX43	Taste disturbance	Very common (>10%)	-	-
	Plant Alkaloids And Other Natural Products	Cabazitaxel	L01CD04	Taste disturbance	Very common (>10%)	-	D

Table A1. Drug induced dysgeusia (PT) in all level 1 ATC categories (*continued*)

ATC level 1	ATC level 3	Generic name	ATC Code	LLT MedDRA	Frequency	Specific type of administration	Coinciding adverse effects
ANTINEOPLASTIC AND IMMUNOMODULATING AGENTS		Docetaxel	L01CD02	Taste disturbance	Very common (>10%)	During monotherapy	-
		Etoposide	L01CB01	Taste disturbance	Frequency not known	-	-
		Paclitaxel	L01CD01	Dysgeusia	Common (1-10%)	-	D
		Trabectedine	L01CX01	Taste disturbance	Common (1-10%)	During monotherapy	-
		Vinflunine	L01CA05	Taste disturbance	Common (1-10%)	-	-
ANTIPARASITIC PRODUCTS INSECTICIDES AND REPELLENTS	Agents Against Leishmaniasis And Trypanosomiasis	Benznidazol	P01CA02	Taste disturbance	Rare or very rare (<0 1%)	-	-
		Pentamidine	P01CX01	Taste disturbance	Common (1-10%)	After injection	-
	Antimalarials	Artesunaat	P01BE03	Taste bitter	Frequency not known	-	-
		Quinine	P01BC01	Taste bitter	Frequency not known	-	-
	Antinematodal Agents	Levamisol	P02CE01	Dysgeusia	Frequency not known	-	-
BLOOD AND BLOOD FORMING ORGANS	Antithrombotic Agents	Clopidogrel	B01AC04	Taste disturbance	Frequency not known	-	P
		Iloprost	B01AC11	Taste disturbance	Uncommon (0 1-1%)	After intravenous administration	-
	Blood And Related Products	Albumine	B05AA01 V07AB	Taste disturbance	Rare or very rare (<0 1%)	-	D
	I.V. Solutions	Fat Emulsions	B05BA02	Dysgeusia	Uncommon (0 1-1%)	-	-
		Iron, Parenteral Preparations	B03AC	Taste disturbance	Common (1-10%)	-	-
	Vitamin K And Other Hemostatics	Efmoroctocog Alfa	B02BD02	Taste disturbance	Uncommon (0 1-1%)	-	-

Table A1. Drug induced dysgeusia (PT) in all level 1 ATC categories (*continued*)

ATC level 1	ATC level 3	Generic name	ATC Code	LLT MedDRA	Frequency	Specific type of administration	Coinciding adverse effects
BLOOD AND BLOOD FORMING ORGANS		Eftrenonacog Alfa	B02BD04	Taste disturbance	Uncommon (0 1-1%)	-	-
		Moroctocog Alfa	B02BD02	Taste disturbance	Uncommon (0 1-1%)	-	-
		Nonacog Alfa	B02BD04	Taste disturbance	Common (1-10%)	-	-
		Nonacog Gamma	B02BD04	Taste disturbance	Common (1-10%)	-	-
		Octocog Alfa	B02BD02	Taste disturbance	Uncommon (0 1-1%)	-	-
		Factor Viii Inhibitor Bypassing Activity	B02BD03	Taste disturbance	Frequency not known	-	-
		Romiplostim	B02BX04	Taste disturbance	Uncommon (0 1-1%)	-	-
CARDIOVASCULAR SYSTEM	Ace Inhibitors Plain	Benazepril	C09AA07	Taste disturbance	Uncommon (0 1-1%)	-	-
		Enalapril	C09AA02	Taste disturbance	Common (1-10%)	-	-
		Fosinopril	C09AA09	Taste disturbance	Common (1-10%)	-	D
		Lisinopril	C09AA03	Taste disturbance	Uncommon (0 1-1%)	-	D
		Perindopril	C09AA04	Taste disturbance	Common (1-10%)	-	D,A
		Quinapril	C09AA06	Taste disturbance	Frequency not known	-	D
	Angiotensin Ii Antagonists Plain	Irbesartan	C09CA04	Taste disturbance	Rare or very rare (<0 1%)	-	D
		Losartan	C09CA01	Taste disturbance	Rare or very rare (<0 1%)	-	-
		Telmisartan	C09CA07	Taste disturbance	Frequency not known	-	-
	Antiarrhythmics Class I And Iii	Amiodaron	C01BD01	Taste disturbance	Very common (>10%)	-	D
		Procaïnamide	C01BA02	Taste disturbance	Rare or very rare (<0 1%)	-	D,A
		Propafenon	C01BC03	Taste disturbance	Common (1-10%)	-	-
		Vernakalant	C01BG11	Taste disturbance	Very common (>10%)	-	D

Table A1. Drug induced dysgeusia (PT) in all level 1 ATC categories (*continued*)

ATC level 1	ATC level 3	Generic name	ATC Code	LLT MedDRA	Frequency	Specific type of administration	Coinciding adverse effects
CARDIOVASCULAR SYSTEM	Antivaricose Therapy	Lauromacrogol 400	C05BB02	Taste metallic	Frequency not known	-	D,A
	Arteriolar Smooth Muscle Agents Acting On	Minoxidil	C02DC01 D11AX01	Taste disturbance	Uncommon (0 1-1%)	After cutaneous administration	-
	Beta Blocking Agents	Metoprolol	C07AB02	Taste disturbance	Uncommon (0 1-1%)	-	-
		Sotalol	C07AA07	Taste disturbance	Common (1-10%)	-	D
	Lipid Modifying Agents Plain	Colestyramine	C10AC01	Taste disturbance	Rare or very rare (<0 1%)	-	-
		Omega-3-Vetzuren	C10AX06	Taste disturbance	Uncommon (0 1-1%)	-	-
	Other Cardiac Preparations	Adenosine	C01EB10	Taste metallic	Uncommon (0 1-1%)	-	-
		Regadenoson	C01EB21	Taste disturbance	Common (1-10%)	-	-
	Potassium-Sparing Agents	Amiloride	C03DB01	Dysgeusia	Frequency not known	-	-
	Selective Calcium Channel Blockers With Mainly Vascular Effects	Amlodipine	C08CA01	Taste disturbance	Uncommon (0 1-1%)	-	D
DERMATOLOGICALS	Anti-Acne Preparations For Topical Use	Clindamycin	D10AF01 G01AA10 J01FF01	Dysgeusia	Rare or very rare (<0 1%)	After cutaneous administration	D
		Clindamycin	D10AF01 G01AA10 J01FF01	Taste disturbance	Uncommon (0 1-1%)	After intravenous administration	-
	Antifungals For Topical Use	Ketoconazol	D01AC08 J02AB02	Taste disturbance	Uncommon (0 1-1%)	When used as shampoo	-
		Ketoconazol	D01AC08 J02AB02	Taste disturbance	Frequency not known	-	D
		Terbinafine	D01AE15 D01BA02	Taste disturbance	Uncommon (0 1-1%)	-	D
	Antipsoriatics For Systemic Use	Acitretine	D05BB02	Taste disturbance	Rare or very rare (<0 1%)	-	-

Table A1. Drug induced dysgeusia (PT) in all level 1 ATC categories (*continued*)

ATC level 1	ATC level 3	Generic name	ATC Code	LLT MedDRA	Frequency	Specific type of administration	Coinciding adverse effects
DERMATOLOGICALS	Chemotherapeutics For Topical Use	Metronidazol	D06BX01 G01AF01 J01XD01 P01AB01	Dysgeusia	Frequency not known	-	D
		Metronidazol	D06BX01 G01AF01 J01XD01 P01AB01	Taste disturbance	Uncommon (0 1-1%)	After cutaneous administration	-
	Corticosteroids Plain	Fluticason	D07AC17 R01AD08 R01AD12 R03BA05	Dysgeusia	Common (1-10%)	After nasal administration	-
		Mometason	D07AC13 R01AD09	Taste disturbance	Rare or very rare (<0 1%)	After nasal administration	-
	Enzymes	Collagenase	D03BA02 M09AB02	Taste disturbance	Uncommon (0 1-1%)	When used intralaesionally by Peyronie's disease	-
	Other Dermatological Preparations	Brimonidine	D11AX21 S01EA05	Taste disturbance	Common (1-10%)	-	-
	Protectives Against UV-Radiation	Afamelanotide	D02BB02	Taste disturbance	Uncommon (0 1-1%)	-	D
GENITO URINARY SYSTEM AND SEX HORMONES	Hormonal Contraceptives For Systemic Use	Drospirenon	G03AC10	Taste disturbance	Uncommon (0 1-1%)	In combination with estradiol	-
	Other Urologicals Incl. Antispasmodics	Dapoxetine	G04BX14	Taste disturbance	Uncommon (0 1-1%)	-	D
		Darifenacine	G04BD10	Taste disturbance	Uncommon (0 1-1%)	-	D
		Fesoterodine	G04BD11	Taste disturbance	Uncommon (0 1-1%)	-	D
	Vasopressin Antagonists	Tolvaptan	G04BX	Taste disturbance	Uncommon (0 1-1%)	-	D

Table A1. Drug induced dysgeusia (PT) in all level 1 ATC categories (*continued*)

ATC level 1	ATC level 3	Generic name	ATC Code	LLT MedDRA	Frequency	Specific type of administration	Coinciding adverse effects
MUSCULO-SKELETAL SYSTEM	Antigout Preparations	Allopurinol	M04AA01	Taste disturbance	Frequency not known	-	D
		Febuxostat	M04AA03	Taste disturbance	Uncommon (0 1-1%)	-	-
	Anti-inflammatory And Anti-rheumatic Products Non-Steroids	Aceclofenac	M01AB16	Taste disturbance	Frequency not known	-	D
		Celecoxib	M01AH01	Taste disturbance	Frequency not known	-	-
		Diclofenac	M01AB05 M02AA15 S01BC03	Taste disturbance	Frequency not known	After systemic administration	A
		Etoricoxib	M01AH05	Taste disturbance	Uncommon (0 1-1%)	-	-
		Ketoprofen	M01AE03 M02AA10	Taste disturbance	Rare or very rare (<0 1%)	-	D
	Drugs Affecting Bone Structure And Mineralization	Alendronic Acid	M05BA04	Taste disturbance	Uncommon (0 1-1%)	-	-
		Ibandronic Acid	M05BA06	Taste disturbance	Uncommon (0 1-1%)	After oral administration	-
		Zoledronic Acid	M05BA08	Taste disturbance	Uncommon (0 1-1%)	-	-
	Muscle Relaxants Directly Acting Agents	Dantrolene	M03CA01	Taste disturbance	Frequency not known	After oral administration	-
	Other Drugs For Disorders Of The Musculo-Skeletal System	Hydroquinine	M09AA01	Taste bitter	Very common (>10%)	-	-
NERVOUS SYSTEM	Anesthetics General	Fentanyl	N01AH01 N02AB03	Taste disturbance	Uncommon (0 1-1%)	After nasal administration	-
		Fentanyl	N01AH01 N02AB03	Taste disturbance	Common (1-10%)	After oral administration	D

Table A1. Drug induced dysgeusia (PT) in all level 1 ATC categories (*continued*)

ATC level 1	ATC level 3	Generic name	ATC Code	LLT MedDRA	Frequency	Specific type of administration	Coinciding adverse effects
NERVOUS SYSTEM		Fentanyl	N01AH01 N02AB03	Taste disturbance	Common (1-10%)	After sublingual administration	D
	Anesthetics Local	Articaine	N01BB08	Taste metallic	Frequency not known	-	D
		Capsaicin	N01BX04 R01AX	Taste disturbance	Uncommon (0 1-1%)	When used as plaster	-
	Anti-Dementia Drugs	Galantamine	N06DA04	Taste disturbance	Uncommon (0 1-1%)	-	-
	Antidepressants	Amitriptyline	N06AA09	Taste disturbance	Common (1-10%)	-	-
		Bupropion	N06AX12	Taste disturbance	Common (1-10%)	-	D
		Citalopram	N06AB04	Taste disturbance	Frequency not known	-	D
		Clomipramine	N06AA04	Taste disturbance	Common (1-10%)	-	D
		Fluoxetine	N06AB03	Taste disturbance	Common (1-10%)	-	D
		Moclobemide	N06AG02	Taste disturbance	Uncommon (0 1-1%)	-	D
		Nortriptyline	N06AA10	Taste disturbance	Common (1-10%)	-	D
		Trazodon	N06AX05	Taste disturbance	Rare or very rare (<0 1%)	-	D
		Venlafaxine	N06AX16	Taste disturbance	Common (1-10%)	-	D
	Antiepileptics	Carbamazepine	N03AF01	Taste disturbance	Frequency not known	-	D
		Phenytoin	N03AB02	Taste disturbance	Frequency not known	-	D
		Topiramaat	N03AX11	Taste disturbance	Common (1-10%)	-	-
	Antimigraine Preparations	Eletriptan	N02CC06	Taste disturbance	Uncommon (0 1-1%)	-	D
		Frovatriptan	N02CC07	Taste disturbance	Uncommon (0 1-1%)	-	D
		Rizatriptan	N02CC04	Taste disturbance	Uncommon (0 1-1%)	-	D
	Antipsychotics	Lithium	N05AN01	Taste disturbance	Rare or very rare (<0 1%)	-	D
		Risperidon	N05AX08	Taste disturbance	Uncommon (0 1-1%)	-	-

Table A1. Drug induced dysgeusia (PT) in all level 1 ATC categories (*continued*)

ATC level 1	ATC level 3	Generic name	ATC Code	LLT MedDRA	Frequency	Specific type of administration	Coinciding adverse effects
NERVOUS SYSTEM	Dopaminergic Agents	Levodopa	N04BA01	Taste bitter	Rare or very rare (<0 1%)	-	D
		Safinamide	N04BD03	Taste disturbance	Frequency not known	-	D
	Drugs Used In Addictive Disorders	Disulfiram	N07BB01	Taste garlic	Frequency not known	-	D
		Disulfiram	N07BB01	Taste metallic	Frequency not known	-	-
		Nicotine	N07BA01	Taste disturbance	Common (1-10%)	-	-
		Varenicline	N07BA03	Taste disturbance	Common (1-10%)	-	D
	Hypnotics And Sedatives	Lormetazepam	N05CD06	Taste disturbance	Common (1-10%)	-	D
		Zopiclon	N05CF01	Taste bitter	Common (1-10%)	-	D
	Opioids	Buprenorfine	N02AE01 N07BC01	Taste disturbance	Uncommon (0 1-1%)	After transdermal administration	D
		Hydromorfon	N02AA03	Taste disturbance	Uncommon (0 1-1%)	After intravenous and subcutaneous administration	D
		Morphine	N02AA01 V04CL	Taste disturbance	Uncommon (0 1-1%)	After oral administration	D
		Oxycodon	N02AA05	Taste disturbance	Uncommon (0 1-1%)	-	-
	Other Analgesics And Antipyretics	Ziconotide	N02BG08	Taste disturbance	Common (1-10%)	-	D
	Other Nervous System Drugs	Sodium Oxybate	N07XX04	Taste disturbance	Common (1-10%)	-	D,A
	Psychostimulants Agents Used For ADHD And Nootropics	Atomoxetine	N06BA09	Taste disturbance	Common (1-10%)	-	-
		Modafinil	N06BA07	Taste disturbance	Uncommon (0 1-1%)	-	D

Table A1. Drug induced dysgeusia (PT) in all level 1 ATC categories (*continued*)

ATC level 1	ATC level 3	Generic name	ATC Code	LLT MedDRA	Frequency	Specific type of administration	Coinciding adverse effects
RESPIRATORY SYSTEM	Adrenergics Inhalants	Formoterol	R03AC13	Taste disturbance	Uncommon (0 1-1%)	-	D
	Antihistamines For Systemic Use	Cetirizine	R06AE07	Taste disturbance	Frequency not known	-	D
		Ebastine	R06AX22	Taste disturbance	Frequency not known	-	D
		Levocetirizine	R06AE09	Taste disturbance	Rare or very rare (<0 1%)	-	D
	Decongestants And Other Nasal Preparations For Topical Use	Azelastine	R01AC03 S01GX07	Dysgeusia	Common (1-10%)	After nasal administration	D
		Azelastine	R01AC03 S01GX07	Taste bitter	Uncommon (0 1-1%)	After ocular administration	D
		Ipratropium	R01AX03 R03BB01	Taste disturbance	Uncommon (0 1-1%)	-	D
		Tramazoline	R01AA09	Taste disturbance	Frequency not known	-	D
	Expectorants Excl. Combinations With Cough Suppressants	Ambroxol	R05CB06	Taste disturbance	Common (1-10%)	-	-
	Other Drugs For Obstructive Airway Diseases Inhalants	Ciclesonide	R03BA08	Dysgeusia	Uncommon (0 1-1%)	-	D
		Nedocromil	R03BC03 S01GX04	Taste disturbance	Common (1-10%)		-
		Tiotropium	R03BB04	Taste disturbance	Uncommon (0 1-1%)	-	-
		Umeclidinium	R03BB07	Taste disturbance	Uncommon (0 1-1%)	-	-
	Other Systemic Drugs For Obstructive Airway Diseases	Roflumilast	R03DX07	Taste disturbance	Uncommon (0 1-1%)	-	D
	Mucolytics	Myrtus	R05CB	Taste disturbance	Rare or very rare (<0 1%)	-	D
	Throat Preparations	Flurbiprofen	R02AX01	Taste disturbance	Uncommon (0 1-1%)	-	-

Table A1. Drug induced dysgeusia (PT) in all level 1 ATC categories (*continued*)

