Dear Editor,

Thank you for considering our article for possible publication in the International Journal of Pharmacy Practice.

The title is: "Where are oral and dental adverse drug effects in product information?"

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LT conceived the methodology, contributed to the acquisition of the data, complied the results, analysed the data, drafted the manuscript and gave final approval.

KS assisted with drafting of the manuscript, analysis and interpretation of the results and gave final approval.

GM conceived the conception and design of the work, the presentation of the results, drafted the manuscript and gave final approval.

All authors had access to the original study data that supported this publication. All authors are in agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

No ethics approval was required for this study, as the most commonly dispensed drugs on the Pharmaceutical Benefits Scheme is publicly available from the Department of Health. Drug product information is also publicly available so therefore ethics approval was not required.

The word count is 2,494.

Yours sincerely,

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Where are oral and dental adverse drug effects in product information?

Abstract

Aims: Oral adverse drug reactions are common and are associated with some of our most frequently used medicines. It is important to identify and manage oral adverse drug effects promptly as they not only negatively impact dental health, but also adversely affect medication adherence, clinical outcomes and patient quality of life. This study assessed the location of oral drug-induced adverse effects in the registered drug company product information of the top 100 most commonly used drugs in Australia as dispensed on the Pharmaceutical Benefits Scheme in 2018.

Method and Results: Publicly available data on dispensed medicines was accessed from the Australian Commonwealth Department of Health, to determine the top 100 medicines. The drug company product information for each of these drugs was manually searched to find their oral adverse effects. The number, type and location of the oral ADRs were recorded. Oral ADRs were commonly found varying in nature and severity. However, they were difficult to find as there is no dedicated section for oral/dental adverse effects in the product information and the section they are in is inconsistently applied.

Conclusion: We recommend that regulatory authorities such as the Therapeutic Goods Administration in Australia create an additional section for oral/dental adverse effects so they are easier to find, which may assist health professionals detect recognise and report adverse drug effects manifesting in the oral cavity.

Introduction

An adverse drug reaction (ADR) is defined by the World Health Organisation as "a response to a medicine which is noxious and unintended, and which occurs at doses normally used in man".[1] Adverse drug effects are frequent consequence of medicine use, especially in the context of polypharmacy. A recent population-based study showed that polypharmacy is common among older Australians, and the number of affected people continuing to rise, despite the increased risk of drug interactions, adverse drug effects and of medication errors.[2] The most recent Australian Institute of Health and Welfare report showed that people of 50 years and over were the recipients of 75% of all dispensed medicines on the Australian national subsidised medicines program, the Pharmaceutical Benefits Scheme (PBS) in 2017.[3] Adverse drug reactions and medication-related issues account for approximately 250,000 yearly hospital admissions, with 50% of this harm being preventable,[4] and are estimated to be between the 4th and 6th leading cause of death in the USA.[5]

ADRs occur frequently in the oral cavity, affecting every structure of the mouth from oral mucosa to the teeth and tongue. These ADRs can arise from medications used either locally in the mouth or systemically. Expected oral side effects such as dry mouth are well documented for drugs such as anticholinergic medicines,[6] but many oral adverse reactions are unrelated to the known pharmacology of the drug (i.e. type B) and therefore may go undiagnosed and unreported. As ype B oral ADRs are unexpected, they can be difficult for patients and health professionals to recognise as being drug-induced. The clinical presentation of oral adverse drug effects, such as oral lichen planus, bruxism and orobuccolingual dyskinesia, can be difficult to assess for non-dental professionals so may be misdiagnosed as a new medical condition or related to an existing medical condition. To make matters rose, there is little current literature on oral ADRs how to diagnose them and, in particular, how frequently they occur. A retrospective study of oral ADR reports from the US Food and Drug Administration (FDA) determined the most frequent oral ADRs associated with the 100 most commonly prescribed medicines and showed that they were varied and common occurrences.[7]

One of the main obstacles to identifying and reporting of oral ADRs is the inconsistency with how they are classified and presented in the medical literature. In addition, oral ADRs detected during clinical trials or in the post-marketing period are difficult to find in the registered product information (PI) as their location tends to vary.

