

# Adverse drug reactions, a guide for dentists

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## ABSTRACT

Adverse drug reactions (ADRs) are unintended or harmful effects due to the use of a medicine. Antibiotics and analgesics, which incidentally, are commonly prescribed by dentists, result in most of the ADRs globally. As with most healthcare professionals, dentists do not report on ADRs regularly. Therefore, the aim of the review was to explore the drugs most used in dental practice in South Africa (SA), their associated ADRs and the ADR reporting channels.

The study undertook a literature review that focused on studies of adverse drug reactions specifically in dental practices. An electronic search was done on EBSCO host to source articles published from 2000 to 2022. There was a plethora of ADRs that were found to occur with the medicines that are prescribed by dentists that ranged from minor to serious. Although all medicines have a risk of ADRs, amoxicillin can result in gastrointestinal disturbances and anaphylactic reactions, while clindamycin has a risk of *Clostridium difficile* infection.

Patients need to be alerted to the risk of a disulfiram reaction with metronidazole and alcohol. Hepatic failure can occur with paracetamol use especially in patients with underlying liver disease, an alcoholic or in an overdose. Ibuprofen, caution in patients with underlying ulcers as gastrointestinal bleeding is a risk. Local anesthetics pose a high threat of severe reactions such as tissue necrosis and direct neurotoxicity while anterograde amnesia, respiratory depression and thrombosis can occur with benzodiazepines.

Dentists can prevent ADRs by having a good knowledge of their prescribed drugs, monitoring their patients and by being judicious in their prescribing habits.

## Keywords

Adverse drug reactions, dentists, adverse drug reaction reporting, SAHPRA

## INTRODUCTION

Adverse drug reactions (ADRs) are unintended or harmful effects attributed to the use of a drug. Unrecognized ADRs may have significant financial consequences for the patient. Globally, studies show that antibiotics and analgesics are among the leading causes of ADRs and coincidentally are also commonly prescribed by dentists.<sup>1,2</sup>

Although, most of these reactions are dose-dependent and predictable, reactions like allergic and idiosyncratic reactions can occur and are unrelated to the normal pharmacological action. ADRs may be compounded (aggravated) by drug-drug interactions, drug-food interactions, drug-physiology interactions and underlying comorbidities of the patient.<sup>3</sup>

Recognizing, managing, and reporting ADRs or any other complications is critical to medication adherence, improving clinical outcomes, and the patients' overall health. The patient's medical history should be evaluated, and the patient counselled on possible adverse effects, before prescribing medications to reduce the risks of ADRs, and increase compliance.<sup>7</sup> As in medical practice, underreporting of ADRs among dental professionals is a common phenomenon.<sup>4-6</sup> Therefore, this study explores the drugs most commonly used in dental practice in South Africa (SA), their associated ADRs, the importance of ADR reporting, and the ADR reporting channels.

## DRUGS USED IN DENTAL PRACTICE

Dentists most commonly use antimicrobials (antibiotics, antifungals, antiviral agents), analgesics (non-steroidal anti-inflammatory drugs (NSAIDs), paracetamol and opioids), local anaesthetics (lidocaine, articaine, lignocaine, mepivacaine), sedatives and general anaesthetics (nitrous oxide, midazolam). Systemic and topical corticosteroids may also be used to manage post-operative inflammation and treat oral immune-mediated diseases.<sup>8</sup>

## ANTIMICROBIALS

### Antibiotics

Antibiotics are prescribed for the treatment of bacterial infections, most commonly of pulpal and periodontal origin. However, it may also be used to prevent cardiac and joint complications due to bacteremia in high-risk patients and local complications following surgery.<sup>9,10</sup> They are used

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### Author contributions

Neelaveni Padayachee conceptualised and drafted the idea for the paper. She contributed to researching and writing part the sections on the policy of the paper. She also edited and reviewed the paper for language and content

Deborah Matesun researched and wrote about the drugs involved in dental practice and assisted with the referencing of the article