ATC level 1	ATC level 3	Generic name	ATC Code	LLT MedDRA	Frequency	Specific type of administration	Coinciding adverse effects
SENSORY ORGANS	Antiglaucoma Preparations And Miotics	Acetazolamide	S01EC01	Taste disturbance	Rare or very rare (<0 1%)	-	-
		Apraclonidine	S01EA03	Taste disturbance	Common (1-10%)	-	D
		Brinzolamide	S01EC04	Taste bitter	Common (1-10%)	-	-
		Dorzolamide	S01EC03	Taste bitter	Common (1-10%)	-	D,A
		Travoprost	S01EE04	Taste disturbance	Frequency not known	-	D
	Antiinfectives	Trifluridine	S01AD02	Taste disturbance	Common (1-10%)	In combination with tipiracil	D
	Antiinflammatory Agents	Fluormetholon	S01BA07	Taste disturbance	Rare or very rare (<0 1%)	-	D
	Decongestants And Antiallergics	Emedastine	S01GX06	Taste disturbance	Uncommon (0 1-1%)	-	-
		Olopatadine	S01GX09	Taste disturbance	Common (1-10%)	-	-
	Diagnostic Agents	Fluorescein	S01JA01	Taste disturbance	Rare or very rare (<0 1%)	After intravenous administration	-
SYSTEMIC HORMONAL PREPARATIONS EXCL.	Anterior Pituitary Lobe Hormones And Analogues	Pegvisomant	H01AX01	Taste disturbance	Uncommon (0 1-1%)	-	-
	Anti-Parathyroid Agents	Calcitonine	H05BA01	Taste disturbance	Common (1-10%)	-	-
		Paricalcitol	H05BX02	Taste disturbance	Uncommon (0 1-1%)	After oral administration	D
		Paricalcitol	H05BX02	Taste disturbance	Common (1-10%)	After intravenous administration	-
	Antithyroid Preparations	Thiamazol	H03BB02	Taste disturbance	Uncommon (0 1-1%)	-	D
	Corticosteroids For Systemic Use Plain	Methylprednisolone	H02AB04	Dysgeusia	Frequency not known	After intravenous administration	D
	Posterior Pituitary Lobe Hormones	Carbetocine	H01BB03	Taste metallic	Common (1-10%)	-	-

Table A1. Drug induced dysgeusia (PT) in all level 1 ATC categories (*continued*)

ATC level 1	ATC level 3	Generic name	ATC Code	LLT MedDRA	Frequency	Specific type of administration	Coinciding adverse effects
VARIOUS	All Other Therapeutic Products	Diazoxide	V03AH01	Taste disturbance	Rare or very rare (<0 1%)	-	-
		Sucroferric Oxyhydroxide	V03AE05	Dysgeusia	Common (1-10%)	-	-
		Lanthanum Carbonate	V03AE03	Taste disturbance	Uncommon (0 1-1%)	-	-
	Allergens	Grass Pollen	V01AA02 V01AA	Taste disturbance	Uncommon (0 1-1%)	After sublingual administration	-
	Cardiovascular System	Technetium (99Mtc) Tetrofosmin	V09GA02	Taste disturbance	Frequency not known	-	-
		Technetium (99Mtc) Tetrofosmin	V09GA02	Taste metallic	Frequency not known	-	-
	Magnetic Resonance Imaging Contrast Media	Gadobenic Acid	V08CA08	Taste disturbance	Uncommon (0 1-1%)	-	-
		Gadobutrol	V08CA09	Taste disturbance	Uncommon (0 1-1%)	-	-
		Gadodiamide	V08CA03	Taste disturbance	Frequency not known	-	-
		Gadoteridol	V08CA04	Taste disturbance	Uncommon (0 1-1%)	-	D
		Gadoversetamide	V08CA06	Taste disturbance	Common (1-10%)	-	-
		Gadoxetic Acid	V08CA10	Taste disturbance	Uncommon (0 1-1%)	-	D
	Other Diagnostic Agents	Corticorelin	V04CD04	Taste disturbance	Common (1-10%)	-	D,A
		Somatorelin	V04CD05	Taste disturbance	Common (1-10%)	-	-
		Dimercaprol	V03AB09	Taste disturbance	Frequency not known	-	-
	Ultrasound Contrast Media	Microspheres Of Human Albumin	V08DA01	Taste disturbance	Common (1-10%)	-	-

Table A1. Drug induced dysgeusia (PT) in all level 1 ATC categories (*continued*)

ATC level 1	ATC level 3	Generic name	ATC Code	LLT MedDRA	Frequency	Specific type of administration	Coinciding adverse effects
VARIOUS		Microspheres Of Phospholipids	V08DA04	Taste disturbance	Uncommon (0 1-1%)	-	-
		Sulfur Hexafluoride	V08DA05	Taste disturbance	Uncommon (0 1-1%)	After intravenous administration	-

ATC= Anatomic Therapeutical Chemical; LLT= lowest level term; D= dry mouth; A= Ansomia; P= Parosmia

Table A2. Drugs documented with "bitter taste" as an adverse effect.

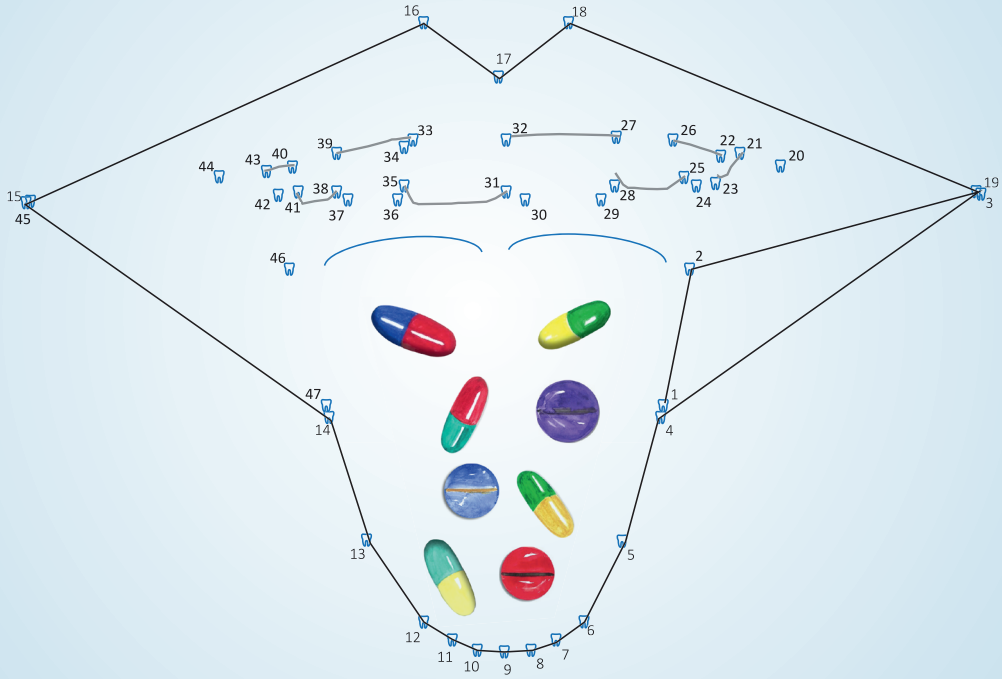
ATC level 1	ATC level 3	Generic name	ATC Code	LLT MedDRA	Frequency	Specific type of administration	Coinciding adverse effects
ANTIINFECTIVES FOR SYSTEMIC USE	Amphenicols	Chloramphenicol	J01BA01 S01AA01	Taste bitter	Frequency not known	After ocular administration	-
ANTIPARASITIC PRODUCTS INSECTICIDES AND REPELLENTS	Antimalarials	Artesunate	P01BE03	Taste bitter	Frequency not known	-	-
		Quinine	P01BC01	Taste bitter	Frequency not known	-	-
MUSCULO-SKELETAL SYSTEM	Other Drugs For Disorders Of The Musculo-Skeletal System	Hydroquinine	M09AA01	Taste bitter	Very common (>10%)	-	-
RESPIRATORY SYSTEM	Decongestants And Other Nasal Preparations For Topical Use	Azelastine	R01AC03 S01GX07	Taste bitter	Uncommon (0 1-1%)	After ocular administration	D
NERVOUS SYSTEM	Dopaminergic Agents	Levodopa	N04BA01	Taste bitter	Rare or very rare (<0 1%)	-	D
		Zopiclon	N05CF01	Taste bitter	Common (1-10%)	-	D
SENSORY ORGANS	Carbonic Anhydrase Inhibitors	Brinzolamide	S01EC04	Taste bitter	Common (1-10%)	-	-
		Dorzolamide	S01EC03	Taste bitter	Common (1-10%)	-	D,A

ATC= Anatomic Therapeutical Chemical; LLT= lowest level term; D= dry mouth; A= Ansomia

Table A3: Drugs documented with "metallic taste" as an adverse effect.

ATC level 1	ATC level 3	Generic name	ATC Code	LLT MedDRA	Frequency	Specific type of administration	Coinciding adverse effects
ANTIINFECTIVES FOR SYSTEMIC USE	Antiinfectives For Systemic Use	Daptomycin	J01XX09	Taste metallic	Rare or very rare (<0 1%)	-	-
		Linezolid	J01XX08	Taste metallic	Common (1-10%)	-	D
		Cotrimoxazol	J01EE01	Taste metallic	Frequency not known	-	-
ANTINEOPLASTIC AND IMMUNOMODULATING AGENTS	Antineoplastic And Immunomodulating Agents	Chloormethine	L01AA05	Taste metallic	Rare or very rare (<0 1%)	After intravenous administration	-
		Methotrexate	L01BA01 L04AX03 S01XA	Taste metallic	Frequency not known	-	-
		Histamin	L03AX14 V04CG03 V04CX	Taste metallic	Frequency not known	After nasal administration	-
CARDIOVASCULAR SYSTEM	Cardiovascular System	Lauromacrogol 400	C05BB02	Taste metallic	Frequency not known	-	D,A
		Adenosine	C01EB10	Taste metallic	Uncommon (0 1-1%)	-	-
NERVOUS SYSTEM	Nervous System	Articaine	N01BB08	Taste metallic	Frequency not known	-	D
		Disulfiram	N07BB01	Taste metallic	Frequency not known	-	-
SYSTEMIC HORMONAL PREPARATIONS EXCL.	Systemic Hormonal Preparations Excl.	Carbetocine	H01BB03	Taste metallic	Common (1-10%)	-	-
VARIOUS	Various	Technetium (99mTc) tetrofosmin	V09GA02	Taste metallic	Frequency not known	-	-

ATC= Anatomic Therapeutical Chemical; LLT= lowest level term; D= dry mouth; A= Ansomia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6 Oral adverse effects of drugs: drug-induced tongue disorders

This chapter is based on the following publication:
Oral adverse effects of drugs: drug-induced tongue disorders

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ABSTRACT

Due to a worldwide increase of 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.

The national drug information database for Dutch pharmacists, composed of scientific drug information, guidelines and summaries of product characteristics, was analyzed for drug-induced tongue disorders. “MedDRA classification” and “Anatomic Therapeutical Chemical codes” were used to categorize the disorders.

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.

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.

INTRODUCTION

The global consumption of drugs to treat acute and chronic diseases continues to increase.[1] 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.[2] 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 effects of drugs in the oral region. The first paper discussed drug-induced taste disorders.[2] 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.[3] Drug-induced tongue disorders belong to the category acquired tongue disorders.

Several studies have reported cases of drug-induced tongue disorders [4-11], 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.

MATERIAL AND METHODS

An elaborated description of the materials and methods used in the current study is described by Rademacher et al. (2019).[2] 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.[12] 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 trails, observational studies, case reports, etc.), but also data from the Netherlands pharmacovigilance centre LAREB, the Dutch knowledge center 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 August, 1 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 Anatomic Therapeutical Chemical (ATC) code of the drug.[13] The MedDRA classification was manually applied after the selection of drugs that have been linked to causing tongue disorders.[14, 15] This system categorize medical terminology in five levels. The ''Lowest Level Term (LLT)'' and the ''Preferred Term (PT)'' were used to categorize drug-induced tongue disorders.[16] 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.

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 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:

1. Alteration in color of the tongue (glossitis, tongue discoloration, hairy tongue, coated tongue)
2. Increase of 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 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

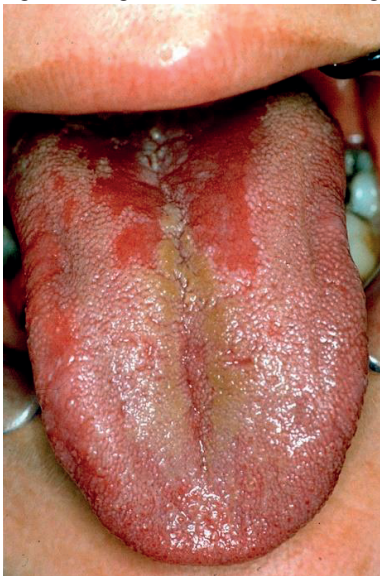
Table 2. Number of drugs associated with tongue disorders per ATC level 1 category.

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
Genito urinary system and sex hormones	1
Musculo-skeletal system	2
Nervous system	26
Respiratory system	4
Sensory organs	1
Systemic hormonal preparations, excl.	1
Various	10
Total:	121

Alteration in color of the tongue

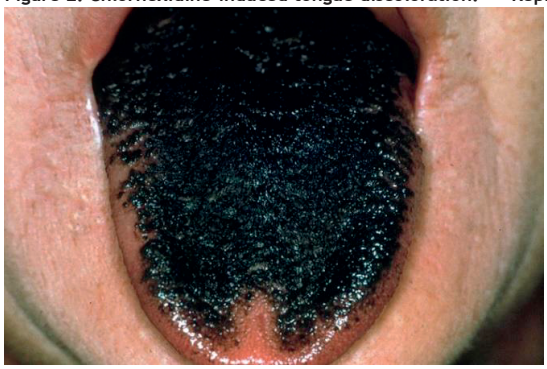
In total, 36 (2.2% of 1645 drugs) drugs were associated with glossitis (Figure 1) as an adverse drug reaction (Table 1). Glossitis was defined as inflammation of the tongue with loss of filiform papillae, leading to pain, swelling and erythema.[17] It was reported in 10 of the 14 ATC level 1 categories 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.

Figure 1: Drug-induced median rhomboid glossitis,[18]. Reprinted with permission.



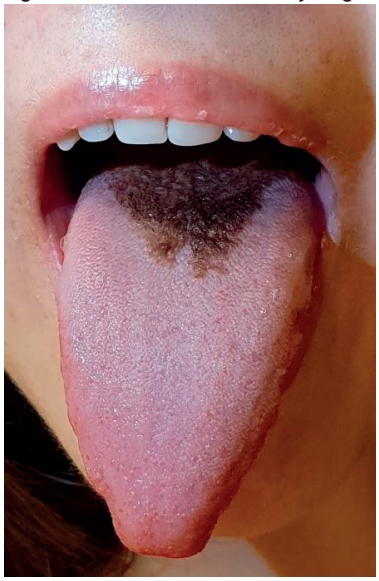
In the Informatorium Medicamentorum database, 21 drugs (1.28% of 1645 drugs) were associated with the development of tongue discoloration (Figure 2) as an adverse drug reaction. Tongue discoloration was defined as pigmentation of the tongue as a result of the drug or its metabolites deposition or by increasing the production of melanin. The discoloration may be blue, brown, gray or black.[19] 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.

Figure 2: Chlorhexidine-induced tongue discoloration. [18] Reprinted with permission.



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 color of the tongue can vary from yellow to brown or black.[20] 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 4 drugs is coated tongue a ''rare'' adverse drug reaction. An overview of all drugs that may alter the color of the tongue is given in Table A1 of the appendix.

Figure 3. Antibiotics-induced hairy tongue

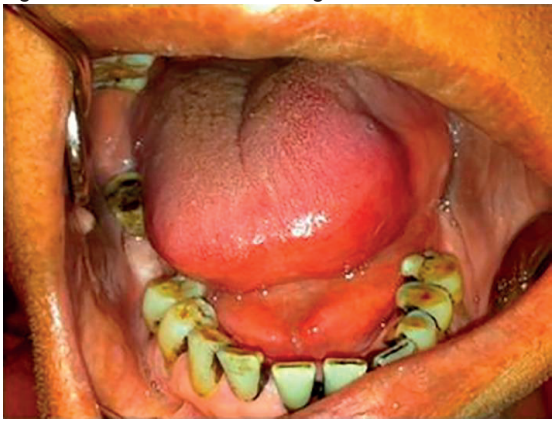


Increase of volume of the tongue

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 A2 of the appendix.

Figure 4. ACE inhibitor-induced tongue oedema



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.[21] 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 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 unpleas-

ant 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 adverse effect of sublingually administrated allergen extracts. Glossodynia was described as burning sensation of the tongue due to an identifiable cause, e.g. 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 A3 of the appendix gives an overview of all drugs that may cause alteration in sensitivity of the tongue.

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 drug), ''cardiovascular system'' (1 drug) and ''nervous system'' (2 drugs). The frequency of tongue ulceration was ''rare'' in 3 out of 4 drugs (Table 3).

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 colestyramine 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 A4.

Table 3. 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 leukemia
CARDIOVASCULAR SYSTEM	VASODILATORS USED IN CARDIAC DISEASES	Nicorandil	C01DX16	Tongue ulceration	Rare (≥ 0.01% and < 0.1%)	Not given
NERVOUS SYSTEM	HYPNOTICS AND SEDATIVES	Melatonin	N05CH01	Tongue ulceration	Rare (≥ 0.01% and < 0.1%)	Not given
	ANTIDEPRESSANTS	Sertraline	N06AB06	Tongue ulceration	Rare (≥ 0.01% and < 0.1%)	Not given

DISCUSSION

Drug-induced tongue disorders was 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 healthcare 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 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 make 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[22, 23], nonsteroidal 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.[4] Early recognition of drug-induced tongue oedema is important as it can be a life-threating 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.[5, 6, 8, 20] Beside the color black, hairy tongue can also be yellow, green, blue, brown or even colorless. 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, hydogen peroxide, antibiotics in combination with amoxicilline and sulfamethoxazole 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 have been reported in the literature. The underlying mechanism for glossitis in those cases was avitaminoses without apparent cause.[7] 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[24] which consist all the medications registered with the Medicines Evaluation Board of the Netherlands. In addition, it also consist drugs that are registered in European Medicines Agency.