To the best of our knowledge, there is no dedicated section for oral adverse effects in product information anywhere in the world, and they tend to be scattered through various sections, from gastrointestinal and musculoskeletal to neurological and psychiatric. This may be one reason why they are often overlooked or considered of lesser importance than other ADRs, or simply not found. We considered an oral ADR to be any adverse drug reaction that would affect the oral cavity and jaw joints, not including or extending past the tonsils. Examples include xerostomia, hypersalivation, bruxism, tooth discolouration and hairy tongue. Although rare, any systemic ADRs that may have oral manifestations were not included, such as drug-induced lupus.

The aim of this study was to characterise two issues in the ADR documentation for the 100 most commonly dispensed systemically administered drugs as recorded on Australia's national prescription database, the Pharmaceutical Benefits Scheme (PBS): 1) which, if any, oral ADRs are listed in the PI, and 2) where they are located, and to assess the consistency of these locations among the various PIs.

Method

The 100 most frequently dispensed drugs on the Australian PBS in 2018 were obtained by accessing publicly available data from the Commonwealth Department of Health on dispensed medicine use.[8] The PBS is a program by which the Australian government subsidises the cost of most medicines. Each dosage form of every drug has a unique PBS code listed on the PBS website with the number of dispensed prescriptions of that particular dose form over a defined timeframe.[8]

The data on dispensed medicines were collected for prescriptions by all prescribers (medical, dental, nursing and optometry) to ascertain the 100 most frequently dispensed drugs for 2018. This list of drugs dispensed on the PBS from 1 January to 31 December 2018 was extracted and arranged using Microsoft Excel by number of dispensed prescriptions. The drugs were sorted by generic name; no proprietary names are included in the database. Each unique PBS medicine code was then correlated with the corresponding drug as indicated on the PBS website.[9] As it is recommended by the Department of Health that the dataset supplied be accessed at least three months after the studied time frame, to account for delayed processing of prescriptions,[8] the dataset was accessed on 30 April 2019. As this data is publicly available, ethics approval was not required.

Only systemically administered drugs were included, as it is known that topically administered drugs are less likely to be associated with oral ADRs. The oral ADRs chosen for analysis were limited to those that manifest in the oral cavity or affect jaw joints.

Once the list of the most commonly dispensed medicines was compiled, the registered product information for the original brand of each drug was accessed from AusDi[10]. This document was scanned manually by the primary researcher (LT), who is a pharmacist and dentist, for each drug for any possible oral ADRs in the "Adverse effects" section. The ADR category in which each oral ADR was located and the number of drugs with which each oral ADR was associated with were also recorded.

Results

The oral ADRs detected from the PI of the top 100 dispensed systemic drugs on the PBS in 2018 included xerostomia, taste disturbance (including dysgeusia and ageusia), mouth ulceration (or stomatitis), tardive dyskinesia, black hairy tongue, bruxism, gingival enlargement, hypersalivation, glossitis, tooth discolouration and pigmentation of mucous membranes, osteonecrosis of the jaw, tooth disorder, caries, parotid swelling, toothache, gingival bleeding and oral hypoesthesia. The number of drugs each oral ADR is associated with is shown in Table 1. The location of the six most frequently cited oral ADRs in the PI is shown in Table 2. This table clearly demonstrates the variety and inconsistency of the location of oral ADRs across drug product information.

Xerostomia was listed as an oral adverse effect of 43 of the top 100 dispensed drugs on the PBS in 2018, and showed the most variability in location, as it was found in six different ADR sections. It was found mostly in the gastrointestinal section, but also in "nervous system", "metabolic", "anticholinergic", or in an unspecified section (see Table 2). Taste disturbance was the second most commonly reported oral ADR, being associated with 36 drugs. Again, there was variability in the location, being in four different sections: "gastrointestinal", "nervous system", "special senses" or "other" sections. Mouth ulceration or stomatitis was listed as an oral adverse effect for 18 drugs, mostly located in the "gastrointestinal" section or "Other". Tardive dyskinesia, a condition that most commonly affects the mouth, lips and tongue, was located in the "nervous system", psychiatric and gastrointestinal section. The PI for metoclopramide ('Maxolon' brand), the drug that is most commonly associated with tardive dyskinesia, listed all ADRs under one section entitled

"Adverse effects (Undesirable effects)" and did not list any according to separate body systems.

The location of the adverse effect 'black hairy tongue' was mostly in the "gastrointestinal" section, despite it only affecting the tongue.[11, 12] This benign, self-limiting adverse effect, where the tongue can have a black, brown, yellow or green discolouration, is mostly associated with antibiotics, postulated to be due to their ability to modify local oral flora.[11, 12] Bruxism, a well-established adverse effect of SSRIs, was inconsistently located in three sections, "psychiatric", "nervous system" and "gastrointestinal".

