

# Analysis of drug interactions in dental prescriptions

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• **Conflicts of interest:** none declared.

## ABSTRACT

**Objective:** to evaluate the potential drug interactions (DI) in prescriptions for patients of a private university's dental clinic. **Material and Methods:** this is an exploratory descriptive study. A total of 204 dental prescriptions were analyzed between April 2015 and October 2016. The databases for the analysis of DI potential were accessed through the programs Medscape, Drugs.com and Micromedex. The DIs were classified by intensity in major, moderate and minor. **Results:** the mean age was  $43 \pm 14$  years old and 61% of the participants were female. Hypertension and Type II diabetes were the most prevalent diseases. 237 non-steroidal anti-inflammatory drugs were prescribed, with nimesulide being the most prevalent in the prescriptions, followed by dipyrone with analgesic and antipyretic effect. Of these, eighty-nine were antimicrobials, mostly amoxicillin. We identified 95 potential drug interactions, 28% being of major intensity and 67% of moderate intensity. Twelve interactions involved non-steroidal anti-inflammatory drugs, mainly ketoprofen, diclofenac and ibuprofen; and nine were related to the antimicrobials amoxicillin, metronidazol and azithromycin. **Conclusion:** The need for a careful analysis of dental prescriptions and a review of the concomitant therapy used by patients, reducing the risk of interactions, and consequently, preventing adverse reactions and preserving the patients' safety, are observed.

**Keywords:** Drug Interactions; Dentistry; Non-steroidal anti-inflammatory drugs; Anti-Infectious.

## Introduction

**D**I occurs as a consequence of polypharmacy which interferes with the pharmacokinetics or pharmacodynamics of drugs administered concurrently, leading to adverse reactions or ineffectiveness of pharmacotherapy. The interactions between drugs involve pharmacodynamic, pharmacokinetic and physicochemical mechanisms.<sup>1</sup>

Pharmacokinetics relate to changes in the processes of absorption, distribution, biotransformation or excretion in one of the drugs administered concurrently. Pharmacodynamic interactions, on the other hand, result in the increase of similar pharmacological effects (through the processes of summation, addition or synergy), or opposite effects (antagonism).<sup>2</sup>

In addition to factors related to the drug, drug interactions are also subject to factors related to the patients, such as: age, genetic conditions, polymorphisms in drug metabolism genes, morbidities, nutritional status and adherence to therapy. Therefore, the interactions are considered potential and theoretical depending on how they are described in the literature, and may occur or not. The DI's diagnosis in the pharmacotherapeutic evaluations of patients must be grounded on evidence-based knowledge, clinical monitoring and laboratory drug administering, the latter being an invasive and costly practice.<sup>3</sup>

Dental procedures include pharmacological prescription, in general, for analgesia, and for prophylaxis of oral infec-

tions in cases of more invasive dental procedures. Non-steroidal anti-inflammatory drugs (NSAIDs) and antimicrobial drugs are among the most prescribed, increasing the risk of DI involving these classes of drugs and other drugs used concomitantly by patients.<sup>4-6</sup>

NSAIDs are recommended to be used for a maximum period of 48 hours in most protocols of therapeutic modulation of inflammation related to lesions in the oral cavity.<sup>6-7</sup> However, a worrying aspect is the use of NSAIDs by individuals with chronic cardiovascular diseases, type II Diabetes, coronary artery disease and arrhythmia, as the use of polypharmacy by these patients may increase the risk of these drugs interacting with drugs prescribed for dental purposes<sup>8</sup>.

In relation to antimicrobial agents, there are several classes available in the market for dental prophylactic and therapeutic use, and the professional is responsible for the patient's correct clinical and microbiological evaluation to reduce the risk of DI. The most common indications are for the treatment of odontogenic or non-odontogenic infections, either disseminated or focal, or for surgical prophylaxis.<sup>6,7,9</sup>

Given the above, the objective of this study was to evaluate the potential drug interactions (DI) in prescriptions for patients of a private university's dental clinic.

## Material and Methods

The research was approved by the Research Ethics Com-

mittee of the Private University Center under opinion No. 459,326.