Mafora Matlala assisted with the language editing and content review for the paper

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Table I: Commonly used antimicrobials in dentistry and their Adverse Drug Reactions<sup>27</sup>

Drug Category	Examples	Adverse Drug Reactions	Frequency/Severity	Special Warnings/Precautions
Antibiotics	Amoxicillin	Gastrointestinal symptoms Opportunistic infections (mucocutaneous candidiasis, clostridium difficile diarrhoea) Cutaneous symptoms (urticaria, pruritus, flushing, angioedema)	Common; mild Common; severe <sup>28</sup>  Common; severe <sup>29</sup>	In cases of any hypersensitivity skin reactions, treatment should be discontinued.
	Amoxicillin/clavulanic acid	Hypersensitivity (Same as for amoxicillin) Hepatotoxicity (marked elevations in AST and ALT)	5-10%; severe <sup>30</sup> Rare; moderate	
	Metronidazole	Gastrointestinal symptoms Nervous system reactions such as seizure Altered taste Disulphiram type reactions; flushing, Headaches, cardiac palpitations <sup>31</sup>	Very common; mild Rare; potentially severe Common; mild Rare; severe (potentially life threatening)	Patients should avoid alcohol intake for at least 3 days after completing full treatment course
	Clindamycin	Gastrointestinal effects (diarrhoea is most common) <sup>32</sup> <i>Clostridium difficile</i> infection Eosinophilia, skin rash, redness Rheumatoid arthritis, hypotension, renal changes (proteinuria or azotemia) <sup>33</sup> Hematological reactions (neutropenia, agranulocytosis)	Very common; mostly mild Common; severe (life threatening) Rare; mild  Rare	High risk of <i>clostridium difficile</i> infections in patients taking clindamycin compared to other antibiotics. In cases of prolonged diarrhoea with fever, blood in stool or urine, patients should be advised to contact clinician for prompt evaluation of clostridium difficile infection
	Azithromycin <sup>34</sup>	Gastrointestinal symptoms Clostridium difficile infections  Cardiovascular reactions (QTC prolongation in the cardiac cycle) Nervous system reactions (altered taste, dizziness, and somnolence)	Common; mild Common; severe life-threatening Common; severe	Azithromycin should be used with caution with other medications such as antipsychotics and antidepressants which can cause QTC prolongation
Antifungals	Topical Miconazole, nystatin and clotrimazole	Nausea, dry mouth, tongue discolouration, taste abnormalities.	Common; mild	
	Systemic Fluconazole	Gastrointestinal symptoms Neurologic effects; dizziness, headache, dysgeusia Pruritus, rashes, angioedema, exfoliative cutaneous reactions, insomnia, seizures Hepatotoxicity	Common; mild Common; mild  Uncommon; severe  Severe	

either empirically based on the anticipated microbiology of odontogenic infections, or based on antimicrobial susceptibility testing.<sup>11,12</sup> Short courses of antibiotics (3-7 days) are effective in managing dental infections. In SA, the most prescribed antibiotic in dental practices is amoxicillin.<sup>13,14</sup> Azithromycin, a macrolide antibiotic, is not suggested as first-line treatment, but may be considered as an alternative for the patient with suspected or confirmed penicillin allergy.<sup>15,16</sup>

Amoxicillin, a penicillin-like antibiotic is bactericidal and acts by inhibiting cell wall synthesis in susceptible organisms.<sup>17</sup> It is the first drug of choice in treating odontogenic infections.<sup>18,19</sup> A combination of amoxicillin and clavulanic acid, a beta lactamase inhibitor, is also commonly administered due to its lower level of bacterial resistance, extended spectrum of activity and convenient dosing characteristics.<sup>20</sup> Amoxicillin is relatively safe in non-allergic patients and has the lowest reported rate of ADRs compared to other antibiotics.<sup>19</sup>