Other oral adverse effects not included in Table 2, but found to be less common, are described here. Gingival enlargement, a well-known but uncommon adverse effect of the calcium channel blockers, valproate, phenytoin and cyclosporin, was listed under the "gastrointestinal section" for amlodipine, verapamil, valproate and felodipine, but under "post-marketing data" for diltiazem.

Glossitis and hypersalivation were consistently listed in the "gastrointestinal" section. While the salivary glands and tongue are part of the gastro-intestinal tract, they are primarily thought of as being part of the oral cavity specifically; however, none of the PIs have used this as a heading listing for ADRs. Doxycycline, minocycline and clarithromycin are associated with causing tooth and tongue discolouration, which was listed under four different sections. For doxycycline and clarithromycin, tooth and tongue discolouration were listed under "musculoskeletal" and "digestive" sections respectively, while minocycline listed tooth discolouration in a dedicated "dental" section. Minocycline is also associated with causing pigmentary changes to the oral mucous membranes, which was listed under the "dermatological" section, most likely because it is associated with causing pigmentary changes of the external skin, eyes and nails as well. Medication-related osteonecrosis of the jaw was listed under its own specific section for denosumab but under the "musculoskeletal" section for risedronate.

Discussion

This is the first study to comprehensively assess the location of reporting of oral ADRs in the product information of commonly dispensed medicines in Australia. The study showed great variation in the location of oral ADRs in the PIs studied, making them difficult to locate for

both clinicians and patients. The most common section for oral ADRs to be located was the gastrointestinal section. Oral ADRs, such as xerostomia, can impact a patient's teeth, caries development, speech, or eating.

Strengths and limitations

Strengths of this study are the objective and critical review of product information rarely made by clinicians in everyday practice, and the broad perspective achieved by analysing a very wide range of drugs. However, an important limitation of this study is that we only examined PI from frequently dispensed drugs which are often popular because they are inherently well-tolerated and therefore may not have had many oral ADRs in their PI anyway. Additionally, we only used Australian PI, but a valuable international perspective would be gained by repeating this study using PI from other countries where, for example, ADR frequency is included more often in the PI than it is in Australia. Nevertheless, this study is directly relevant to healthcare for professionals unaware of or having difficulty finding oral ADRs in PI sources.

Underscoring the findings from this study, previous studies assessing the prevalence of oral ADRs have confirmed that they are a common occurrence, with side effects such as xerostomia, hypersalivation, tardive dyskinesia and bruxism being commonly associated with medications used to manage conditions including mental illness and multiple sclerosis.[13, 14] Xerostomia has also been reported in literature as being common among older people, mostly due to the effect of medicine use and polypharmacy.[15] A study which assessed the accessibility of the available information about xerostomia in drug monographs and published literature found that dry mouth is a common adverse effect, associated with 61% of the most commonly prescribed medications in Canada, but warnings are not readily available to health professionals or patients.[16] This study also found that the information provided by the medicine references could be confusing, as there are conflicting reports and information is not consistent across the various drug information sources. The authors postulate that this may be one reason why physicians do not routinely inform patients about this adverse effect and how to manage it, despite it being not only common, but also significantly affecting patients' quality of life.[16] This hypothesis as to why physicians do not routinely inform patients of possible orofacial side effects may well apply to the Australian context, given the findings of our study. [16]

In addition to being common, it is well established that oral ADRs can have varying degrees of impact on both the oral and general health of patients. The long-term use of drugs that are associated with xerostomia, such as anticholinergics or tricyclic antidepressants, can have a significant effect on the oral environment, with patients at significant risk of an increase in the rate of tooth decay, gum disease, dental pain and eventually loss of teeth.[11, 16] Patients with dry mouth are also at increased risk of developing oral candidiasis, having difficulty with mastication, swallowing and speech.[11] this common adverse effect can therefore have a profound effect on oral health and quality of life .In agreement with other studies,[6, 15] our study showed that a wide range of drugs are associated with xerostomia. ,