This is an exploratory descriptive study. A total of 204 dental prescriptions pertaining to patients of a Private University Center's dental clinic located in the municipality of São José do Rio Preto, in the period from April 2015 to October 2016, were analyzed. Patients with 18 years of age or older, regardless of gender, were included in the study. The medical records in which there was no prescription of drugs intended for dental purposes were excluded.

Demographic (age, gender, marital status, educational level and origin), epidemiological (concomitant diseases), and pharmacological (concomitant drugs being used and those prescribed by a dentist) data were collected through the medical records of the participants. The data from the records were transferred to spreadsheets in Microsoft® Excel (2010). The data collection was carried out by three students of the course in Pharmacy under the supervision of two professors.

For evaluation of the DI, the computerized databases Medscape<sup>10</sup>, Drugs.com<sup>11</sup> e Micromedex<sup>12</sup> were used. The Micromedex database is available at CAPES/MEC's Portal of Scientific Journals, however, its access is restricted to related institutions only. The Drugs and Medscape São databases are free to use and available online, becoming important sources of information on public health. Links for access to the databases are available in the references section of this article.

The DIs were classified according to level of intensity in:

- Major – Contraindicated, important or serious (when the interaction represents a risk to life and/or requires an intervention to reduce or prevent serious damage or when the drugs are contraindicated for concomitant use);
- (2) Moderate or significant (DI results in exacerbation of the patient's health problem and/or requires changes in pharmacotherapy);
- (3) Minor or secondary (DI results in limited clinical effects that usually do not require any major change in pharmacotherapy).

A descriptive statistical analysis was developed, the continuous variables with normal distribution having been presented as mean  $\pm$  standard deviation. The categorical variables are presented as numbers and proportions (%). Chi-square test was used for statistical analyses of possible associations between potential DIs and conditions such as type II Diabetes and SAH. The associations between the number of patients and interactions in their prescriptions and the presence and absence of non-infectious morbidity were obtained through the analyses. *P* values lower than

0.05 were considered statistically significant. The BioEstat software version 5.0 was used for these analyses.

## Results

During the period from April 2015 to October 2016, the medical records containing dental prescriptions of 204 patients were analyzed. The median age was  $43 \pm$  (sd 14 years) years old, with a minimum age of 15 years old, and a maximum age of 79 years old. Table 1 represents the demographic and epidemiological profile of the study group.

**Table 1.** Demographic and epidemiological data pertaining to 204 patients of a private university's dental clinic (N = 204)

Variable	N	%
<b>Gender</b>		
Female	124	61
Male	80	39
<b>Marital status</b>		
Single	74	36
Married	85	42
Divorced/Widowed	32	16
No information	13	6
<b>Education level</b>		
Some elementary school	9	4
Elementary school	12	6
Some high school	18	9
High school	1	1
Incomplete higher education	9	4
Higher education degree	2	1
No information	153	75
<b>Origin</b>		
Urban	195	96
Rural	9	4
<b>Clinical condition</b>		
Systemic arterial hypertension	34	17
Type 2 diabetes mellitus	18	9
HIV-positive	3	1.5
No information	45	72.5

In the 204 records analyzed, 597 drugs were found. The mean was  $3 \pm 1$  by prescription with a maximum of seven per patient. Of the total, 109 prescriptions (53%) contained two drugs, 30 (15%), three drugs, among other less frequent amounts.

In total, 237 NSAIDs were prescribed, nimesulide (46%), ibuprofen (9%), and diclofenac (5%) being the most prescribed. Of those with analgesic and antipyretic activity,

metamizole (33%) and paracetamol (5%) were the most prescribed. In relation to antimicrobials, dental prescription resulted in 89 drugs, amoxicillin being the most prescribed (83%). The consumption of NSAIDs and antimicrobials is detailed in Table 2.