Anti-rheumatic drugs such as leflunomide are reported to cause ulcers in the tongue.[11] Tongue ulcers are also associated with nicorandil use. The pathophysiology of nicorandil induced tongue ulcers is still unclear.[9] 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 are very specific. According to the farmacotherapeutisch kompas, an adverse effect of leflunomide is ulcers in the mouth which is unspecific compared to tongue ulceration.

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 health care workers in the recognition, diagnosis and eventual treatment of drug-induced tongue disorders.

CONFLICT OF INTEREST

None.

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APPENDIX

Table A1. Alteration in color 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 (≥ 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 ANTIINFECTIVES	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 (≥ 0.01% and < 0.1%)	Not given
ANTIINFECTIVES FOR SYSTEMIC USE	BETA-LACTAM ANTIBACTERIALS, PENICILLINS	Benzylpenicillin	J01CE01	Glossitis	Uncommon (0.1-1%)	Not given
	TETRACYCLINES	Minocycline	J01AA08	Glossitis	Rare (≥ 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

Table A1. Alteration in color of the tongue (glossitis, tongue discoloration, hairy tongue, coated tongue) (*continued*)

ATC level 1	ATC level 3	Generic name	ATC Code	LLT MedDRA*	Frequency	Specific type of administration
ANTIINFECTIVES FOR SYSTEMIC USE	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 cilastatin	J01DH51	Glossitis	Rare (≥ 0.01% and < 0.1%)	Not given
	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 (≥ 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

Table A1. Alteration in color of the tongue (glossitis, tongue discoloration, hairy tongue, coated tongue) (*continued*)

ATC level 1	ATC level 3	Generic name	ATC Code	LLT MedDRA*	Frequency	Specific type of administration
ANTIINFECTIVES FOR SYSTEMIC USE	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 cilastatin	J01DH51	Tongue discoloration	Rare (≥ 0.01% and < 0.1%)	Not given
	SULFONAMIDES AND TRIMETHOPRIM	Sulfamethoxazole and trimethoprim	J01EE01	Tongue discoloration	Frequency not known	Not given
	DIRECT ACTING ANTIVIRALS	Darunavir	J05AE10	Tongue coated	Rare (≥ 0.01% and < 0.1%)	Not given
	COMBINATION OF ANTIBACTERIALS	Combination of antibacterials	J01RA	Hairy tongue	Very rare (<0.01%)	In combination with amoxicillin
	SULFONAMIDES AND TRIMETHOPRIM	Sulfamethoxazole and trimethoprim	J01EE01	Hairy tongue	Frequency not known	Not given
ANTINEOPLASTIC IMMUNOMODULATING AND AGENTS	IMMUNOSTIMULANTS	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 (≥ 0.01% and < 0.1%)	Not given

Table A1. Alteration in color of the tongue (glossitis, tongue discoloration, hairy tongue, coated tongue) (*continued*)

ATC level 1	ATC level 3	Generic name	ATC Code	LLT MedDRA*	Frequency	Specific type of administration
CARDIOVASCULAR SYSTEM	ACE INHIBITORS, PLAIN	Captopril	C09AA01	Glossitis	Rare (≥ 0.01% and < 0.1%)	Not given
	ACE INHIBITORS, PLAIN	Enalapril	C09AA02	Glossitis	Rare (≥ 0.01% and < 0.1%)	Not given
	ACE INHIBITORS, PLAIN	Ramipril	C09AA05	Glossitis	Rare (≥ 0.01% and < 0.1%)	Not given
	ACE INHIBITORS, PLAIN	Quinapril	C09AA06	Glossitis	Rare (≥ 0.01% and < 0.1%)	Not given
	ANTIADRENERGIC AGENTS, CENTRALLY ACTING	Methyldopa (levorotatory)	C02AB01	Tongue discoloration	Very rare (<0.01%)	Not given
DERMATOLOGICALS	ANTIFUNGALS FOR TOPICAL USE	Ketoconazole	D01AC08	Tongue discoloration	Frequency not known	Not given
	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
	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

Table A1. Alteration in color of the tongue (glossitis, tongue discoloration, hairy tongue, coated tongue) (*continued*)

ATC level 1	ATC level 3	Generic name	ATC Code	LLT MedDRA*	Frequency	Specific type of administration
GENITO URINARY SYSTEM AND SEX HORMONES	OTHER GYNECOLOGICALS	Fenoterol	G02CA03	Glossitis	Rare (≥ 0.01% and < 0.1%)	In combination with ipratropium
MUSCULO-SKELETAL SYSTEM	ANTIINFLAMMATORY AND ANTIRHEUMATIC PRODUCTS, NON-STEROIDS	Diclofenac	M01AB05	Glossitis	Rare (≥ 0.01% and < 0.1%)	After systemic use
	DRUGS AFFECTING BONE STRUCTURE AND MINERALIZATION	Risedronic acid	M05BA07	Glossitis	Rare (≥ 0.01% and < 0.1%)	Not given
NERVOUS SYSTEM	ANTIEPILEPTICS	Carbamazepine	N03AF01	Glossitis	Rare (≥ 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	Modafinil	N06BA07	Glossitis	Uncommon (0.1-1%)	Not given
	ANESTHETICS, LOCAL	Mepivacaine	N01BB03	Glossitis	Very rare (<0.01%)	Not given
	ANTIDEPRESSANTS	Amitriptyline	N06AA09	Tongue discoloration	Very rare (<0.01%)	Not given
	DRUGS USED IN ADDICTIVE DISORDERS	Varenicline	N07BA03	Tongue coated	Rare (≥ 0.01% and < 0.1%)	Not given
RESPIRATORY SYSTEM	OTHER DRUGS FOR OBSTRUCTIVE AIRWAY DISEASES, INHALANTS	Tiotropium bromide	R03BB04	Glossitis	Rare (≥ 0.01% and < 0.1%)	Not given

Table A1. Alteration in color of the tongue (glossitis, tongue discoloration, hairy tongue, coated tongue) (*continued*)

ATC level 1	ATC level 3	Generic name	ATC Code	LLT MedDRA*	Frequency	Specific type of administration
SENSORY ORGANS	OPHTHALMOLOGICALS	Betaxolol	S01ED02	Glossitis	Very rare (<0.01%)	Not given
VARIOUS	ALLERGENS	Allergen extracts	V01AA V01AA02	Glossitis	Common (1-10%)	After sublingual administration
	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 metabolites 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.

Table A2. Increase of 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 ANTIBACTERIALS	Cefazolin	J01DB04	Tongue oedema	Rare (≥ 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 (≥ 0.01% and < 0.1%)	Not given
	CARBAPENEMS	Imipenem and cilastatin	J01DH51	Hypertrophy of tongue papillae	Rare (≥ 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 HEMOSTATICS	Eltrombopag	B02BX05	Tongue oedema	Common (1-10%)	In case of patients with immune thrombocytopenic purpura or aplastic anemia

Table A2. Increase of volume of the tongue (tongue oedema, hypertrophy of tongue papillae) (*continued*)

ATC level 1	ATC level 3	Generic name	ATC Code	LLT MedDRA*	Frequency	Specific type of administration
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 (≥ 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
	ANTIEPILEPTICS	Pregabalin	N03AX16	Tongue oedema	Rare (≥ 0.01% and < 0.1%)	Not given
	DOPAMINERGIC AGENTS	Rotigotine	N04BC09	Tongue oedema	Uncommon (0.1-1%)	In case of Parkinsons'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
	ANESTHETICS, LOCAL	Mepivacaine	N01BB03	Tongue oedema	Rare (≥ 0.01% and < 0.1%)	Not given
RESPIRATORY SYSTEM	ADRENERGICS, INHALANTS	Indacaterol	R03AC18	Tongue oedema	Uncommon (0.1-1%)	Not given

Table A2. Increase of volume of the tongue (tongue oedema, hypertrophy of tongue papillae) (*continued*)

ATC level 1	ATC level 3	Generic name	ATC Code	LLT MedDRA*	Frequency	Specific type of administration
SYSTEMIC HORMONAL PREPARATIONS, EXCL.	ANTI-PARATHYROID AGENTS	Calcitonin (salmon synthetic)	H05BA01	Tongue oedema	Rare (≥ 0.01% and < 0.1%)	Not given
VARIOUS	MAGNETIC RESONANCE IMAGING CONTRAST MEDIA	Gadoteridol	V08CA04	Tongue oedema	Rare (≥ 0.01% and < 0.1%)	Not given
	ALL OTHER THERAPEUTIC PRODUCTS	Palifermin	V03AF08	Tongue oedema	Very rare (<0.01%)	Not given
	ALLERGENS	Allergen extracts	V01AA V01AA02	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 A3. 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 ANTIINFECTIVES	Colistin	A07AA10	Burning tongue	Very rare (<0.01%)	After inhalation
	ANTIPROPULSIVES	Loperamide	A07DA03	Burning tongue	Rare (≥ 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
	SULFONAMIDES AND TRIMETHOPRIM	Trimethoprim	J01EA01	Glossodynia	Very rare (<0.01%)	Not given
ANTINEOPLASTIC AND IMMUNOMODULATING AGENTS	OTHER ANTINEOPLASTIC AGENTS	Cabozantinib	L01XE26	Burning tongue	Very common (≥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

Table A3. Alteration in sensitivity of the tongue (burning tongue, dysaesthesia of tongue, pruritus of tongue, glossodynia, tongue numbness) (*continued*)

ATC level 1	ATC level 3	Generic name	ATC Code	LLT MedDRA*	Frequency	Specific type of administration
NERVOUS SYSTEM	ANTIMIGRAINE PREPARATIONS	Sumatriptan	N02CC01	Burning tongue	Common (1-10%)	Not given
	ANTIEPILEPTICS	Topiramate	N03AX11	Burning tongue	Uncommon (0.1-1%)	Not given
	ANESTHETICS, LOCAL	Ropivacaine	N01BB09	Numbness of tongue	Uncommon (0.1-1%)	Not given
	ANESTHETICS, LOCAL	Bupivacaine	N01BB01	Numbness of tongue	Uncommon (0.1-1%)	Not given
	ANESTHETICS, 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	V01AA V01AA02	Burning tongue	Very rare (<0.01%)	After subcutaneous administration
	ALLERGENS	Allergen extracts	V01AA V01AA02	Burning tongue	Common (1-10%)	After sublingual administration
	ALLERGENS	Allergen extracts	V01AA	Tongue pruritus	Common (1-10%)	After sublingual administration
	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.*

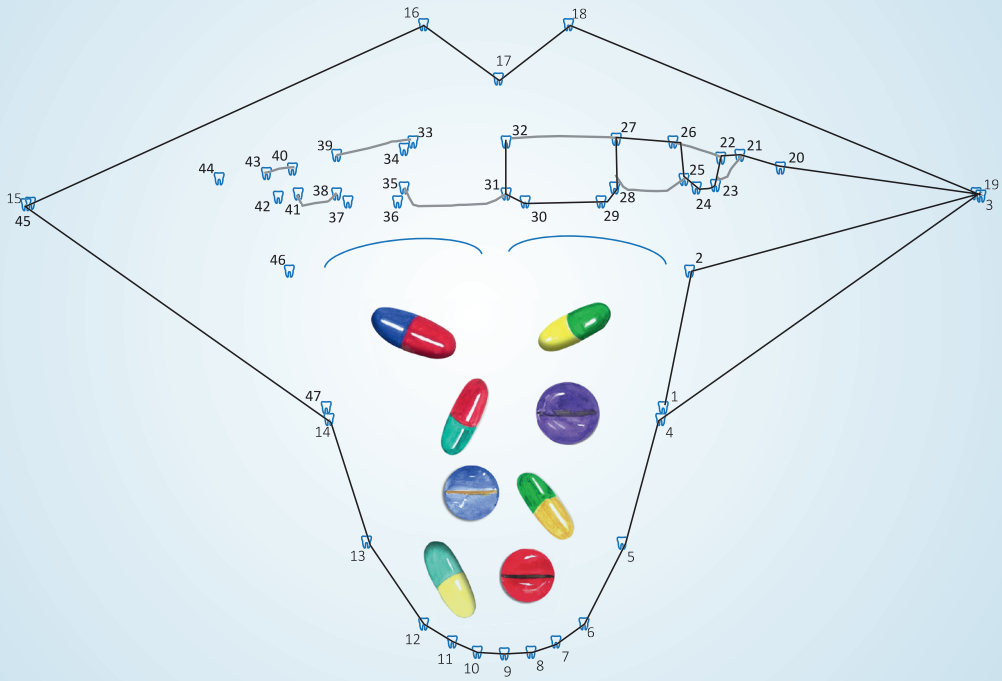
Table A4. Other tongue disorders (tongue irritation, tongue disorders NOS)

ATC level 1	ATC level 3	Generic name	ATC Code	LLT MedDRA*	Frequency	Specific type of administration
ANTI-INFECTIVES FOR SYSTEMIC USE	SULFONAMIDES AND TRIMETHOPRIM	Sulfamethoxazole 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	Colestyramine	C10AC01	Tongue irritation	Very rare (<0.01%)	Not given
NERVOUS SYSTEM	ANTIDEPRESSANTS	Imipramine	N06AA02	Tongue disorder NOS	Frequency not known	Not given
	ANTIDEPRESSANTS	Sertraline	N06AB06	Tongue disorder NOS	Uncommon (0.1-1%)	Not given

Table A4. Other tongue disorders (tongue irritation, tongue disorders NOS) (*continued*)

ATC level 1	ATC level 3	Generic name	ATC Code	LLT MedDRA*	Frequency	Specific type of administration
VARIOUS	ALLERGENS	Allergen extracts	V01AA	Tongue disorder NOS	Uncommon (0.1-1%)	After sublingual administration

* Tongue disorder NOS: tongue disorder not otherwise specified.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7 Medicaments and oral healthcare: adverse effects of medication on the oral mucosa

This chapter is a translated and edited version of the following article:
[Medicaments and oral healthcare. Adverse effects of medications on the oral mucosa]

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ABSTRACT

Many drugs prescribed have adverse effects on the oral mucosa. Commonly described adverse effects include stomatitis, white lesions, pigmentation abnormalities, and sensitivity disturbances. Stomatitis is frequently seen in patients on medication for malignancies and autoimmune diseases. Such drug categories of note are alkylating agents, anthracycline derivatives, monoclonal antibodies, protein kinase inhibitors, purine derivatives, pyrimidine antagonists, taxanes, and vinca alkaloids. White lesions often involve candida infections and are seen particularly with the use of certain types of immunosuppressants and antibiotics. Pigmentary abnormalities are often seen with the use of hydroxycarbamide, an oncolytic. Sensitivity disorders of the oral cavity are seen with the use of various medications, including protein kinase inhibitors. It is very important for oral health care providers to recognise potential adverse effects on the oral mucosa. If a symptom is likely due to medication, whether the medication can be adjusted or discontinued should be discussed with the prescribing physician.

INTRODUCTION

In the Netherlands, a very large proportion of the population is using drugs. According to figures from the CBS, in 2017, 66% of the Dutch population took one or more drugs. This percentage increases with age; 87% of those aged 65 years and over and 90% of those aged over 75 years use medication.[1] These medications are prescribed for a specific purpose, but they can also cause various adverse effects. Some of these adverse effects manifest themselves in and around the oral cavity. Knowledge of these adverse effects is important for oral health care providers. After all, they are often the first to notice any abnormalities in the oral cavity. To prevent unnecessary or incorrect treatment, oral health care providers must be able to distinguish these abnormalities from oral manifestations of diseases.

In addition to previously published articles in the "oral adverse effects of medications" series, this article outlines the main adverse effects of medications on the oral mucosa. This does not include adverse effects on the gingiva as these have already been discussed in a previous article.[2] The Informatorium Medicamentorum of the Royal Dutch Pharmacists Association (KNMP) collects and processes drug information in a database. The database includes information about scientific articles, guidelines, and product summaries and is updated every 2 weeks. For this study, the database was searched for relevant adverse effects of medications on the oral mucosa. The version of the database dated August 1, 2018[3] was used for this purpose.

To keep the overview of medications as relevant as possible to clinical practice, only medications that had an adverse effect in more than 1% of patients are included in this study. Therefore, this article does not provide a complete overview of all medications that have adverse effects on the oral mucosa. For the sake of this overview, some descriptions of adverse effects are grouped together under the same adverse effect group.

Possible adverse effects on the oral mucosa

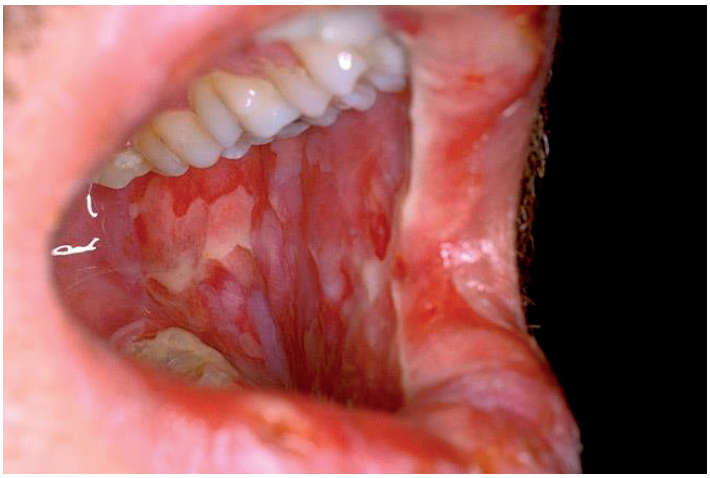
Adverse effects on the oral mucosa that are frequently seen can be divided into the following groups: oral inflammation (stomatitis), white lesions (candida or lichenoid abnormalities), pigmentation abnormalities, and sensitivity disorders.