Other oral adverse effects, such as drug-induced movement disorders, including bruxism and dyskinesia, are underreported and less well known. These effects are associated with the SSRIs and antipsychotics.[17-19] Bruxism can result in profound wear of the teeth, jaw-muscle hypertrophy, fracture or failure of teeth, restorations or implants, and sensitivity or pain of teeth, jaw and temporo-mandibular joints.[20] Although it affects the orofacial region, the complex and multifactorial aetiology of bruxism results in its being placed in the "psychiatric" or "nervous system" sections, which makes it difficult for health professionals to locate as an oral ADR since many patients who experience bruxism do not have a diagnosed psychiatric disorder. Orobuccal lingual dyskinesias are persistent, involuntary abnormal movements that usually present as lip-smacking, grimacing, puckering, rapid eye blinking and dyskinetic tongue movements and can persist even after the medication is stopped.[21-23] As the most common symptoms of OBLD involve the oral cavity, being able to locate this ADR in the PI as an oral adverse effect would be very helpful for dentists and other health professionals. who, may be unlikely to consider the "nervous system" as the area in which to find this adverse effect in the PI.

Many other oral adverse effects were associated with the commonly utilised medicines in Australia as determined from the analysis, such as hairy tongue, hypersalivation, gingival enlargement, tooth discolouration and other mucosal disorders induced by medicines that can have oral manifestations. Taste disturbance was the second most commonly identified oral ADR, which can impact on patients' dietary choices, and potentially contribute to caries development as well as affecting general health.[13] This adverse effect is inconsistently scattered in different sections in the PI for different drugs and is therefore difficult to find. Being able to recognise, locate and manage oral ADRs is clearly important to prevent dental

caries, gum disease, tooth abrasion, and dental and tooth pain,[13] as well as to maintain general health.

Policy, practice, research implications

Identifying that a condition may be drug-induced is essential for effective management. In fact, medication-related osteonecrosis of the jaw, associated with drugs such as bisphosphonates and denosumab, was only identified through post-marketing reporting and has consequently influenced the management of patients taking these medicines by both dentists and medical practitioners. As the management of oral ADRs often involves a multidisciplinary approach, all health professionals need to be easily able to locate oral ADRs in drug information sources, and as such, they should be consistent.

However, for the purposes of highlighting inconsistencies, drug product information sources, including drug sources for Europe, the UK and the US, all have similar findings.[24, 25]

We call on drug regulatory authorities such as the TGA in Australia to update the section on adverse effects in registered product information and create an additional category for oral/dental adverse effects so they may be more readily identified. This would not preclude the listing of such ADRs under other appropriate sections. This may assist with reporting of ADRs and may help with detection during pre-marketing trials, as researchers will be alerted to their possible presence.

The fact that most oral adverse effects were located in the gastrointestinal section, or inconsistently in various sections throughout the PI makes them difficult to find. Not only does this obscure useful information for all health professionals as they can be easily overlooked, but gives the misconception that they are not important enough to list separately or that they do not exist. Most clinicians have time constraints and so being able to quickly and practically locate oral adverse effects may assist with their detection and highlights their importance. Appropriate management can have a significant impact on a patient's overall health and well-being.

Conclusion

Oral ADRs are common, varied and associated with commonly prescribed medicines. A significant proportion of the population would experience and need to manage the effects of drug-related oral ADRs, which can have a significant impact on their oral health, clinical

outcomes and quality of life. Making oral ADRs easier to find in the PI would help with ADR recognition, management and reporting. Regulatory authorities such as the TGA could create an additional category for oral adverse effects in the PI so that both clinicians and patients can more readily identify them.

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Table 1. Number of drugs that were associated with each oral ADR

Oral ADR	Number of drugs
Xerostomia	43
Taste disturbance	36
Mouth ulceration/stomatitis	18
Tardive dyskinesia	11
Hairy tongue	7
Bruxism	7
Gingival enlargement	5
Hypersalivation	5
Glossitis	4
Tooth discolouration/pigmentation of mucous membranes	3
Osteonecrosis of the jaw	2
Other*	7

*Includes parotid swelling, tooth disorder, bleeding gums, salivary gland enlargement, tooth caries, toothache.

Table 2. The 6 most frequently associated oral ADRs of the most commonly dispensed 100 drugs on the PBS in 2018 and their location in the product information.