**Table 2.** Non-steroidal anti-inflammatory drugs, analgesics/antipyretics and antimicrobials prescribed to 204 patients of a private university's dental clinic

Medicine	N	%
Non-steroidal anti-inflammatory drug		
Analgesics and antipyretics		
Ketoprofen	2	1
Diclofenac	12	5
Dipyron	77	33
Fenoprofen	1	1
Ibuprofen	23	9
Nimesulide	111	46
Paracetamol	11	5
<b>Total</b>	<b>237</b>	<b>100</b>
Antimicrobial		
Amoxicillin	74	83
Amoxicillin + Clavulanate	2	2
Azithromycin	2	2
Cephalexin	1	1
Clindamycin	4	5
Metronidazole	6	7
<b>Total</b>	<b>89</b>	<b>100</b>

Ninety-five potential DIs were observed in 48 (23%) records with an average  $1 \pm 2$  interactions. There was a minimum of one DI and a maximum of eight per prescription. The use of four drugs ( $n = 12$ ) and three drugs ( $n = 10$ ) were the ones most commonly associated with DI, totaling 22 records.

In relation to intensity, of the 95 potential DIs, 28% ( $n = 26$ ) were of major, 67% ( $n = 64$ ) of moderate, and 5% ( $n = 5$ ) of minor intensity. The potential drug interactions of major intensity are presented in Table 3.

**Table 3.** Drug interactions of major intensity ( $N = 26$ ) in patients undergoing dental treatment

Drug interaction	Clinical implication	Database	N
Amitriptyline + Fluoxetine	Risk of Serotonin Syndrome and lengthening of the QT interval	1,2,3	1
Amitriptyline + metronidazole	Risk of lengthening of the QT interval and arrhythmia	1,3	1
Amoxicillin + ethinylestradiol	Reduction in contraceptive effect	1,3	2
Atenolol + Doxazosin	Risk of postural hypotension	1,2,3	1
Carbamazepine + Ritonavir	Increase in the serum levels of carbamazepine	1,2,3	1
Lithium carbonate + citalopram	Risk of Serotonin Syndrome	1,2,3	1
Lithium carbonate + clomipramine	Risk of Serotonin Syndrome	1,2	1
Lithium carbonate + hydrochlorothiazide	Risk of lithium toxicity	1,2,3	1
Lithium carbonate + losartan	Risk of lithium toxicity	1,2,3	1
Citalopram + Clomipramine	Lengthening of the QT interval	1,2,3	1
Citalopram + hydrochlorothiazide	Risk of hyponatremia	1,2	1
Clomipramine + clonazepam	Increased sedation	1,2	2
Diclofenac + Fluoxetine	Risk of bleeding	1,2,3	1
Famotidine + Metronidazole	Risk of lengthening of the QT interval and arrhythmia	3	1
Fluoxetine + Haloperidol	Increase in the serum levels of haloperidol	1,2,3	2
Fluoxetine + Ibuprofen	Risk of bleeding	1,2,3	1
Fluoxetine + Nortriptyline	Increased risk of toxicity by TCA, lengthening of the QT interval and Serotonin Syndrome	1,2,3	3
Fluoxetine + Propranolol	Increased toxicity risk of propranolol	1,2,3	1
Fluoxetine + Quetiapine	Lengthening of the QT interval	1,2,3	1
Fluoxetine + Sertraline	Lengthening of the QT interval and Serotonin syndrome	1,2,3	1
Levothyroxine + Nortriptyline	Risk of toxicity	3	1

Databases: (1) Medscape, (2) Drugs.com, (3) Micromedex

Potential DIs were described in 28 (60%) of the 47 patients with SAH ( $p = 0.1169$ ), and in 56 of the 153 patients who were not hypertensive. However, there was no significant association with arterial hypertension. There was no significant association between diabetes and drug interactions.

Twelve patients had potential DIs involving NSAIDs. Ketoprofen, diclofenac and ibuprofen were the most involved in those of major or moderate intensity (Table 4). As for amoxicillin, metronidazol, antimicrobials and azithromycin, they were involved in the potential DI of nine patients of the study, according to the data in Table 5.