Inflammation of the oral mucosa

A multitude of drugs can cause stomatitis (Table. 1). Stomatitis includes inflammation of the oral cavity in the broadest sense; any type of tissue may be affected.[4] Further distinctions are often made in this regard. For example, some manifestations of

stomatitis are accompanied by ulcerations. A number of drugs have been specifically described as capable of causing oral ulcerations.[5] Table 2 provides an overview of these medications. A distinct entity within stomatitis is oral mucositis (Figure. 1), which is defined as "*inflammation of the oral mucosa resulting from antineoplastic therapy*".[6] It is often accompanied by a burning or tingling sensation or pain. Histologically, atrophy of the squamous epithelium, vascular damage, inflammatory infiltrates, and ulcers can be observed.[4] However, stomatitis and mucositis are often used interchangeably. This article specifies the type of stomatitis as applicable.

Figure 1. Oral mucositis



Stomatitis is frequently seen with drugs used in oncology and in patients treated for autoimmune diseases (antineoplastic drugs and certain types of anti-inflammatory drugs, respectively). Important drug groups herein are alkylating agents, anthracycline derivatives, monoclonal antibodies, protein kinase inhibitors, purine antagonists, pyrimidine antagonists, taxanes, and vinca alkaloids. Table 1 provides an overview of substance names within these drug groups. Interlude 1 lists drug groups that inhibit cell function and/or cell division. These drug groups work by inhibiting cell function and/or cell division. Alkylating drugs do this by alkylating DNA, causing single- or double-stranded breaks in the DNA of the cell. As a result, the cell is unable to synthesize proteins that are required for, among other things, cell division. Anthracycline derivatives inhibit the production of the enzyme topoisomerase II, also causing DNA breaks. Monoclonal antibodies are a heterogeneous collection of drugs that act via specific antigen receptors and can thus inhibit or activate certain intracellular processes. Protein kinase inhibitors are another heterogeneous group of drugs that can inhibit the phosphorylation of signal proteins, among other things, via certain enzymes. Purine antagonists inhibit purine synthesis, thereby disrupting the formation of DNA and/or RNA, which can lead

to cell death, particularly in leukocytes. Pyrimidine antagonists inhibit DNA precursor synthesis and disrupt protein synthesis. Inhibition of the enzyme methyltransferase and DNA polymerase disrupts DNA methylation and synthesis, leading to cell apoptosis. Taxanes, platinum compounds, and vinca alkaloids act by disrupting the organization and formation of the microtubule network. During cell division, microtubules ensure that DNA is distributed between the existing and the newly formed cell. When the microtubules do not function properly, cell division is not possible.[7]

The pathophysiology of the development of stomatitis is known for a number of drug groups. This is particularly the result of research into the development of mucositis. Less is known about the pathophysiology of other forms of stomatitis.

In oral mucositis caused by chemotherapy, the pathophysiology has been described in five phases.

- **Phase 1**. Initiation phase: DNA damage occurs due to reactive oxygen components and the peroxidation of lipids, triggering cell apoptosis.
- **Phase 2**. Signalling phase: DNA damage continues, leading to the expression of nuclear factor kappa B, among others. This leads to the production of pro-inflammatory cytokines, including TNF-alpha, IL-1 beta, and IL-6.
- **Phase 3**. Amplification phase: pro-inflammatory cytokines are released, causing more tissue damage, increasing blood vessel permeability, and activating the enzyme cyclooxygenase 2. Cells go into apoptosis.
- **Stage 4.** Ulceration phase: epithelial defects develop, providing an entry point for microorganisms. This activates macrophages, which in turn produce pro-inflammatory cytokines.
- **Phase 5**. Healing phase: mucosal damage resolves through the proliferation and differentiation of epithelial cells.[8, 9]

Although the five pathophysiological phases of mucositis have been described for 'classical' chemotherapy, such as 5-fluoro-uracil (pyrimidine antagonist) and cisplatin (platinum compound), it is plausible that other drugs causing DNA damage trigger a similar cascade. However, the clinical presentation of mucositis caused by the so-called '*targeted*' anti-cancer therapies, such as protein kinase inhibitors, is essentially different to that of classical chemotherapy. The type of mucositis associated with *targeted* therapies more often manifests as aphthous stomatitis, wherein sharply defined ulcers with a red halo are observed. These ulcers often disappear spontaneously even during cancer treatment.[10] In contrast, with chemotherapy, erythema is often seen first, accompanied by a burning sensation in the mouth. In some cases, this is followed by oedema and ulceration. The ulcerations are often poorly circumscribed

and are almost never surrounded by erythema. Sometimes, the ulcerations are covered by a pseudomembrane and usually heal without sequelae within 2–4 weeks.[11]

Methotrexate, a folate antagonist, is a drug prescribed for malignancies. It is also prescribed for autoimmune diseases, albeit in lower doses. Methotrexate has a cytostatic effect. It inhibits the conversion of folic acid to tetrahydrofolic acid by binding to the enzyme dihydrofolate reductase. This conversion is essential for the synthesis of nucleic acids, which are required for cell division. The effect of methotrexate in autoimmune diseases is not entirely clear. It is hypothesized that the inhibition of other enzymes, including thymidilate synthase and amino-imidazole carboxamide ribosyl 5-phosphate, brings about the anti-inflammatory effect. These two enzymes are involved in the synthesis of pyrimidines and purines, respectively. The accumulation of intermediate amino acids leads to the release of adenosine, which has an anti-inflammatory effect.[7]

Stomatitis is a frequently occurring adverse effect of methotrexate. This adverse effect can occur throughout the course of treatment, even when patients have been taking methotrexate for years. Patients experience a painful mouth with or without ulcerations. Although the occurrence of stomatitis is dose-dependent, even at low doses, stomatitis can be bothersome enough that therapy must be interrupted or stopped altogether.[12]

The risk of adverse effects depends on many factors, including genetic factors and environmental factors.[13-15] Many adverse effects of methotrexate, such as nausea and vomiting, can be relatively easily treated by folic acid or folinic acid supplementation. Folic acid supplementation has no negative effect on the efficacy of methotrexate. However, a recent Cochrane review found that the incidence of stomatitis is not significantly reduced when folic acid or folate is supplemented.[16]

Table 1. Medication with stomatitis as frequent adverse effect

Group	Generic name
alkylating agents	Bendamustine
	Lomustine
	Melfalan
	Temozolomide
	Thiotepa
anti-androgens	Flutamide
antibacterial agents, other	Clindamycin
adrenergic and dopaminergic agents	Midodrine

Table 1. Medication with stomatitis as frequent adverse effect (*continued*)

Group	Generic name
antracyclinederivates	Daunorubicine
	Doxorubicine
	Epirubicine
	Idarubicine
	Mitoxantron
	Pixantron
cytostatic antibiotic	Bleomycine
folium acid antagonist	Methotrexate
gonadorelin-antagonists	Leuprorelin
gold preparations	Sodium aurothiomalate
immunostimulant others	Aldesleukin
immunosuppresive, selective	Sirolimus
	Thymocyte immunoglobulin
	Belatacept
immunosuppressives, others	Lenalidomide
interferons	Interferon alfa 2b
	Peginterferon alfa 2b
agents used by nicotine addiction	Nicotine
monoclonal antibodies	Dinutuximab beta
	Gemtuzumab ozogamicine
	Inotuzumab ozogamicine
	Nivolumab
	Panitumumab
	Rituximab
	Trastuzumab
MS-agents	Alemtuzumab
oncolytics, others	Aflibercept
	Amsacrine
	Bortezomib
	Eribuline
	Hydroxycarbamide
	Niraparib
	Olaparib
	Pegaspargase
	Pemetrexed
	Temoporfin
platinum compounds	Oxaliplatin
podofyllotoxin derivates	Etoposide
protein kinase inhibitors	Afatinib

Table 1. Medication with stomatitis as frequent adverse effect (*continued*)

Group	Generic name
	Alectinib
	Axitinib
	Cabozantinib
	Dasatinib
	Erlotinib
	Everolimus
	Gefitinib
	Ibrutinib
	Lapatinib
	Lenvatinib
	Midostaurine
	Nintedanib
	Osimertinib
	Palbociclib
	Pazopanib
	Ponatinib
	Regorafenib
	Ribociclib
	Sorafenib
	Sunitinib
	Tivozanib
	Trametinib
	Vandetanib
purin derivates	Clofarabine
	Fludarabine
	Mercaptopurine
	Nelarabine
	Tioguanine
pyrimidin-antagonists	Capecitabine
	Cytarabine
	Decitabine
	Gemcitabine
	Tegafur
	Trifluridine
	Acitretine
taxanes	Docetaxel
	Paclitaxel
trombopoetin antagonists	Eltrombopag
vinca-alkaloids	Vinflunine
	Vinorelbine

Table 2. Medication in which specific oral ulceration was mentioned

Group	Generic name
alkylating agents	Chloorambucil
penicillamine	Penicillamine
coxib's/NSAID	Etoricoxib
folium acid antagonist	Methotrexate
HIV protease inhibitor	Ritonavir
HIV protease inhibitor	Saquinavir
immunostimulants, others	Talimogen lagerparepvec
immunosuppressive agents, selective	Abatacept
interferon	Peginterferon alfa 2a
interferon	Peginterferon alfa 2b
interleukin inhibitors	Siltuximab
interleukin inhibitors	Tocilizumab
interleukin inhibitors	Dupilumab
interleukin inhibitors	Sarilumab
monoclonal antibodies with malignancies	Obinutuzumab
NSAID's, others	Flurbiprofen
oncolytics, others	Bortezomib
oncolytics, others	Temoporfine
oncolytics, others	Eribuline
protein kinase inhibitors	Everolimus
protein kinase inhibitors	Pazopanib
protein kinase inhibitors	Sunitinib
protein kinase inhibitors	Temsirolimus
purin derivates	Clofarabine
pyrimidin-antagonists	Cytarabine
taxanen	Paclitaxel
trombopoetin antagonists	Eltrombopag
vinca alkaloids	Vinblastine

Intermezzo 1. Drug groups that inhibit cell function and/or cell division

- *Alkylating agents: normally, controlled alkylation of DNA (the addition of an alkyl group to the DNA; in the case of DNA, this is usually in the form of methylation, the addition of a methyl group) is necessary during cell division to allow DNA transcription to take place. This allows RNA synthesis to occur, which allows proteins to be synthesized (translation). When alkylating agents are used, the alkylation process is uncontrolled, causing single- or double-stranded breaks in the DNA of the cell. As a result, the cell is unable to synthesise the proteins that are required for cell division, among other things.*

- *Anthracycline derivatives form complexes with the DNA and thus inhibit nucleic acid synthesis (necessary for building DNA and RNA) and mitosis (cell division) and inhibit the enzyme topoisomerase II, among others, causing DNA breaks.*
- *Monoclonal antibodies: a heterogeneous collection of drugs that act via specific antigen receptors and can thus inhibit or activate certain intracellular processes.*
- *Protein kinase inhibitors: another heterogeneous group of drugs that can inhibit the phosphorylation of signal proteins, among others, via certain enzymes. The phosphorylation of proteins is essential for the functioning of signal proteins via the activation of the latter. Without phosphorylation, certain cell processes, such as cell division, cannot take place.*
- *Purine antagonists inhibit purine synthesis. Purines are the building blocks for nucleic acids (the major elements of DNA and RNA), disrupting the formation of DNA and/or RNA, which can lead to cell death, particularly of leukocytes.*
- *Pyrimidine antagonists: inhibit DNA precursor synthesis and disrupt protein synthesis. By inhibiting the enzymes methyltransferase and DNA polymerase, DNA methylation and synthesis are disrupted, resulting in cell apoptosis.*
- *Taxanes, platinum compounds, and vinca alkaloids work by disrupting the organization and formation of the microtubule network. During cell division, microtubules ensure that DNA is distributed between the existing and the newly formed cell by pulling the DNA apart. If the microtubules do not function, cell division is not possible.*[7]

Blistering of the oral mucosa

A single drug, eltrombopag, frequently causes blistering of the oral mucosa. Eltrombopag is a thrombopoietin agonist. It binds to the thrombopoietin receptor, stimulating the growth and maturation of the megakaryocyte, the precursor of blood platelets. This results in an increase in platelet production. It is indicated for haematological disorders in which the platelet count is very low, such as immune thrombocytopenia and aplastic anaemia.[(7)] It is not entirely clear what causes the oral blisters when using this medication. Previous studies on medication-induced bullous pemphigus have shown histological evidence of acantholysis, a phenomenon in which cell connections, such as desmosomes, are lost. This was mainly seen with drugs containing thiol groups. However, intercellular antibodies were also found, which would indicate an immune-mediated cause of the blistering. The clinical picture is hardly distinguishable from idiopathic forms of pemphigus. In a previous study, an improvement in the clinical picture was seen when the causative medication was discontinued.[(17)]

Oral candidiasis

The development of oral candidiasis is a known effect of immunosuppressive medications (Table 3). Candida is part of the commensal oral flora in many people. In contrast, oral candidiasis is an opportunistic infection that occurs almost exclusively as a manifestation of underlying diseases, such as in immunocompromised patients. When the immune system is suppressed systemically or locally by certain drugs, the body is unable to inhibit the growth of *Candida species*. The balance in the mouth is disturbed and an overgrowth occurs, so to speak, leading to infection.[18] Oral candidiasis is also often seen as an adverse effect of drugs that cause dry mouth.[19] Drugs that cause dry mouth have been previously described.[20]

Table 3. Medication with oral candidiasis as frequent adverse effect

Group	Generic name
beta2-sympathicomimetics	Vilanterol
beta-lactamase inhibitors	Avibactam
fluorchinolonen	Moxifloxacine
monoclonal antibodies with malignancies	Brentuximab vedotine
monoclonal antibodies with malignancies	Yttrium Y-90 ibritumomab
MS-agents	Alemtuzumab
nucleoside en nucleotide analoga	Valganciclovir
oncolytics, others	Eribuline
other antibacterials	Linezolid
penicillins	Amoxicillin
purin derivates	Clofarabine
pyrimidin-antagonists	Azacitidine
pyrimidin-antagonists	Tegafur
taxanen	Cabazitaxel

In addition, the KNMP database describes other medications that can cause oral candidiasis, including various types of antibiotics. A disruption of the oral microbiome may underlie the occurrence of oral candidiasis. Antibiotics can have a bacteriostatic or bactericidal effect. Depending on the spectrum of the antibiotics, certain species of bacteria are inhibited or killed. When the total number of bacteria in the mouth is reduced, other microorganisms, including yeasts, such as *Candida species*, have the opportunity to grow further.[18, 21]

The presentation of oral candidiasis varies according to the cause. In patients taking immunosuppressants, pseudomembranous candidiasis is most commonly seen (Figure 2). This is classically manifested as white lesions on the mucosa. The lesions can be scraped off, and the underlying mucosa is erythematous and histopathologically

shows flaking epithelia. Patients experience a burning sensation in the mouth. When antibiotics are used, acute erythematous candidiasis is frequently seen (Figure 3). This form is often painful, unlike other forms of candidiasis and is often seen on the dorsum of the tongue and the hard palate. Oral candidiasis disappears spontaneously when the causative medication is discontinued.[18, 22] If necessary, oral candidiasis can be treated with miconazole oral gel or nystatin suspension. In severely immunocompromised patients, systemic treatment with fluconazole may be considered.[7, 23]

Figure 2. Pseudomembranous candidiasis (picture from the archive of prof. Sol Silverman)

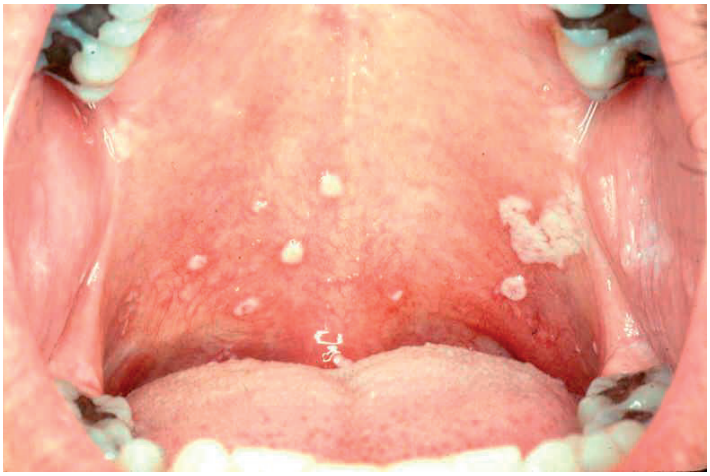
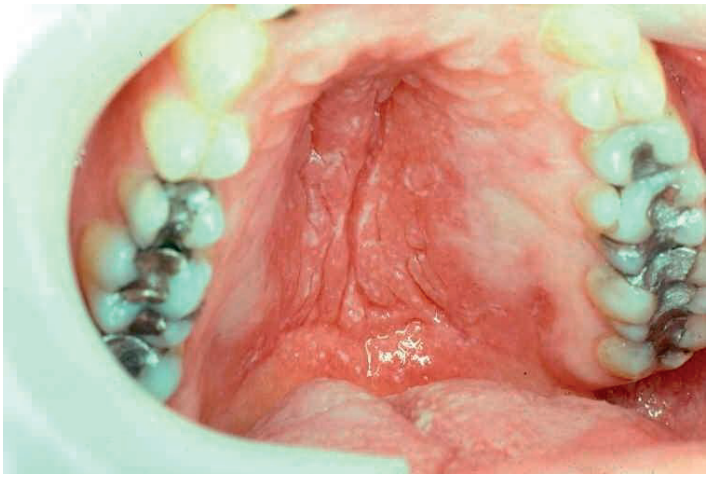


Figure 3. Erythematous candidiasis (picture from the archive of prof. Sol Silverman)



Lichenoid reactions

A recent systematic review showed that there is no strong scientific evidence for a relationship between medication use and lichenoid reactions.[24] Studies on medication-related oral lichenoid reactions are mainly based on *case reports*, where the methodology is insufficient to demonstrate a causal response between the medication and the adverse reaction. A *case control* study of 110 patients with oral lichen planus concluded that medication very rarely causes lichenoid reactions.[25] The KNMP database also does not list any medications that frequently cause lichenoid reactions of the oral mucosa.