Drug	Brand - PI	Xerostomia	Taste disturbance	Mouth ulceration/stomatitis	Tardive dyskinesia	Black hairy tongue	Bruxism
Allopurinol	Progout		Other	Other			
Amitriptyline	Endep	Gastrointestinal	Gastrointestinal	Gastrointestinal	Nervous system	Gastrointestinal	
Atenolol	Tenormin	Gastrointestinal					
Amlodipine	Norvasc	Gastrointestinal	Other				
Amoxicillin	Amoxil					Gastrointestinal	
Amoxicillin with clavulanate	Augmentin Duo			Gastrointestinal		Gastrointestinal	
Buprenorphine	Norspan	Gastrointestinal	Nervous system				
Celecoxib	Celebrex	Gastrointestinal	Nervous system	Gastrointestinal			
Citalopram	Cipramil	Gastrointestinal	Special senses	Gastrointestinal	Nervous system		Psychiatric
Clarithromycin	Klacid	Gastrointestinal	Special senses	Gastrointestinal		Gastrointestinal	
Clopidogrel	Plavix		Nervous system				
Clopidogrel with Aspirin	CoPlavix		Nervous system				
Colchicine	Colgout			Gastrointestinal			
Desvenlafaxine	Pristiq	Gastrointestinal	Nervous system		Nervous system		
Diazepam	Valium	Gastrointestinal					
Diclofenac	Voltaren		Nervous system	Gastrointestinal			
Diltiazem	Cardizem	Gastrointestinal	Gastrointestinal				
Domperidone	Motilium	Nervous system		Other			
Doxycycline	Doryx					Gastrointestinal	
Duloxetine	Cymbalta	Gastrointestinal	Nervous system	Gastrointestinal	Nervous system		Psychiatric
Dutasteride/Tamsulosin	Duodart	Post-marketing data					
Escitalopram	Lexapro	Gastrointestinal	Special senses		Nervous system		Psychiatric
Fluoxetine	Prozac	Gastrointestinal	Special senses		Nervous system		Nervous system
Furosemide	Lasix	Metabolic					
Irbesartan	Avapro	Gastrointestinal	Special senses				
Irbesartan with Hydrochlorothiazide	Avapro HCT	Gastrointestinal	Special senses				
Lansoprazole	Zoton	Gastrointestinal	Nervous system				
Lercandipine	Zanidip		Special senses				
Linagliptin	Trajenta			Gastrointestinal			
Meloxicam	Mobic			Gastrointestinal			
Metformin	Diabex		Nervous system				
Metoclopramide	Maxolon				No specified section		
Metoprolol	Betaloc	Gastrointestinal	Special senses				
Metronidazole	Flagyl		Gastrointestinal	Gastrointestinal		Gastrointestinal	
Moxonidine	Physiotens	Nervous system					
Olanzapine	Zyprexa	Gastrointestinal					
Omeprazole	Losec	Gastrointestinal	Nervous system	Gastrointestinal			
Oxycodone	Endone	No specified section					
Oxycodone/naloxone	Targin	Gastrointestinal	Nervous system	Gastrointestinal			
Oxybutynin	Ditropan	Gastrointestinal					
Pantoprazole	Somac	Gastrointestinal	Nervous system				
Paracetamol with Codeine	Panadeine Forte	No specified section					
Paroxetine	Aropax	Gastrointestinal	Special senses	Gastrointestinal	Nervous system		Gastrointestinal
Perindopril	Coversyl	Gastrointestinal	Gastrointestinal				
Perindopril with indapamide	Coversyl Plus	Gastrointestinal	Nervous system				
Phenoxymethylpenicillin	Cilicaine VK					No specified section	
Prazosin	Minipress	Gastrointestinal					
Pregabalin	Lyrica	Gastrointestinal	Nervous system				
Prochlorperazine	Stemetil	Gastrointestinal			Nervous system		
Rabeprazole	Pariet	Gastrointestinal	Special senses				
Rampril	Tritace	Gastrointestinal	Gastrointestinal				
Risedronate	Actonel	Gastrointestinal					
Rivoroxaban	Xarelto	Gastrointestinal					
Roxithromycin	Rulide		Other				
Sertraline	Zoloft	Gastrointestinal			Nervous system		Psychiatric
Sotalol	Sotacor		Special senses				
Tapentadol	Palexia SR	Gastrointestinal					
Telmisartan	Micardis	Gastrointestinal					
Trimethoprim with sulfamethoxazole	Bactrim			Gastrointestinal			
Valproate	Epilim			Gastrointestinal			
Venlafaxine	Efexor-XR	Nervous system	Nervous system		Nervous system		Psychiatric
Verapamil	Isoptin	Gastrointestinal					
Warfarin	Coumadin		Nervous system				