Metronidazole inhibits nucleic acid synthesis with intracellular macromolecules. It is prescribed as an adjunct to penicillin in severe infections such as severe periodontitis. Additionally, it can be used to treat cases of predominantly anaerobic infections. Metronidazole and alcohol should not be used in combination due to a disulfiram reaction. Metronidazole causes an increase in acetaldehyde because it inhibits the enzyme acetaldehyde dehydrogenase in the ethanol degradation pathway. Patients present with flushing, headache, nausea, and cardiac palpitations and alcohol must be avoided for 3 days after use of metronidazole.<sup>17,21</sup>

Clindamycin is a lincosamide antibiotic which inhibits protein synthesis by reversibly binding to 50S ribosomal subunits and a good choice for penicillin sensitive patients.<sup>22</sup> It is known for its good oral absorption (low incidence of bacterial resistance and high antibiotic concentrations reached in tissues, including bone.<sup>23</sup> Nevertheless, there is a greater risk

of *Clostridium difficile* infections reported with clindamycin compared with other antibiotics prescribed in dentistry.<sup>24</sup> The anaerobic gram-positive bacteria, *Clostridium difficile* is transmitted via the fecal-oral route in humans and the usage of ampicillin, amoxicillin, cephalosporins and clindamycin are commonly associated with an increased risk of *C. difficile* infection. Watery diarrhea, fever, nausea, abdominal pain, nausea, vomiting, weakness, and loss of appetite are common features of *C. difficile*.<sup>25,26</sup>

### ANTIFUNGALS

Oral candidiasis, caused by *Candida albicans*, is managed topically (using miconazole or nystatin) or systemically with fluconazole and itraconazole. Topical antifungals such as nystatin have few and mild adverse effects because of their limited absorption. However, patient compliance to topical formulations such as nystatin oral suspension may be compromised by unpleasant taste, frequent application, and lengthy use and its prolonged treatment pattern.

In general, the principal risks associated with antibiotics are opportunistic infections, especially oral candidiasis, and gastrointestinal disturbances such as nausea, vomiting and diarrhea, often due to the disruption of the gut flora.<sup>27</sup> A summary of the commonly used antimicrobials and their adverse reactions are provided in Table I.

### ANALGESICS

Dentists most commonly prescribe two types of analgesics: non-narcotic analgesics (paracetamol and non-steroidal anti-inflammatory drugs) and narcotic analgesics (opioids). Paracetamol is used for treating mild dental pain when NSAIDs are contraindicated. It is one of the safest analgesics when administered to healthy individuals in usual therapeutic doses.<sup>35</sup> However, hepatotoxicity may be a concern due to the buildup of N-acetyl-p-benzoquinone imine, a potentially toxic metabolite, in individuals with compromised liver function (such as alcoholics) or in cases of overdose.<sup>36</sup> The commonly accepted maximum dosage of acetaminophen in a healthy individual is 4 g per day. However, the Food and

Drug Administration recommends a maximum dose to 3 g per day to reduce the risk of severe liver injury.<sup>37</sup>

NSAIDs are the first line of analgesics in treating dental pain, with ibuprofen prescribed most for mild odontogenic pain. It is usually prescribed either alone and in combination with paracetamol.<sup>38</sup> Occasionally, maxillofacial surgeons also prescribe etoricoxib and celecoxib, a selective COX-2 inhibitor as short-term treatment for mild to moderate pain associated with dental surgery.<sup>39</sup> Due to its selectivity, etoricoxib and celecoxib is usually considered in patients at risk of gastric ulceration or those taking blood thinners such as warfarin.<sup>40</sup>

Opioids produce analgesia by activation of opioid receptors and are used for managing moderate or severe dental pain. When NSAIDs combined with paracetamol, does not yield sufficient pain relief, a weak opioid analgesic such as tramadol, may be added. However, a short course of a strong opioid, such as oxycodone, may be used in patients suffering from insomnia due to severe pain.<sup>41</sup> These patients should be closely monitored due to the high risk of ADR such as constipation. Table II highlights ADR of commonly used analgesics in dentistry.