**Table 4.** Drug interactions involving non-steroidal anti-inflammatory drugs and other classes of medications in twelve patients undergoing dental treatment (N = 12)

Drug interaction	Clinical implication	Intensity	Database	N
Ketoprofen + enalapril	Reduction in the effect of enalapril	Moderate	1,2,3	1
Diclofenac + fluoxetine	Risk of bleeding	Major	1,2,3	1
Diclofenac + ibuprofen	Risk of hyperkalemia and gastrointestinal bleeding	Moderate	1	1
Diclofenac + losartan	Reduction of the antihypertensive effect and risk of renal failure	Moderate	1,2,3	1
Diclofenac + atenolol	Reduction of the antihypertensive effect	Moderate	1,2,3	2
Ibuprofen + phenytoin	Risk of phenytoin toxicity	Moderate	2,3	1
Ibuprofen + phenobarbital	Reduction of ibuprofen's serum level	Minor	1	1
Ibuprofen + Fluoxetine	Risk of bleeding	Major	1,2,3	1
Ibuprofen + Losartan	Reduction of the antihypertensive effect and risk of renal failure	Moderate	1,2,3	2
Ibuprofen + sertraline	Risk of bleeding	Moderate	1,2	1

Databases: (1) Medscape, (2) Drugs.com, (3) Micromedex

**Table 5.** Drug interactions involving antimicrobials in nine patients undergoing dental treatment (N = 9)

Drug interaction	Implication Clinic	Intensity	Database	N
Amoxicillin + azithromycin	Reduction of the effect of amoxicillin	Minor	1,2	3
Amoxicillin + ethinylestradiol	Reduction in contraceptive effect	Moderate	1,2	2
Amoxicillin + levonorgestrel	Reduction in contraceptive effect	Minor	3	2
Metronidazole + amitriptyline	Risk of lengthening of the QT interval and arrhythmia	Major	1,3	1
Metronidazole + famotidine	Risk of lengthening of the QT interval and arrhythmia	Major	3	1

Databases: (1) Medscape, (2) Drugs.com, (3) Micromedex

### Discussion

Most of the evaluated sample was made up of female patients. Other studies involving dental prescriptions also obtained a higher number of female patients, such as those conducted in Porto Alegre – RS<sup>4</sup> and São Paulo – SP.<sup>13</sup> The researchers of the study conducted in Porto Alegre – RS had an average age of  $35 \pm 11$  years old and a higher frequency of patients with complete high school.<sup>4</sup> It is worth noting that in this study, most of the records did not include information on the patients' education level.

SAH was the most common chronic illness described in the medical records. Anesthesia can cause changes in blood pressure. The dental surgeon has an important role in detecting and referring hypertensive patients. In addition, checking blood pressure is recommended during the dental treatment for monitoring hypertensive patients.<sup>14</sup>

Another chronic disease reported in the records analyzed in this study was type II Diabetes mellitus. Having knowledge on the disease, its oral manifestations, as well as its interference in the glycemic control of drugs used to prevent or combat oral infections, is crucial. Knowing the possible interactions between hypoglycemic drugs and the drugs used in the treatment of periodontal disease is also important.<sup>15,16</sup>

In this study, three patients were HIV-1-positive. Non-discriminatory prophylactic measures should be used for the disinfection of the office and equipment, in addition to the sterilization of instruments and use of individual protection equipment, between each of the patients, in order to prevent the transmission of HIV and other infectious diseases. Furthermore, the possible interactions between the



use of dental prescription drugs and antiretrovirals must be evaluated.<sup>17</sup> Dentists must be cautious when prescribing antimicrobial agents that alter enzymes of the hepatic P450 microsomal system, as changes in the plasma concentration of anti-retroviral drugs have been mentioned.

Nimesulide and ibuprofen (9%) were the most prescribed NSAIDs in this study, and among the drugs chosen for hyperthermia, dipyron and paracetamol were the most prescribed. In Porto Alegre – RS, paracetamol, ibuprofen and diclofenac were the most prescribed.<sup>4</sup> In the studied university clinic, the dental prescription of paracetamol and dipyron is generally accompanied by nimesulide. The prescription of nimesulide follows a three-day 12h dosing regimen, and paracetamol and dipyron are prescribed with the indication of use in case of pain only, in an interleaved manner, due to its weak effect as an anti-inflammatory. The latter two medicines need to be interleaved to prevent the presence of potential adverse reactions such as, respectively, hepatotoxicity and agranulocytosis. The differences between the different types of NSAIDs on the market relate to antipyretic, analgesic, anti-inflammatory potential, and their adverse reactions, mostly stomach discomfort, changes in the systemic blood pressure and effects on pregnant women, including the decrease of PGF2 alpha and possible absence of uterine contraction.<sup>18</sup>