Pigmentation defects

Hydroxycarbamide, an oncolytic prescribed for sickle cell disease and some haematologic malignancies, frequently produces pigmentary abnormalities of the oral mucosa. The mechanism of action of hydroxycarbamide is not known. Presumably, the drug blocks the ribonucleotide reductase system, inhibiting DNA synthesis. How the pigment abnormalities occur is not known. Hypotheses are that pigment abnormalities of the oral mucosa of patients taking medication arise from the induction of pigment synthesis or melanin accumulation, from precipitation of drug metabolites in the oral mucosa, or from iron precipitation in the mucosa as a result of vascular wall damage.[26]

Sensitivity disorders of the oral cavity

Several drugs can cause sensitization disorders of the oral cavity. Specifically, oral paraesthesia, oral hypoesthesia, burning sensation in the mouth, oral pain, oral discomfort, and irritation of the oral mucosa have been described. Table A1 in the appendix provides an overview of drugs that frequently cause oral paraesthesia. This includes the medications that cause burning sensation in the mouth, oral pain, oral discomfort, and irritation of the oral mucosa. Table A2 in the appendix lists the drugs that frequently cause oral hypoesthesia. The mechanism of action of both sensibility disorders is unclear.[27] Orofacial sensitization disorders are often accompanied by xerostomia and hyposalivation, adverse effects that were not included in this article but are very frequent with medication use.[28]

CONCLUSION

Many medications are frequently associated with adverse effects that manifest themselves in the oral mucosa. It is very important for oral care providers to recognise these adverse effects. An earlier published study[2] indicated that one should be aware that medications that can cause adverse reactions on the oral mucosa are not neces-

sarily the causative factor. Thorough research is needed to determine the possible aetiological factor of the abnormality.

If it is likely that the abnormality is indeed caused by medication, one should consult the prescribing physician before adjusting or discontinuing the medication. This is of great importance since many of the described medications are prescribed for malignancies or autoimmune diseases. It goes without saying that discontinuing these medications can have major consequences for the course of the patient's illness. It is advisable to consult the prescribing physician at an early stage if an adverse effect of medication is suspected. In this way, it can be considered in good time whether an intervention to remove the negative adverse effects is feasible.

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APPENDIX

Table A1. Medication with oral paresthesia as frequent adverse effect

Group	Generic name
anti-arithmics class I and III	Vernakalant
anti-epileptics	Topiramate
blood coagulation factors	Eftrenonacog alfa
HIV protease inhibitors	Fosamprenavir
imidazole, others	Miconazol
potassium channel blocker	Amifampridine
agents used in metabolic disorders, others	Glycerolfenylbutyraat
mucolytics	Ambroxol
nicotine	Nicotine
NSAID's, others	Flurbiprofen
prostacyclin analogs	Iloprost
protein kinase inhibitors	Cabozantinib
protein kinase inhibitors	Lenvatinib
protein kinase inhibitors	Sorafenib
protein kinase inhibitors	Sunitinib
protein kinase inhibitors	Temsirolimus
riluzol	Riluzol
trombopoetin antagonist	Eltrombopag

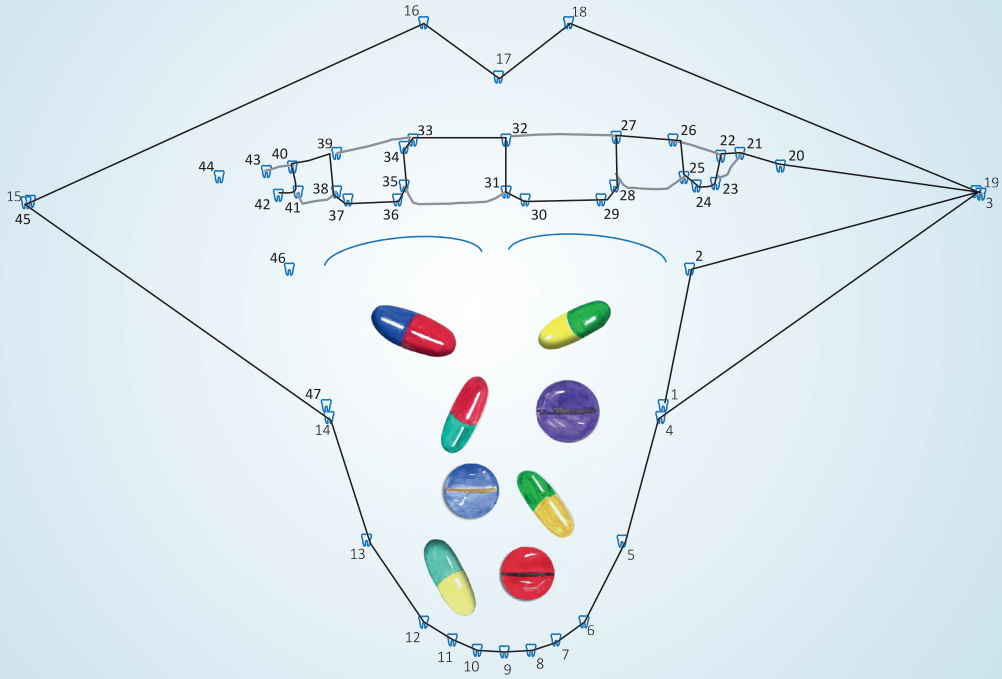
Table A2. Medication with oral hypoesthesia as frequent adverse effect

Group	Generic name
immunostimulants, others	Plerixafor
potassium channel blocker	Amifampridine
agents used in metabolic disorders, enzymes	Agalsidase beta

Table A3. Top 5 medication mostly used in the Netherlands (according to GIPdatabank over 2014)

Rang	Generic
1.	Amoxicillin (1.048.000)
2.	Miconazole (236.680)
3.	Eteroricoxib (141.980)
4.	Methotrexate (65.676)
5.	Clindamycin (57.970)

IV Making medical history and adverse drug reaction data real-time applicable for daily dental practise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8 The MDI-Scanner: An EPD integrated clinical decision support module for Medical and Dental Interactions.

This chapter is a translated and edited version of the article:
[The medical-dental interactions scanner: an Electronic Health Record-integrated quality and safety module for medical-dental interactions]

Willem M.H. Rademacher; Yalda Aziz; Densie E. van Diermen and Fred R. Rozema.

Ned Tijdschr Tandheelkd. 2019 Jan;126(1):23-28. doi: 10.5177/ntvt.2019.01.18204.

ABSTRACT

Owing to the aging population, the oral healthcare provider will increasingly be confronted with medically complex patients. Both physical conditions and drug use can have consequences for oral health or dental treatment. In practice, it is often impossible to keep track of all medical-dental interactions. A tool has been developed to support the dental care provider in providing safe care. The medical-dental interaction scanner supports both the patient and dental care provider in taking a medical history, and links the information obtained to available literature. This makes it possible to provide the caregiver with patient-specific recommendations on potential drug adverse effects, intraoral manifestations of somatic conditions and the prevention of acute situations.

INTRODUCTION

Double aging

The composition of the Dutch population has been changing significantly for several decades. An increasing part of the population is 65 years of age or older. Simultaneously, the average life expectancy is also increasing. Together, this is called double aging, a trend that is likely to continue until 2040.[1] Double aging is accompanied by an increase in chronically ill patients. In 2016, 3 million people (18%) were 65 years or older. Of these people, 50% had one or more chronic somatic conditions and 25%–50% were known to have polypharmacy, the use of five or more different drugs per dag.[2, 3] In addition, 63% of people over 65 years old visit the dentist on average 2.5 times a year.[4] Oral healthcare providers are thus increasingly confronted with medically complex patients.

Medical-dental interactions

The increase in the number of medically complex patients is relevant to the oral healthcare provider, because providing good care to this group requires more general medical knowledge. The oral healthcare provider should be aware that intraoral abnormalities may be a manifestation of somatic conditions or drug use. The effects of general health on oral health or dental treatment and vice versa are called medical-dental interactions (MDI). To consider MDI, the patient's medical history and drug use must be known. This requires a medical history to be taken. In most practices, this is asked and recorded using a health questionnaire. However, the questionnaires typically used mainly screen for the risk of acute situations during or after dental treatment, and not for potential intraoral adverse effects or manifestations of somatic diseaseas. Theoral heathcare provider must, therefore, have sufficient ready knowledge to be able to treat the patient safely with the information obtained. However, due to the extensive literature on MDI, it is often impossible in clinical practice to be prepared for all MDI and their possible consequences. In practice, only the serious complications (e.g. postoperative bleeding with anticoagulants), serious drug adverse effects (e.g. medication related osteonecrosis of the jaw), and the most common associations between somatic diseases and oral health (e.g. periodontitis and diabetes mellitus) are usually considered. As a result, some MDI are often missed.

To assist oral healthcare providers in providing safe care to the medically complex population, researchers developed and populated a tool with literature related to MDI: the MDI-scanner. The MDI-scanner supports both the patient and oral healthcare provider in taking a medical history and links the information obtained with recent literature. This link allows the provider to access patient-specific recommendations

on potential drug adverse effects, intraoral manifestations of somatic conditions, and precautions to be taken. In addition, the MDI-scanner provides the ability to safely prescribe medication in accordance with the current KNMG guideline.[5] This article describes the functionalities and background of the MDI-scanner.

The MDI scanner

The MDI-scanner consists of three modules: medical history, MDI-check, and medication prescription and interactions check.

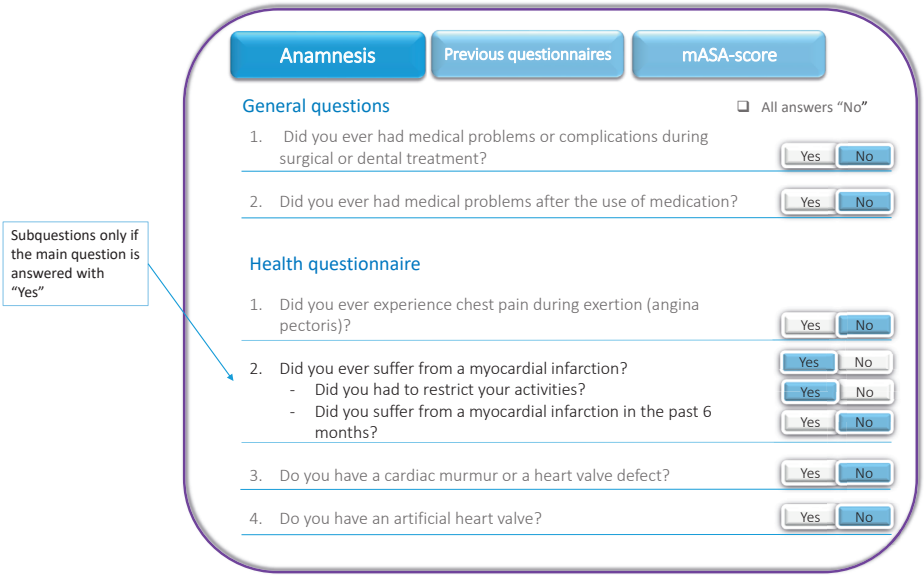
Medical anamnesis

A complete overview of the patient's medical situation is the basis for checking MDI. In this module, this overview is obtained by means of a health questionnaire derived from the *European Medical Risk Recording Anamnesis* (EMRRH).[6] The EMRRH was developed for dentists and is used to assess the risk of acute situations during and after dental treatment. In this list, the patient answers questions about general health and possible drug use. The answers determine the risk of acute situations. The magnitude of the risk is expressed in the American Society of Anesthesiologists (ASA) classification modified for dentistry. The EMRRH screens primarily for the risk of acute situations. It is, therefore, not a complete medical anamnesis. However, the healthcare provider can use this questionnaire to ask structured questions about, for example, drug use or diseases that do not cause an acute situation but do manifest themselves intraorally (e.g. Crohn's disease). Since the introduction of the EMRRH, more has become known about MDI and some questions may have become redundant (e.g. risk of thyreotoxic crisis) or missing (e.g. about drug use in the past; bisphosphonates). The health questionnaire used in the MDI scanner is, therefore, a modified EMRRH. The medical history can be entered into the MDI scanner in three ways:

- The patient fills out the health questionnaire on paper in the waiting room. The healthcare provider checks and authorizes the answers and then manually enters them into the Dental Information System (DIS). This procedure is cumbersome and prone to error but offers an option for patients who cannot or do not want to use digital input.
- The health questionnaire is filled in digitally on a tablet in the waiting room. The answers are, after checking and authorization by the care provider, automatically transferred into the DIS. This prevents input errors and saves time.
- The patient uses an online patient portal. Here too, the data are automatically transferred to the DIS after verification and authorization by the healthcare provider. The advantage of this is that the patient can collect the necessary information (e.g. the current drug overview) and can subsequently enter the data online.

Digital input has the advantage of structured and efficient questioning. Depending on the answers, the health questionnaire may or may not be expanded to include additional questions (Figure 1). The digital input of drug use and somatic conditions is done with the help of a selection menu. Brand names are directly linked to generic drug names. This makes the information obtained consistent and easier to use for the oral healthcare provider.

Figure 1: Completing the health questionnaire.



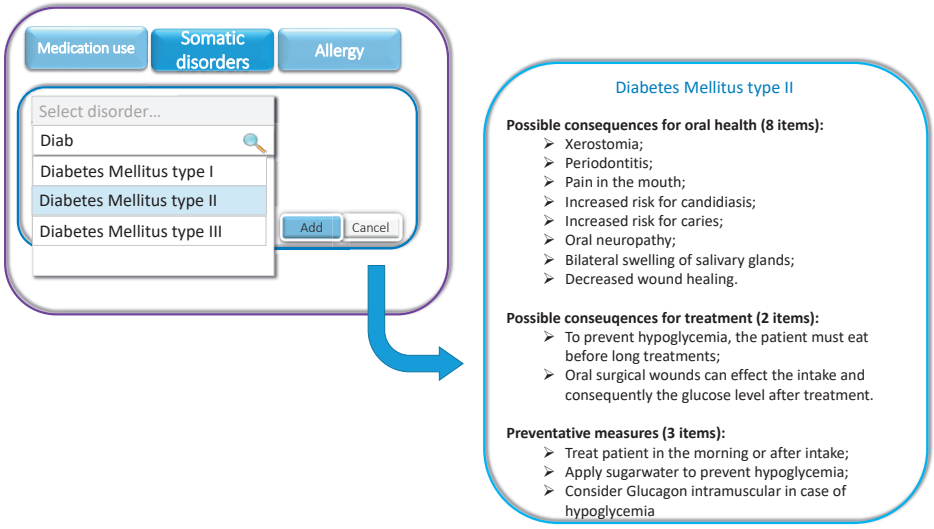
MDI-check

The information obtained by entering the medical anamnesis is linked to two databases. These databases have been set up by the researchers and are periodically updated with new information.

The first database checks for consequences of physical conditions on oral health or dental treatments and vice versa. This database is filled with information from textbooks/reference books, obtained through a search engine for book collections from libraries around the world (WorldCat). We searched for books related to MDI and Oral Medicine. The most relevant Dutch and English books were manually searched for pathologies relevant to MDI. The information on these pathologies was linked in the database to the codes of the International Classification of Diseases (ICD-10).[7] The ICD-10 is an internationally used list of medical conditions, each with a unique code. The information from (inter)national sources is structured per disorder using

the ICD-10. The physical conditions entered by the patient are also given a code and are, therefore, directly linked to the database. This makes it easy for the caregiver to see the information on MDI from textbooks and reference books. This information is divided into: (1) possible consequences for dental health, (2) possible consequences for treatment, and (3) possible precautions to be taken during treatment (Figure 2).

Figure 2: Entering somatic disorders and MDI reports under somatic disorders.