### LOCAL ANAESTHETICS AND THEIR VASOCONSTRICTORS

Local anesthesia is commonly used in invasive dental procedures, and include lidocaine, articaine, prilocaine, lignocaine and mepivacaine. These can be applied topically (not all are available as topical preparations) or injected for local infiltration or nerve blocks. Local anaesthetics (LA) are often combined with a vasoconstrictor such as epinephrine, to retain the LA to increase the duration of action, and limit systemic absorption.<sup>42</sup>

Local anaesthetics are generally considered safe but can cause systemic and local toxicity due to the irritating nature of the solution, pressure from large volumes, or vasoconstriction.<sup>43</sup> The dose and concentration should be

Table II: Commonly used analgesics in dentistry and their Adverse Drug Reactions<sup>17</sup>

Drug	Name	Adverse Drug Reactions	Frequency/Severity	Special Warnings/Precautions
Non-narcotic drugs	Paracetamol <sup>36</sup>	Gastrointestinal reactions Non-narcotic drugs Hepatotoxicity Pruritus, erythematous skin rashes Blood dyscrasias	Common; mild Uncommon; severe Rare; mild Uncommon; severe Rare; mild	In cases of compromised liver function, overdoses, individuals with high alcohol intake or patients taking enzyme-inducing drugs (e.g., anti-epileptics and rifampicin), hepatotoxicity is a major concern.
	NSAIDs Ibuprofen	Gastrointestinal ulceration and bleeding Bronchospasm Renal dysfunction/ cardiovascular events (elevated blood pressure) Nervous reactions (dizziness)	Common; severe  Rare; severe Rare  Common; severe	Caution is required in patients with a history of hypertension and/or heart failure as fluid retention and oedema have been reported. Risk of gastrointestinal bleeding is higher with increasing doses. NSAIDs should be used at the lowest effective dose for the shortest duration.
Narcotic drugs/ opioids	Opioids	Dose-dependent respiratory depression sedation Gastrointestinal upset, including constipation and emesis Mood alterations (euphoria or dysphoria) Opioid abuse and addiction	Common; severe  Common; mild to severe  Common  Common	

tailored towards each patient to prevent potential adverse reactions. Table III details the adverse reactions relating to local anaesthetics and their vasoconstrictors.

## SEDATIVES AND GENERAL ANAESTHETIC AGENTS

Sedatives and general anaesthetics are classes of drugs which induce sedation, altered consciousness, and reduces anxiety during major dental procedures. They are broadly classified into three categories: oral sedation (diazepam), inhalation sedation (nitrous oxide) and intravenous sedation (propofol, midazolam). Commonly reported ADRs to this class include nausea, vomiting, headache, slurred speech, dry mouth, dizziness, chills, and lockjaw.<sup>46</sup> Respiratory depression is a major ADR following the administration of sedatives and general anaesthetic agents<sup>47</sup>(Table IV). Most adverse reactions to these drugs are dependent on the level of sedation and the number of agents being administered, with more severe effects occurring at high doses and combination therapy.

## SYSTEMIC AND ORAL CORTICOSTEROIDS

Both oral and topical corticosteroids have a wide range of uses in dentistry. For example, oral cortisones are used to reduce pulpal inflammation or for post operative inflammation while topical steroids are used for the treatment of lichen planus. However, although useful, corticosteroids pose risks which are dependent on the route of delivery (topical, oral, inhaled, intranasal or intravenous), the length of time that was taken, the type and strength of the cortisone, dosing schedule and systemic other factors. A low dose cortisone is 10mg or less, while a moderate dose is 15-40mg and high dose is over 40mg. Increases in blood sugar and behavioral changes are potential concerns with short-term use of cortisones, while osteoporosis, oral candidiasis, cataracts, glaucoma, arthritis, hypertension, myopathy, Cushing's disease and adrenal suppression can occur after long-term use.<sup>50</sup>