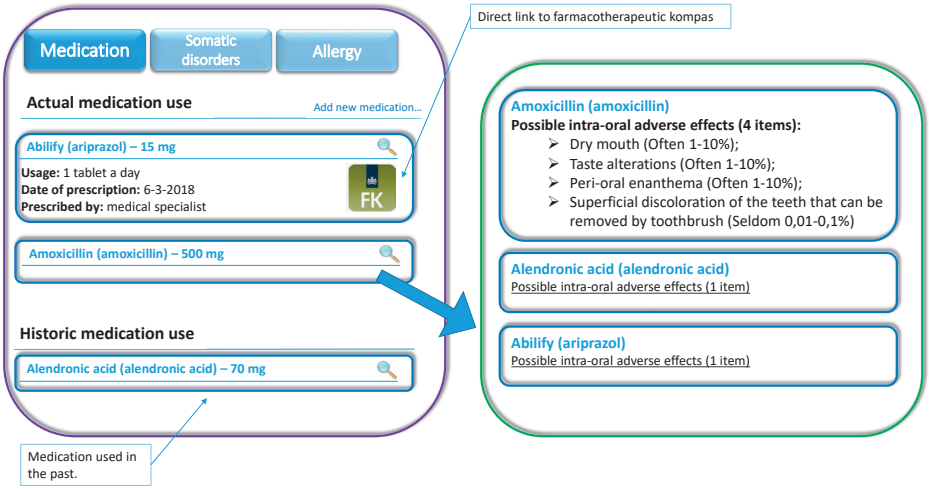


The second database checks for medication-related MDI and is based on the Informatorium Medicamentorum (IM).[8] The IM is the reference work of the Royal Dutch Pharmacists Association (KNMP) and describes the adverse drug reaction category of all medicines registered in the Netherlands. For each drug in the IM, the adverse effect category was manually searched for adverse effects that may be relevant for the oral healthcare provider. For all drugs that can cause relevant adverse effects, the incidence of these adverse effects and the anatomical therapeutic chemical (ATC) codes are included in the database. The ATC-classification is used internationally for drug registration and communication about drugs.[9] The medication entered by the patient is also linked to the ATC and, thus, communicates directly with the database. As a result, the healthcare provider only sees adverse effects that are relevant to oral care (Figure 3).

This means, for example, that the adverse effect “irritated oral mucosa” is displayed, but “mucous membrane irritation” is not. This is because the latter can also relate to irritation of the intestinal or pulmonary mucosa. Another example is “enanthema (particularly around the oral cavity)” and “enanthema,” whereby the former cer-

tainly affects oral health and the latter can also occur elsewhere on the skin. Whether an adverse effect is relevant or not remains a difficult question. Whether or not an adverse effect was included was determined based on the adverse effect term (explicitly dental) and clinical experience. The information will be further refined based on user feedback.

Figure 3: Medication overview and MDI notifications for medication use.



Prescribing medication and checking interactions

To support the healthcare provider in prescribing the correct drugs, the MDI-scanner displays drug suggestions and dosages based on the current evidence based clinical guidelines. The healthcare provider can also create “favorite prescriptions” to minimize repetitive actions and reduce the time spent on prescribing. The Dutch Healthcare and Youth Inspectorate does not consider it responsible to prescribe drugs without using a Computerized Prescription System (CPS) equipped with a Drug Prescription Screening System (DPSS).[10] The MDI-scanner offers this possibility. The DPSS is based on the Cerner Multum database and looks for contraindications, hypersensitivity, DPSS interactions, and incorrect dosages. After the selected drugs has been checked by the DPSS, the prescription is automatically generated. It is possible to directly send the prescription digitally to the local pharmacy, provided that they have a secure email connection.

Data protection

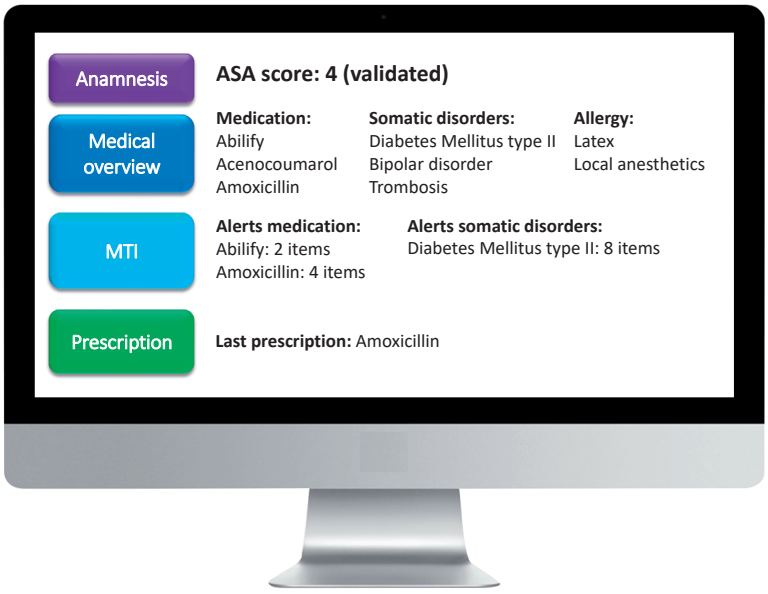
The MDI-scanner processes patient-specific medical information. The storage, processing, and protection of this information must, therefore, comply with current guidelines and legislation. The software and data storage comply with the require-

ments of the Personal Data Protection Act, ISO 27001, and the international General Data Protection Regulation, which has been in force since May 2018.

Connection to the dental health record

To prevent the healthcare provider from logging in separately to view patient data, the MDI-scanner is offered as an integral part of the existing Dental Health Record (DHR; see Intermezzo 1). This allows the data entered in the MDI-scanner to be viewed directly in the DHR. The final interface will differ per the linked DHR. However, the information generated is always the same (Figure 4).

Figure 4: Overview page of DHR.



Intermezzo 1. Making the MDI-scanner available in the Netherlands

On the initiative of the Royal Dutch Dental Association (KNMT), a meeting was organized for DHR suppliers. During this meeting, the MDI-scanner was discussed, and DHR suppliers expressed their intention to integrate the MDI-scanner into their DHR. Currently, the MDI-scanner is available to healthcare providers working with Exquise Next Generation® (Vertimart), TabDents® (Tabdents) and Robadent® (Vertimart). Integration with Novadent® (Complan), Evolution® (Software of Excelence) and Axium® (Exan) is being explored. The software developer of the MDI-scanner manages the availability: Insight Pharma Services, www.meamedicadental.com.

Software testing

The MDI-scanner has been extensively tested in the beta version. The current software is continuously tested by dentists, researchers, and the software vendor.

CONCLUSION

Using the MDI-scanner does not relieve the oral care provider of the final responsibility for the care provided. However, it can be seen that, using the MDI-scanner, care is taken regarding patient-specific (health) situation, which is becoming increasingly important in liability cases.

In future, it will also be possible for oral care providers to analyze data from their own practice and mirror them with anonymized national data.

ACKNOWLEDGEMENTS:

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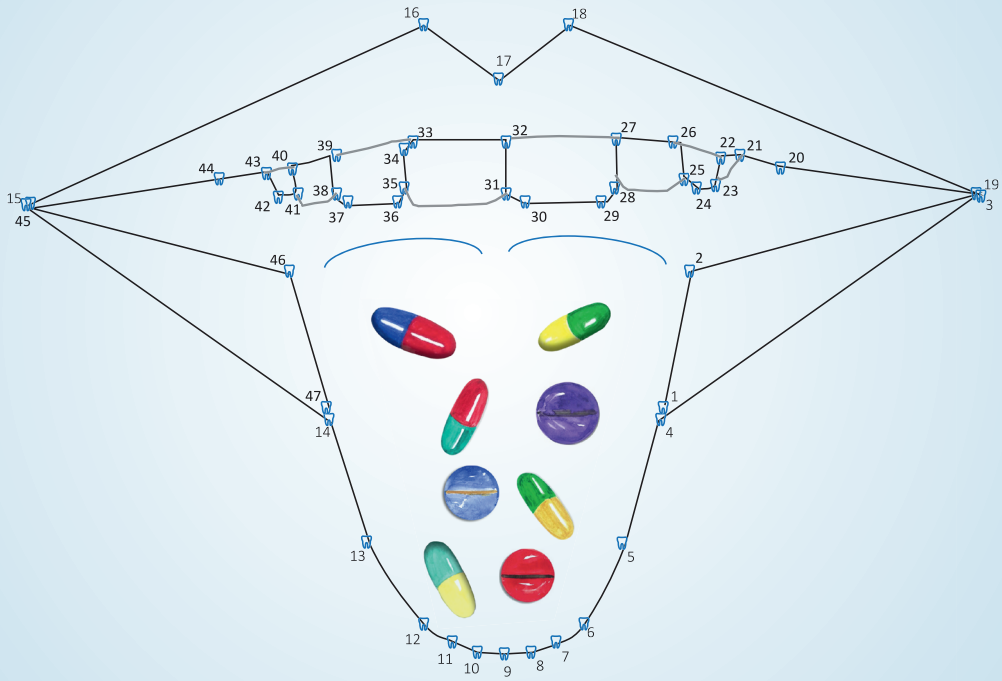
V | Summarizing discussion and future perspectives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9 Summarizing discussion and future perspectives

Implications of Medication Use for Oral Health and Oral Healthcare. Development of a Dental Clinical Decision Support System

SUMMARIZING DISCUSSION AND FUTURE PERSPECTIVES

In the Netherlands, the number of patients with complex medical histories who seek consultation from oral healthcare providers is increasing. This may be attributed to the following reasons: first, an aging Dutch population with an increased percentage of the older adults aged 65 and above. In 1990, 9.9% of the Dutch population was aged 65 and over and this has increased to 14.5% in 2019[1]; second, older adults retain their own dentition for a longer period[2]; and third, approximately 70% of people over 65 years have one or more chronic somatic conditions such as asthma, arthralgia, or diabetes mellitus,[3, 4] which could require long-term treatment with single or multiple drugs. These chronic somatic conditions and the drugs used can have adverse effects for oral health and dental treatment.[5-7] As a result, the oral healthcare providers must obtain extensive knowledge of the consequences of medication use and somatic conditions on the perioral region and dental treatment. **(Chapter 1)**

Oral healthcare providers often find it difficult to implement the extensive information available on these consequences into their daily practice. For information on adverse drug effects relevant for the oral healthcare provider, the main source for information in the Netherlands is the 'Farmacotherapeutisch Kompas' (FK). The FK is an openly accessible web-based repository. However, the FK does not specifically pertain to oral healthcare and with over 1500 drugs registered it is extensive. Therefore, retrieving information on relevant perioral adverse effects during daily dental practice is difficult and time consuming. Consequently, the ready knowledge of oral healthcare providers is mainly focused on the adverse effects of frequently used drugs such as antibiotics, analgesics, and drugs with potentially serious adverse effects such as antithrombotics and bisphosphonates. However, in recent years adverse effects occurring in the perioral region with less serious consequences (e.g. lichenoid lesions) have also received increased attention in the scientific literature. Additionally, long-awaited oral healthcare guidelines have contributed to the awareness of consequences of drug use for oral health (Dutch Institute of expertise for Oral Healthcare (KIMO) guidelines 'Oral healthcare for vulnerable housebound elderly', 'Xerostomia and hyposialia related to medication and'polypharmacy').[8, 9]

In short, the increasing amount of medically complex patients seeking dental care and the extensive information available has led to oral healthcare providers requiring support in safely managing this patient population.[10]

Therefore, this thesis aims to support oral healthcare providers to provide adequate and safe care to medically complex patients by:

1. Analysing medication-related risks during dental treatment and formulating appropriate therapeutic interventions;
2. Analysing adverse effects of drugs in the perioral region;
3. Developing of a *Clinical Decision Support System (CDSS)*, which offers user-friendly, clinically applicable, and evidence-based recommendations on the impact of medical co-morbidities and drug use on oral health and care.

1. Analysing medication-related risks during dental treatment and formulating appropriate therapeutic interventions

In previous years, oral healthcare providers in the Netherlands have focused on the risks of a small group of frequently used drugs and drugs with potentially serious adverse effects. Lack of definitive protocols, standards, or guidelines about the treatment of patients who use these drugs has led to different regional treatment protocols that were often based on defensive choices. To support the development of uniform guidelines, this thesis discusses the indications for prophylactic antibiotics in the prevention of Hematogenous Peri-prosthetic Joint Infections (HPJI) and the perioperative management of patients who use antithrombotics.

Antibiotic Prophylaxis in the prevention of HPJI

The prescription of prophylactic antibiotics for the prevention of HPJI varied across regions. Based on a systematic literature review **(Chapter 2)**, this thesis concludes that: (1) there is no indication for antibiotic prophylaxis during a dental procedure for the prevention of HPJI in patients with a prosthetic joint; (2) even if the patient has an impaired immune system function, antibiotic prophylaxis before dental treatment for prevention of HPJI is not indicated; and (3) patients should be aware of the importance of good oral health since there is a relationship between oral health and general health which could also affect HPJI.[11-14] The results of this systematic literature review have led to the current Dutch clinical guideline on this matter.[15]

Advising against prophylactic antibiotics to prevent HPJI could potentially lead to an increase of HPJI. Since the introduction of the guidelines of Chapter 2 in 2016, the number of total hip revision surgeries in the Netherlands has not increased. The Dutch Arthroplasty Register reveals that a total of 32,711 total hip surgeries were performed in 2015, and 3,834 (11%) were revisions. In 2019, 37,081 total hip surgeries were performed, of which 3828 (10%) were revisions.[16, 17] This suggests that omitting antibiotic prophylaxis to prevent a HPJI post-dental surgery did not result in additional cases of HPJI. However, total hip revision is merely a surrogate marker and further studies are

needed to truly evaluate the effect of our guideline on the incidence of HPJI. A recent systematic review by Ariel Slullitel et al. corroborates the conclusions of the study in Chapter 2, namely, that there is no evidence that prophylactic antibiotics during dental procedures prevents infection of a prosthetic joint.[18]

Antibiotic use has potential disadvantages. Bacterial resistance is the most serious and frequently described disadvantage of (incorrect) antibiotic use. Antibiotics are essential in medical and dental healthcare for preventing and controlling infections. However, the efficacy and availability of antibiotics in recent decades has led to frequent use, resulting in bacterial resistance.[19, 20] The World Health Organization (WHO) has indicated that emerging antibiotic resistance, combined with the decline in the development of new antibiotics, will have a major impact on public health. In the absence of restrictions or guidelines on the appropriate use of antibiotics, infections with resistant micro-organisms will become the primary cause of mortality globally.[21] In the Netherlands, The Dutch Working Party on Antibiotic Policy (SWAB) was established to regulate antibiotic usage, particularly in secondary and tertiary care, and to limit the development of bacterial resistance.[22]

The total number of amoxicillin prescriptions issued per year in the Netherlands has decreased from 1,362,568 in 2016 to 1,269,190 in 2019, possibly due to increased awareness of microbial drug resistance.[23] Conversely, the total number of amoxicillin prescriptions prescribed by dentists increased from 335,000 in 2008[24] to 365,000 in 2018.[25] This increase may be attributed to the continued lack of clear guidelines on both therapeutic and prophylactic antibiotic use in oral healthcare. It is estimated that 20%–50% of antibiotics prescribed in hospitals are potentially unnecessary,[26-28] a number that might be true for the oral healthcare as well. Dentists and oral- and maxillofacial surgeons routinely prescribe empirical antibiotics for patients who do not require them to avoid potential undertreatment of oral infection and ultimate litigation.[29, 30] Doing so deviates from the principles of prescribing drugs. Restraint should be exercised to avoid long-term negative effects of antibiotic use for the individual patient and ultimately (e.g. adverse effects, alteration of microbiome[31]), society (e.g. costs, bacterial resistance).

Antibiotics should only be prescribed according to the MINDME principles of *antimicrobial stewardship,* which include:

- Microbiological examination, if possible
- Indications for antibiotics are based on latest information on efficacy and effectiveness
- Use narrow spectrum antibiotics

- Dosage should be adjusted according to the type and location of infection
- Reduce duration of treatment
- Prescribing a single antibiotic

A Dutch evidence-based antibiotic use guideline for oral healthcare is currently under development. It is expected that this will result in fewer antibiotics being prescribed by oral healthcare providers.

Antithrombotics and postoperative bleeding

In patients on antithrombotics, oral healthcare providers must assess the risk of peri-procedural bleeding during invasive dental treatment, i.e. perioperative and postoperative bleeding. In the case of a clinically significant risk of peri-procedural bleeding, local hemostatic measures (suturing and tranexamic acid mouthwash (TXA)), antithrombotic dose reduction or temporarily stopping of the antithrombotic, can be considered. However, an adjustment in antithrombotic policy may result in an increased risk of thrombosis and the magnitude of this risk depends on the type of antithrombotic and its medical indication. Hematologists categorise all dentoalveolar treatments (e.g. implant placement, tooth removal) as having a low risk of peri-procedural bleeding[32]; however, for oral healthcare providers there is an apparent difference in risk between different dentoalveolar treatments (e.g. extracting one tooth versus extracting the total residual dentition). The ACTA guideline 'Policy for dental procedures during antithrombotic treatment, 2012'[33] provided evidence-based recommendations for perioperative policy. The recommendations were provided only for a limited number of procedures and some frequently occurring clinical situations were not discussed. For example, according to the guideline extraction of 1–3 teeth, surgical removal of the wisdom tooth, or placement of up to 3 dental implants could be safely performed on patients with vitamin K antagonists (VKAs), provided certain conditions were met, including prescription of TXA and an INR <3.5. Platelet aggregation inhibitors did not need be discontinued for such procedures. While for more extensive treatments (extraction of >4 tooth or placement of 4 implant), no recommendations could be provided because of a lack scientific evidence at that time. Which led to discussion about the best perioperative management in these procedures.

To assist dentists in assessing the peri-procedural bleeding risks and to decide on perioperative policy, a retrospective database study **(Chapter 3)** examined the incidence of postoperative bleeding after various invasive dental treatments in patients using VKAs. In this cohort, predictors of oral postoperative bleeding were identified. The dental procedures with a low-risk (as defined in the ACTA guideline) of periopera-

tive bleeding and high-risk (interventions that were outside the scope of the ACTA guideline) of perioperative bleeding were defined. Oral postoperative bleeding was observed in 67/2004 (3.3%) low-risk and 21/325 (6.5%) high-risk procedures. In low-risk procedures, VKA continuation with TXA was associated with a decreased risk of postoperative bleeding than continuation without TXA or compared to VKA interruption with heparin bridging. A similar risk of postoperative bleeding was observed when comparing VKA continuation with TXA and VKA interruption without heparin bridging. In high-risk procedures, continuation of VKA was associated with an increased risk of postoperative bleeding compared to VKA interruption. Multivariate analyses confirmed that heparin bridging, use of platelet aggregation inhibitors, and a supra-therapeutic or non-objective INR prior to the dental procedure were the strongest predictors of oral postoperative bleeding. Despite the methodological limitations, it can be concluded that the incidences of postoperative bleeding were low and the bleeding had a mild course when the ACTA-guidelines were applied, where possible. The results are in line with previous studies wherein the use of TXA reduced the risk of postoperative bleeding.[34] The incidences of postoperative bleeding in this study are difficult to compare to the reported incidence of postoperative bleeding after dental treatment in the general literature. In the literature, the incidence varies widely and comparison is difficult because of the heterogeneity of the results. This is partly due to the several types of available antithrombotics and the wide range of dental treatments being studied. In addition, different definitions for postoperative bleeding are used and the methodology of measuring postoperative bleeding differs across studies (measured by healthcare provider versus reported by patient).

This also accounts for patients that do not use antithrombotic drugs and are otherwise healthy. A few studies have described the incidence of postoperative bleeding (0%–61.3%) after wisdom tooth (M3) extraction in otherwise healthy patients.[35-42] These incidence rates can serve as a baseline for estimating the potential increased risk of postoperative bleeding associated with the use of antithrombotics. Accurate incidence rates of postoperative bleeding in such patients are essential to formulate guidelines, which will aid in reducing postoperative bleeding in patients on antithrombotics. However, for the Dutch population there was limited data available that could function as a baseline postoperative bleeding risk after dental treatment. Therefore, a prospective multicenter study on the incidence and risk factors of postoperative bleeding after M3 removal in healthy patients was conducted. **(Chapter 4)** The cohort included 1877 patients, of whom 1035 had completed follow-up. Complete follow-up was achieved when the questionnaires on day 1 (on treatment characteristics) and day 7 (on postoperative course) were collected. Patients were instructed to contact the physician by phone if they experienced postoperative bleeding. Of the 1035 patients,

330 patients (31.8%) reported postoperative bleeding; however, they did not consult a physician. Only 15 patients (1.5%) were advised to visit the hospital for clinical examination after consulting the physician by telephone, of whom 8 patients (0.8%) required minimally invasive treatment (e.g. suturing). There were no hospital admissions. Statistical analysis showed an increased risk of postoperative bleeding when M3s were surgically removed (i.e. after incision of the mucosa) (OR = 1.686, 95%CI [1.130 – 2.515], p = .01). It is likely that the presence of blood in saliva for several days is more prevalent after surgical removal of a third molar compared to non-surgical removal, due to a larger surgical mucosal wound. Unexpectedly, multivariate binary regression analysis with backward selection revealed a statistically significant decrease in risk of postoperative bleeding with increasing age (OR = 0.969, 95%CI [0.951 – 0.987], p = .001). It is possible that older patients were simply more willing to accept their symptoms as normal postoperative symptoms, compared to younger patients. However, these statistically significant findings might not be clinically relevant since only a few patients required treatment for postoperative bleeding. There was a marked difference between the incidence of bleeding reported by the patients and bleeding that required clinical examination and/or treatment. Hence, it is recommended that patients are provided with adequate information on the normal course of recovery following wisdom tooth removal and the risk of post-operative bleeding to prevent unnecessary anxiety in patients and unnecessary visits to the clinic.

The results of the studies in Chapters 3 and 4 suggest that patients using VKAs have a significantly increased risk of postoperative bleeding after low-risk invasive dental procedures compared to healthy patients, 3.3% versus 0.8%, respectively. However, based on a meta-analysis of 6 articles Yang et al. concluded that on day 1 and 7 postoperatively, there is no significant difference in bleeding risk between patients who continue or discontinue VKAs for dental extractions. Some limitations of the aforementioned meta-analysis were that the perioperative INR differed among the studies analyzed, only 1 of the 6 studies had a low risk of bias, and the studies had a limited number of patients.[43]

In recent years several new antithrombotics have become available and the guideline has yet to be updated. The new KIMO clinical guideline 'Invasive oral procedures in patients using antithrombotics'[34] emphasizes on the invalidating risk of thrombosis. When possible, avoid reducing or stopping antithrombotics. Reducing or discontinuation of antithrombotics should only be considered in a patient who uses antithrombotics with factors that increase the risk of perioperative bleeding such as: large wound area, wound that is difficult to close or where alveolar compression is not possible; an

infected wound area; and a frail patient. Also, some combinations of antithrombotics and VKA-use need adjustments of regime.

2. Analysis of adverse effects of drugs in the perioral region

In 2019, a 'Research Agenda for Oral Care' was proposed by van der Wouden et al. [10] to prioritize topics for future scientific research in dentistry. Based on a survey conducted among oral healthcare professionals and patients, it was concluded that there is a need for better information about the interactions between somatic conditions and oral health among both groups. The adverse effects of drugs in the perioral are a major part of this interaction.

Information pertaining to adverse effects in the perioral region is mainly available in the FK as *Summary of Product Characteristics (SmPC)* and in scientific publications. As mentioned, the FK is a reference work used by medical and dental professionals. Extensive FK adverse effect texts are a collection of all reported adverse effects. It is time consuming for oral healthcare professionals to distill only the perioral adverse effects from these texts. This is particularly true if the patient uses several drugs, which is increasingly the case in the ageing population. For example, if oral healthcare providers are looking for the adverse effect 'xerostomia', it is not easy in the current form of the SmPCs in the FK to find effects effectively using one specific search term due to the use of multiple synonyms in the FK (e.g. 'dry mouth', 'the sense of dry mouth', 'mouth dryness' or 'hyposalivation'). Therefore, oral healthcare providers need to know these synonyms and carry out multiple searches for each drug, otherwise there is a risk of overlooking the adverse effects in the perioral region.

In order to map the extent of adverse effects in the perioral region, an extensive analysis of the Informatorium Medicamentorum (IM) of the Royal Dutch Pharmacists Association (KNMP) was conducted as part of this thesis.[44] The IM, mainly used by pharmacists, also contains extensive information on all drugs registered in the Netherlands. It uses fewer synonyms than the FK and is updated every month based on the latest scientific research. The various synonyms for adverse drug reaction that were still in the IM were placed under one term using the Medical Dictionary for Regulatory Activities (MedDRA classification).[45] The MedDRA classification provides standardised medical terminology for publishing information on drugs (e.g. adverse reactions).

A total of 1645 drugs (active ingredients) were registered in the IM until 2018, when the analysis was conducted. Since each drug could cause multiple adverse reactions, approximately 65,000 unique combinations of a drug and its adverse reactions were extracted from the IM. Of these 65,000 combinations, 2335 (3.5%) were defined as

adverse effects pertaining to the perioral region and thus, relevant to oral healthcare providers. There were 875 (53%) drugs that caused at least one adverse effect in the perioral region. Frequencies of these adverse effects ranged from 'very rarely (<0.1%)' to 'very frequently (>10%)'.

The most frequently reported adverse effect was 'dry mouth' in 353/1645 (21.4%) drugs. In addition, 'taste disorders' and 'tongue disorders' were common. The subgroup analysis for taste disorders, described in **Chapter 5**, revealed that 282/1645 (17%) drugs were documented with 'dysgeusia' and 61/1645 (3.7%) with 'hypogeusia'. Drug-induced taste disorders were reported across all drug categories, though mainly under 'nervous system', 'antineoplastic and immunomodulatory drugs' and 'anti-infectives for systemic use'**.** Of the 1645 drugs, 121 (7.4%) were documented to have 'tongue disorder' as an adverse effect. The most common drug-induced tongue disorders are 'glossitis', 'tongue edema', 'tongue discolouration', and 'burning tongue' **(Chapter 6)**. Drug-induced tongue disorders were most common in the drug categories: 'nervous system', 'anti-infectives for systemic use' and 'digestive tract and metabolism'.

Some comments can be made on the results of this analysis:

Firstly, only terms that specifically describe abnormalities in the perioral region were included in the analysis. For example, 'intraoral blistering' was included, and not 'blistering' because the latter could occur elsewhere in the body. This may result in the underestimation of the number of adverse effects in the perioral region. There is no method to categorize these terms because the source data often were derived from premarketing studies which use only global terminology.

Second, as mentioned earlier, the terms used in the SmPC are not standardised. The SmPCs in the IM are drawn up by 'the Dutch Medicines Evaluation Board' and are the result of a combination of information from premarketing drug studies, postmarketing drug studies, and the information from the 'Dutch Pharmacovigilants Centre' (LAREB). Once a drug is authorized the SmPC is updated monthly. However, already listed adverse effect terms are rarely updated. For example, some SmPCs have been included in the IM since 1990 and some drugs have only been included in the IM in 2022. This may result in the usage of different adverse event terms in the SmPCs based on the scientific insights prevailing at the time of drug authorisation. To address this heterogeneity, the MedDRA classification was applied manually in the analysis. A majority of the adverse reaction terms in the SmPCs had clear corresponding terms in the MedDRA classification. In cases where the MedDRA classification could not be

applied accurately, the most similar term was chosen by the investigators, which creates a risk of misclassification and biased results. However, this only occurred in a few SmPCs.

Third, in some cases the exact incidence of the adverse effect is uncertain. In pre-marketing studies, the incidence of an adverse effect is determined by the number of patients who have reported an adverse effect in that study population. Although often large, these study populations are sometimes not large enough to be reported for adverse effects that occur 'very rarely' (<0.1%). Such rare adverse events will be reported via LAREB, only if a healthcare provider has suspected an adverse event and reports it. However, since the exact patient population using a particular drug cannot be accurately determined, the incidence and clinical relevance of these adverse effects cannot be estimated.

Fourth, some drugs (e.g. antineoplastic agents) are prescribed and used only in clinical hospital settings. Meaning that not all findings of our analysis are necessarily relevant for the general dentist who treats primarily outpatients. In addition, some adverse effects (e.g. hyperpigmentation) probably do not require treatment. Oral healthcare providers should therefore make a clinical assessment for each patient of what information on perioral adverse effects is relevant.

The results from the analysis are mainly useful as a reference, for research purposes, or for development of guidelines. Considering time investment required from a general dental to analyse these data, it is not realistic for use during daily dental practice. Alternative sources of information on adverse effects in the perioral region are scientific articles written from a clinical perspective. The publication series 'Medication and Oral Care' of the Dutch Journal of Dentistry (NTVT) is a good example. This series provides oral healthcare providers with extensive information on the appropriate prescription of drugs, and clinical photographs with background information on adverse effects of drugs pertaining to the perioral region, in the form of various articles.[46-53] The article from **Chapter 7** on adverse effects on the oral mucosa is based on the database analysis carried out in the context of this thesis. The conclusion of this chapter is that many drugs prescribed in the Netherlands have adverse effects on the oral mucosa. Adverse effects that are often described include stomatitis, white lesions, pigmentation abnormalities, and sensitivity disorders. Stomatitis and candidiasis are particularly common in drugs that are prescribed for the treatment of malignancies.

The NTVT series distills clinically relevant information from the extensive literature on the effects of drugs and balances the provision of comprehensive information with

clinically applicable information. By definition, the articles are not all-encompassing and the risk of missing (rare) perioral adverse effects remains.

Considering the huge amount of data harvested, as presented in Chapter 5, 6 and 7, and in the context of this thesis, it seemed logical to develop a user-friendly tool which easily discloses this information.

3. Development of a Clinical Decision Support System for dental practices

In hospitals, software applications such as Clinical Decision Support Systems (CDSS) are used to improve the quality of healthcare. A CDSS assists a healthcare provider in making patient-specific, evidence-based choices in the care process (e.g. best diagnostic test, most appropriate drug). To prevent drug prescription errors (e.g. wrong dose, wrong drug, or interactions with other drugs) a CDSS in the form of a Computerized Prescription System (CPS) with Drug Prescription Screening System (DPSS) is already widely used in hospitals and general physician practices. Research reveals that the use of a CPS/DPSS has a positive effect on patient safety and that costs and drug-related errors can be reduced.[54-56] The Dutch Health and Youth Care Inspectorate (IGJ) indicates in the guideline 'Electronic Prescribing, KNMG, 2013' that electronic prescribing must be considered as part of the responsible care provided and that prescribing medicines without using a CPS/DPSS is considered irresponsible.[57] However, until recently, apart from the application developed in the context of this thesis, CPS/DPSS, was not included in dental electronic health records in the Netherlands.

Chapter 8 describes the development of a *Dental* CDSS (DCDSS). The aim was to create a user-friendly tool which presents evidence-based recommendations on the impact of somatic conditions on oral health, their consequences for dental treatment, and patient-specific drug-induced adverse effects (perioral region). Additionally, the DCDSS was designed to include a CPS/DPSS functionality relevant to dentistry. A source database was built based on information from scientific articles, standard textbooks, guidelines, and the analysed IM data. In the DCDSS, the medical history can be recorded via a structured questionnaire, which is partly based on the European Medical Risk Related History (EMRRH).[58] The source database is linked via the ICD-10 and ATC classifications to the medical history of the patient with regard to somatic diseases and drug use.[58] The link with the source database is essential for DCDSS because it enables oral healthcare providers to receive scientifically substantiated patient-specific recommendations. CPS/DPSS functionality was obtained by linking the patient's prescribed drugs to the source data of Cerner's Drug Database solution.

[59] This DCDSS is available to dentists as *stand-alone* (online) software or integrated into existing dental electronic health records.

Developing the DCDSS is the first step in the process of improving dental healthcare for medically complex patients. Trivedi et al. observed that the barriers to implementing a CDSS can be categorised into human factors (e.g. will the clinician actually use the program); the culture and management within an organisation (e.g. how is the clinician supported during implementation); and technological factors (e.g. is the program user-friendly).[60, 61] Based on a systematic review, Kilsdonk et al. suggest recommendations for the development and implementation of a CDSS,[62] which include involving end users in the process at an early stage and providing hands-on training before the system is implemented. The DCDSS was developed and field-tested by oral healthcare providers in collaboration with a software developer and is therefore likely to meet the needs of the end user. However, the end user will need to fit the DCDDS into their existing clinical workflow. This will inevitably involve a change in logistics and, in principle, a time investment. However, with the increasingly medically complex patient population, the oral healthcare provider will need more time than is currently customary in taking a medical history and assessing the implications for oral healthcare. It is expected that using the support of DCDDS will reduce time investment.

For optimal effectiveness of the implementation and use of the developed tool, training remains essential. The DCDSS has been primarily developed for the Dutch oral healthcare sector. However, in future, this software application can be used internationally because of its compliance to international standard classifications (ATC codes, MedDRA classification and ICD-10 codes). Providing regular updates on the content will be necessary. This includes updating information from new sources, revalidating existing information based on new scientific insights, and verifying data with the appropriate authorities. For drug information, the National Healthcare Institute (ZN) and the Royal Dutch Pharmacists Association (KNMP) could be utilized. Information on interactions between somatic conditions and oral healthcare could be verified by the quality committees of Dutch Dental Scientific Associations and the Royal Dutch Dental Association (KNMT).

Future prospects

Healthcare of dental patients is expected to become more complex in future, partly, due to the development of personalized medicine. By taking advantage of technological opportunities, oral healthcare providers can be able to continue to provide the most optimal care and identify perioral consequences in a timely manner. New drugs

will continue to be developed and their use, in some cases, may lead to adverse effects on oral health and subsequent dental treatment. Therefore, it is essential that new drug registries use the MedDRA classification when reporting on adverse effects. Moreover, standardization of terms used to describe an adverse effect will reduce the heterogeneity of results and make them more patient-specific.

As mentioned earlier, the development of the DCDSS is only the first step in an ongoing process to improve oral healthcare for patients with medically complex histories. Follow-up studies may be required to assess whether the DCDSS meets the requirements of the end users, institutions, and EHRs within which it is used. Further investigation is necessary to evaluate whether the DCDSS actually leads to better and more effective care.

The DCDSS facilitates the collection of dental demographic patient information and user data, in line with the current technological trend ('big data'). By collecting data on drug use, somatic conditions, and the prescribing habits of dentists in a structured manner, a better picture of the medical demographics of the dental patient population can be obtained. This can be used to formulate new guidelines and research agendas, (e.g. comparing the care provided within the profession [practice variation benchmark]), and as the basis for the preparation of continuing education courses, or for shaping the dental curriculum.

In future, DCDSSs can be further extended to provide suggestions for diagnosis and treatment. The oral healthcare provider will be able to use these suggestions for differential diagnoses, have access to pathophysiological background information with clinical pictures, and receive recommendations based on protocols and guidelines. Thus, the module can be developed into an expert system that can provide qualitative support for clinical decision-making.

This thesis should be viewed holistically. The aim of this thesis was the recognition, prevention, and possible treatment of adverse effects of drug use across the (dental) population. However, it is known that there are large inter-individual differences in the pathophysiology of diseases and the way patients respond to a drug (pharmacogenetics). For example, the effect of warfarin, a VKA, is strongly determined by the presence or absence of gene mutations in the *VKORC1* and *CYP2C9* genes. [63] These gene mutations additionally determine the risk of adverse effects such as bleeding. The increasing application of new technologies such as DNA sequencing, proteomics, and wearable self-monitoring devices have led to the realization that these large inter-individual differences require personalized treatment (personalized

medicine). Instead of developing a drug and subsequently using observational studies to analyse inter-individual variations and effectiveness, targeted therapy can be used to determine the genetic profile of the patient or disease and the effectiveness of the treatment and the risk of adverse effects for that patient. Currently, this is being applied in the form of immunotherapies for oncological treatments.[64] Despite the challenges associated with personalized medicine, it is expected that this method of treatment will become widely applied in the future, which will help to predict the occurrence of adverse effects (perioral) and their prevention. Newer treatments will be accompanied by new consequences for oral health and dental treatment. The existing DCDSS will have to be continuously maintained in order to keep up with these developments. No matter how the developments unfold, the oral healthcare provider will make use of technological support to make the available scientific insights clinically applicable.