## REPORTING ADRS

As per regulation 40 of the Medicines and Related Substances Act, 1965 (Act 101 of 1965) as amended, a healthcare professional, veterinarian or any other person should inform the South African Health Products Regulatory Authority (SAHPRA), of any suspected ADRs; or any new or existing safety, quality, or effectiveness concerns, occurring because of the use of any medicine or scheduled substance (Medicines Act). Although clinical trials identify ADRs, they

are limited due to the number of participants in the trial; the timeframe of the trial as drugs may act differently over a longer period; and also, may exclude high risk individuals such as the elderly or pregnant women. For these reasons, post marketing surveillance is crucial in identifying ADRs and thus informing better prescribing practices which ensures the safety and efficacy of medicines. A spontaneous report, which is a common method of reporting a suspected ADR, is not generated from a controlled study (active surveillance). Spontaneous reports can generate a signal which is 'reported information on a possible causal relationship between an adverse event and a medicine, the relationship being unknown or incompletely documented previously'. More than one ADR report is needed to generate a signal depending on the seriousness.<sup>51</sup> For this reason, reporting any ADR is important in identifying signals whereby the necessary course of action can be taken.

The South African adverse drug reaction monitoring system is managed by the regulatory pharmacovigilance unit at SAHPRA. Healthcare professionals including dentists are required to report all suspected adverse reactions to medicines by completing the eReporting link available on the SAHPRA website or completing the Adverse Drug Reaction (ADR)/Product Quality Problem Report form on the SAHPRA website and emailing it to [adr@sahpra.org.za](mailto:adr@sahpra.org.za).<sup>51</sup> Additionally, SAHPRA has launched a MedSafety App, which is a platform whereby both healthcare professionals and the public can report ADRs.

For a report to be considered valid, the following minimum requirements should be included in the report: information about the patient, suspect medicine, suspected reaction, and information about the reporter.

## CONCLUSION

Medicines are essential for improving the quality of life of patients, yet they do come with risks. Dentists should consider their patients' comorbidities and current drug use, to select the appropriate drug and dose, which will limit the risk of ADRs. Although dentists have a fair knowledge on ADRs, it is likely that dentists, just like other healthcare professionals, under report these events. To effectively manage the dental patient, dentists need to understand the risks associated with the medicines they prescribe and the importance of reporting ADRs.

Table III: Local anaesthetics and their vasoconstrictors and their adverse reactions<sup>17</sup>

Category	Examples	Adverse Drug Reactions	Frequency/ Severity	Special Warnings/ Precautions
Local anaesthetics	Lidocaine, Articaine, Prilocaine, Lignocaine and Mepivacaine	Tissue necrosis and direct neurotoxicity (high concentrations such as 4% articaine)	Common	
		Paraesthesia in higher concentrations	Common; severe (disabling/incapacitating)	
		CNS depression: seizures, drowsiness, ultimately cardiovascular collapse at high levels in cerebral circulation <sup>44</sup>	Common; mild to severe	
Vasoconstrictors	Epinephrine	Hypertension, tachycardia, and potential cardiovascular emergency at high doses <sup>45</sup>	Common	Dental clinician must be cautious with regards to how much dose is administered
		Anxiety, restlessness, headache, weakness, respiratory difficulties	Common	

Table IV: Adverse drug reactions associated with sedatives and general anaesthetic agents<sup>48,49</sup>

Adverse drug reaction	Oral sedation		Inhalation sedation	IV sedation
	Benzodiazepines	Opioids	Nitrous oxide	Propofol
Respiratory depression	++	++	++	++
Depress central hypercapnic drive (Depress both tidal volume respiratory rate)		++		++
Depress hypoxic drive (depress tidal volume while increasing respiratory rate)			++	
Reduction in arterial blood pressure	++	++	++	++
Reduction in heart rate (at doses required for general anaesthesia)	++	++	++	++
Anterograde amnesia (at sedative doses)	++			++
Thrombophlebitis/ thrombosis	++			
Falls/ Ataxia/ Confusion	++			

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