In conclusion, in the immediate future, the increase in complexity of the patient population is a trend that will not only be limited to oral healthcare; it will also be flagged by general practitioners, pharmacists, and other healthcare providers. Since the mouth is an inseparable part of the body for the treatment and prevention of diseases, dentists can no longer focus solely on dental procedures. Conversely, medical professionals cannot ignore oral health. Patient care requires a multidisciplinary approach with low-threshold communication within primary care between healthcare providers, pharmacists, and patients. To facilitate this, the DCDSS used by dentists should be linked with the healthcare systems of GPs, hospitals, and pharmacists (LSP) to enable the exchange of medical data securely, to reduce the risk of errors, and ultimately, improve patient care.

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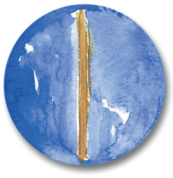
A Appendices



SUMMARY IN DUTCH

Deel I: Algemene inleiding

Mondzorgverleners worden steeds vaker geconfronteerd met medisch complexe patiënten die één of meerdere geneesmiddelen gebruiken. Dit komt doordat de gemiddelde leeftijd van de Nederlandse bevolking toeneemt en het aandeel oudere leeftijdsgroepen groter wordt. In 1990 was 9,9% van de Nederlandse inwoners 65-jaar en ouder. In twee decennia is dit percentage gestegen tot 19,5% in 2020. Van de 65-plussers is 70% bekend met één of meerdere chronische medische aandoeningen zoals astma, gewrichtsaandoeningen en diabetes mellitus. Dergelijke aandoeningen worden vaak (langdurig) behandeld met één of meerdere geneesmiddelen. Een groeiend aantal wetenschappelijke publicaties toont aan dat zowel lichamelijke aandoeningen als het gebruik van geneesmiddelen negatieve consequenties kunnen hebben voor het gezond functioneren van de mond en/of de (noodzakelijkerwijs) uit te voeren tandheelkundige behandelingen. Om doelmatige zorg te kunnen leveren, moeten mondzorgverleners op de hoogte zijn van deze consequenties.

De doelstelling van dit proefschrift is de mondzorgverlener te ondersteunen bij het leveren van doelmatige en veilige zorg aan medisch complexe patiënten door:

1) Het analyseren van medicatie-gerelateerde risico's voor de mondzorgkundige behandeling en het formuleren van aanbevelingen.
2) Het gestructureerd ontsluitenvan periorale bijwerkingen van medicatiegebruik.
3) De ontwikkeling van een gebruikersvriendelijk tandheelkundig Klinisch Digitaal Beslissingsondersteuning Systeem dat op wetenschap gebaseerde aanbevelingen geeft over de implicaties van medische comorbiditeit en medicatiegebruik voor de mondgezondheid en mondzorg.

Deel II: Medicatie gerelateerde vraagstukken binnen de tandheelkunde

Hoofdstuk 2 komt voort uit de onduidelijkheden rondom de indicatie van antibioticaprofylaxe bij tandheelkundige ingrepen, ter preventie van periprothetische gewrichtsinfecties, zoals die vóór 2015 gangbaar was in Nederland. Het betreft een samenwerking tussen mondzorgverleners en orthopedisch chirurgen. Uit deze systematische review blijkt dat antibiotische profylaxe niet geïndiceerd is voorafgaand aan een mond- of tandheelkundige ingreep bij patiënten met een gewrichtsprothese ter preventie van een hematogene infectie van de gewrichtsprothese. Ook niet in het geval van verminderde immuniteit van de patiënt. Wel wordt er benadrukt dat de patiënten bewust moeten zijn van het belang van een goede mondgezondheid. Regelmatige tandheelkundige controles zijn in dit kader aan te raden. De resultaten uit dit

onderzoek hebben geleid tot de herziening van de richtlijn 'Antibioticaprofylaxe bij gewrichtsprothese'.

In **hoofdstuk 3** wordt middels een retrospectief database onderzoek gekeken naar de incidentie van nabloedingen na diverse invasieve tandheelkundige behandelingen bij patiënten die vitamine k-antagonisten (VKA) gebruiken. In dit cohort identificeren we voorspellers van orale nabloedingen en evalueren we de incidentie van nabloedingen na tandheelkundige ingrepen. Hierbij wordt er onderscheid gemaakt tussen laag- en hoog-risico ingrepen. Bij laag-risico ingrepen trad een nabloeding op na 67/2004 (3,3%) procedures. In deze groep is het continueren van de VKA in combinatie met tranexaminezuur mondspoeling geassocieerd met een lager nabloedingsrisico in vergelijking met het continueren van de VKA zonder tranexaminezuur mondspoeling. Het continueren van de VKA in combinatie met tranexaminezuur mondspoeling is ook geassocieerd met een lager nabloedingsrisico in vergelijking met het onderbreken van de VKA met overbrugging middels een LMWH. Continueren van de VKA in combinatie met tranexaminezuur mondspoeling heeft een vergelijkbaar risico op nabloeding als onderbreking van de VKA zonder overbrugging met LMWH. Bij hoog-risico procedures trad een nabloeding op na 21/325 (6,5%) procedures. Bij de procedures met een hoog risico is continueren van de VKA geassocieerd met een verhoogd nabloedingsrisico in vergelijking met onderbreking van de VKA. Uit een multivariate analyses komen de volgende voorspellers voor orale nabloeding naar voren: overbrugging met LMWH, gelijktijdig gebruik van trombocytenaggregatieremmers, en een supratherapeutische of niet-geobjectiveerde INR vóór de procedure.

Tijdens het uitvoeren van de systematische review, zoals beschreven in hoofdstuk 3 van dit proefschrift, bleken er slechts 16 artikelen beschikbaar over de incidentie van nabloedingen na het extraheren van tanden of kiezen bij gezonde patiënten. Slechts enkele onderzoeken werden verricht in de Nederlandse patiëntenpopulatie en deze hadden onvoldoende bewijskracht. Hierdoor lijkt het niet mogelijk om de resultaten uit hoofdstuk 3 in de volle breedte te interpreteren en te plaatsen in het klinische perspectief. Er was behoefte aan een basale uitgangsmaat voor de incidentie van nabloedingen na tandheelkundige behandeling, zonder het effect van (antitrombotische) medicatie. Het prospectieve multicenter onderzoek van **hoofdstuk 4** onderzoekt de incidentie en risicofactoren van nabloedingen na verstandskies verwijdering in verder gezonde patiënten. Het cohort omvatte 1877 patiënten, waarvan 1035 met een volledige follow-up. Van de 1035 meldden 329 patiënten (31,8%) een nabloeding, maar consulteerden de arts niet. Slechts 15 patiënten (1,5%) werden telefonisch geadviseerd het ziekenhuis te bezoeken voor klinisch onderzoek, waarvan acht patiënten (0,8%) een minimaal invasieve behandeling (bijv. hechten) nodig hadden. Er waren

geen ziekenhuisopnames. Een hogere leeftijd van de patiënt was geassocieerd met een licht verlaagd risico op nabloeding. Chirurgische verwijdering, dus na (tenminste) incisie van het slijmvlies, was geassocieerd met een verhoogd risico op nabloeding. Er was een duidelijk verschil tussen de incidentie van bloedingen die door patiënten werden gemeld (subjectief) en nabloedingen die klinisch onderzoek en/of behandeling vereisten (objectief). Patiënten dienen daarom gedetailleerde informatie te krijgen over het normale beloop na het verwijderen van een verstandkies om dit verschil te verkleinen.

Deel III: Medicatie bijwerkingen in het periorale gebied

Hoofdstukken 5 en 6 zijn het resultaat van een uitgebreide analyse van het Informatorium Medicamentorum (IM) van de Koninklijke Nederlandse Maatschappij ter bevordering der Pharmacie. De analyse heeft als doel om gestuctureerd maat en getal te geven aan alle mogelijke periorale bijwerkingen waarmee een mondzorgverlener geconfronteerd kan worden. In totaal zijn er 1645 geneesmiddelen (werkzame stoffen) in Nederland geregistreerd in het IM. Elk geneesmiddel kan meerdere bijwerkingen veroorzaken, wat resulteert in ongeveer 65.000 unieke combinaties tussen een geneesmiddel en een bijwerking. Van deze 65.000 combinaties zijn er 2335 (3,5%) door de auteurs gedefinieerd als relevant voor de mondzorgverlener. Van de 1645 geneesmiddelen kunnen er 314 (19%) potentieel leiden tot smaakstoornissen (hoofdstuk 5) en 121 (7,4%) tot afwijkingen op de tong (hoofdstuk 6).

Hoofdstuk 7 is onderdeel van de publicatiereeks: “Medicatie en Mondzorg” van het Nederlands Tijdschrift voor Tandheelkunde (NTVT). Het artikel beschrijft bijwerkingen op de orale mucosa en is onder andere gebaseerd op de database-analyse die uitgevoerd is in het kader van dit proefschrift. De conclusie van dit hoofdstuk is dat veel van de in Nederland voorgeschreven geneesmiddelen bijwerkingen hebben op de orale mucosa. Bijwerkingen die vaak beschreven worden zijn stomatitis, witte laesies, pigmentafwijkingen en sensibiliteitsstoornissen. Met name bij de behandeling van maligniteiten worden frequent stomatitis en orale candidiasis gesignaleerd.

Deel IV: Het klinische toepasbaar maken van wetenschappelijke informatie

Hoofdstuk 8 beschrijft de ontwikkeling en functionaliteiten van een tandheelkundig Klinisch Digitaal Beslissingsondersteuning Systeem: MEAMEDICA-dental. De applicatie is ontwikkeld om de mondzorgprofessional te ondersteunen bij het leveren van veilige zorg aan medisch complexe patiënten. De resultaten van de geneesmiddelen analyse van het IM vormen de basis voor deze applicatie. MEAMEDICA-dental ondersteunt zowel patiënt als mondzorgprofessional bij het afnemen van de medische anamnese en

koppelt de daarbij verkregen informatie aan de beschikbare wetenschappelijke literatuur. Hierdoor is het mogelijk om de zorgverlener te voorzien van patiënt-specifieke aanbevelingen over potentiele periorale medicatie bijwerkingen, acute situaties en intra-orale manifestaties van lichamelijke aandoeningen. Daarnaast voorziet deze applicatie in een elektronische voorschrijfmodule met medicatiebewakingssysteem die tot voor kort niet beschikbaar was voor de tandheelkundige praktijk.

Deel V: Samenvattende discussie en toekomstperspectief

Hoofdstuk 9 geeft een samenvatting van het proefschrift en plaatst met een algemene discussie de onderzoeksresultaten uit dit proefschrift in een breder perspectief. Er wordt tot slot geconcludeerd dat medicatiegebruik een breed scala aan consequenties heeft voor de mondgezondheid en tandheelkundige behandelingen. Met de ontwikkeling van gepersonaliseerde geneeskunde zal de zorg voor medisch complexe patiënten nog ingewikkelder worden. Zonder de ondersteuning van hedendaagse digitale technologie blijft het onmogelijk voor de mondzorgverlener om de beschikbare wetenschappelijke informatie hieromtrent toe te passen in de dagelijkse praktijkvoering. Gelukkig zijn er technologische oplossingen beschikbaar die de mondzorgverlener kunnen ondersteunen bij het leveren van adequate (tandheelkundige) zorg en de essentiële interdisciplinaire communicatie met andere 1^{e}-lijns zorgverleners.

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Antibiotic prophylaxis is not indicated prior to dental procedures for prevention of periprosthetic joint infections: A systematic review and new guidelines of the Dutch Orthopaedic and Dental Societies

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Chapter 3

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Predictors of oral cavity bleeding and clinical outcome after dental procedures in patients on vitamin K antagonists A cohort study

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Thrombosis and Haemostasis, 2017

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LIST OF PUBLICATIONS

Brinkman DJ, Brand HS, **Rademacher WMH**, Bots CP, Rozema FR. 'Het gebruik van pijnstillers in de mondzorg in de periode 2016 tot en met 2022.' *Ned Tijdschr Tandheelkd. 2021 Sep*

Brinkman DJ, Brand HS, **Rademacher WMH**, Bots CP, Rozema FR. 'Toepassing van pijnstillers in de mondzorg.' *Ned Tijdschr Tandheelkd. 2021 Sep*

Haverman TM, Raber-Durlacher JE, Raghoebar II, **Rademacher WMH**, Rozema FR, Hazenberg MD, Epstein JB, Treister NS.´ Oral chronic graft-versus-host disease: What the general dental practitioner needs to know.´ *J Am Dent Assoc. 2020 Nov*

Dubois L, **Rademacher WHM**, Braun AK. 'Dental trauma: an overview.' *Ned Tijdschr Tandheelkd. 2020 Feb*

Rooijers W, **Rademacher WHM**, Raber-Durlacher JE, Aziz Y, Hielema AP, Rozema FR. *Ned Tijdschr Tandheelkd. 2020 Jul*

Rademacher WMH, Aziz Y, Hielema A, Cheung KC, de Lange J, Vissink A, Rozema FR.' Oral adverse effects of drugs: Taste disorders.' *Oral Dis. 2020*

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Rademacher WMH. 'Gebruikt u medicijnen? En welke medicijnen heeft u in het verleden gebruikt?' *Quality Practice 2019 sept*

Rozema FR, **Rademacher WMH** 'AB-profylaxe bij patiënten met een gewrichtsprothese' *Ned Tijdschr Tandheelkd. 2019 Oct*

Rademacher WMH, Aziz Y, van Diermen DE, Rozema FR. 'The medical-dental interactions scanner: an Electronic Health Record-integrated quality and safety module for medical- dental interactions. *Ned. Tijdschr. Tandheelkd. 2019 jan*

Rademacher WMH, Walenkamp GHIM, Moojen DJF, Hendriks JGE, Goedendorp TA, Rozema FR. Antibiotic prophylaxis is not indicated prior to dental procedures for prevention of periprosthetic joint infections. *Acta Orthop. 2017*

Rademacher WMH, Biedermann JS, Hazendonk HCAM, van Diermen DE, Leebeek FWG, Rozema FR, Kruip MJHA. 'Predictors of oral cavity bleeding and clinical outcome after dental procedures in patients on vitamin K antagonists. A cohort study.' *Thromb Haemost. 2017 Jun*

Haverman TM, Raber-Durlacher JE, **Rademacher WMH**, Vokurka S, Epstein JB, Huisman C, Hazenberg MD, de Soet JJ, de Lange J, Rozema FR.' Oral complications in hematopoietic stem cell recipients: the role of inflammation.' *Mediators Inflamm. 2014*

Rademacher WMH, van Rijssel RH, Bierenbroodspot F. 'Painful submandibular swelling appears to be a rare odontogenic tumor.' *Ned Tijds Tandheelkd. 2013 Nov*

Steenks M, Peters J, **Rademacher WMH,** Nieuwenhuijs VB, Padbury RT, Barritt GJ. J 'Intermittent ischemia enhances the uptake of indocyanine green to livers subject to ischemia and reperfusion.' *Gastroenterol Hepatol. 2012 May*

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Specific courses; year; ECTS

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Presentations; year; ECTS

- NVMKA, autumn meeting 'Digital disclosure of adverse effects affecting the head and neck region; 2015; 0.5'
- NVMKA, PAOK spring meeting 'Medication and dental care; 2021; 0.5'

(Inter)national conferences; year; ECTS

NVMKA autumn meeting; 2018; 0.5
NVMKA autumn meeting;2015; 0.5
VMTI "the wild side of life"; 2015; 0.5
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Supervising thesis: (each 1 ECTS)

- Broekman, M.W. 'Oral Heamorrhage, after third molar removal, in healthy patients.' 2016-2017
- Knoef, C; Rusinkiewicz,M, 'Literature analysis of medical and dental interactions of thyoroid disorders.' 2016-2017
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ABOUT THE AUTHOR

Willem Maria Hubertus Rademacher was born in Maastricht, the Netherlands, on December 30, 1985. Together with his three brothers he spent his youth in the city and on the countryside (Noorbeek). He completed his secondary education (HAVO) at the Montessori College Maastricht and subsequently completed his pre-university education (VWO) at the Erasmus College Maastricht.

In his choice of study there was always doubt between dentistry and medicine. In 2005 he chose the latter. During his medical studies he worked as an explantation assistant at the BIS life foundation where he performed post-mortem donation procedures in order to obtain bones, eyes and heart valves. In 2010, an academic internship took him to Adelaide, Australia for nine months.

During the final year of medicine (2012), interests in dentistry began to shine through again. After a week at the oromaxillofacial surgery department of the Amsterdam Medical Center (AMC) he decided to combine his interests in dentistry and medicine. Immediately after completing his studies in medicine, he started in 2013 as a lecturer and researcher at the department of medical dental interaction at the Academic Center for Dentistry Amsterdam (ACTA). Under the always cheerful, accessible and above all patience guidance of Prof. Rozema, the interest in the interaction between systemic- and oral health was further shaped. In 2014 he started studying dentistry at the same faculty and completed it in 2018. Meanwhile, he was working as a blood donation physician of Sanguine, attended scientific congresses and educated dental students, dental hygienists and dentists on several occasions. He also received several research grants (NTVT science prize, Hokwerda award) as incentives to continue his research.

After a very enlightening conversation with Prof. De Lange as head of the OMFS department at AUMC in December 2018, he decided to dedicate himself to become an OMFS. Currently, he is in the completion phase of his residency.

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