The main antimicrobial agents of systemic use in dental practice are amoxicillin, azithromycin, metronidazole, clindamycin, tetracycline, and ciprofloxacin.<sup>7</sup> These drugs are available in their active form, in the gingival fluid and salivary flow, which enables them to carry out their actions in the gingival sulcus and subgingival plaque.<sup>9</sup> In this study, the antimicrobial agent that was most prescribed was amoxicillin. A study conducted in Belo Horizonte – MG, where the prescription of amoxicillin with or without clavulanate, followed by macrolides, was described, corroborates this.<sup>5</sup> The predominance of gram-positive and anaerobic bacteria can partly justify the prescription pattern observed. However, the absence of drugs for periodontitis caused by gram-negative bacteria is a fact that requires further studies, to answer if they did not occur in the patients evaluated or if the appropriate medication was not prescribed.

Polypharmacy is defined as the concomitant use of five or more medications daily.<sup>19</sup> However, in this study, this rate was not achieved, the average concomitant use of three medicines having been obtained. Despite the non-occurrence of polypharmacy, DIs were identified in 23% of the medical records analyzed.

A common interaction identified took place between antimicrobials and oral contraceptives. In this case, caution is recommended in the association of these pharmacological classes.<sup>9</sup> Another contraceptive method should be used, such as sexual abstinence or condoms, during treatment

and for one week after the concomitant use. There are also guidelines on the possible common adverse reactions to antimicrobial usage, such as diarrhea which can also reduce the absorption of oral contraceptives due to changes in the microbiota that participates in their disintegration.<sup>20</sup> The activity of induction of hepatic microsomal enzymes by antimicrobials, resulting in increased metabolism and sub-dosage of oral contraceptives, also corroborates this. Still in relation to antimicrobials, the association between metronidazole and drugs that lengthen the QT interval such as amitriptyline, famotidine and quinolones, should be monitored to avoid possible arrhythmia and torsades pointes.<sup>12</sup>

Another pharmacological class involved in the interactions identified in this study were anticonvulsants. Some details need to be considered in the dental treatment of patients that use these drugs, such as the safety of the use of local anesthetics and the implications of DIs, especially those considered to be of major intensity and that may prevent the antiepileptic drug's absorption or increase its metabolism, through the concomitant use with erythromycin, penicillins, metronidazole, salicylic acid and ibuprofen.<sup>21,22</sup>

Drug interactions involving NSAIDs and antihypertensive drugs are common. NSAIDs may cancel the antihypertensive effects of thiazide or loop diuretics, of the antagonists of alpha and beta-adrenergic receptors, as well as of agents that inhibit the renin-angiotensin-aldosterone system, resulting in decompensation of the patient's blood pressure.<sup>8</sup> Avoiding the concomitant use between antihypertensive drugs and NSAIDs is recommended, especially in patients with heart and renal failure. If their use is indeed necessary, the patient's blood pressure and urine output should be monitored.<sup>12</sup>

For the identification and proper management of DIs, interdisciplinary interaction is essential, especially in establishments associated with education.<sup>23</sup> The professional's active role when detecting an interaction is to preserve the patient's safety and evaluate the risks and benefits of pharmacotherapy. The actions to be taken depend on the intensity of the interaction's effects, including changes in dosage only, or, in more severe cases, discontinuation of therapy, referral to the appropriate health service and reporting of the reaction to health surveillance.<sup>23,24</sup>

This study has as a limiting factor the fact that there were no interviews with patients for the collection of data on the evaluation of possible symptoms that could predict the actual occurrence of DIs. Also, the unavailability of information in most of the records may be subject to adjustments through the collecting of the patients' full clinical history, including at least the complete demographic data, the history of prior and current diseases, and all drugs being used concurrently, as well as their respective dosage.

## Conclusion

The data obtained in this study allow us to identify the drug prescription profile in a sample of users of a private university's dental service with varied ages, predominance of the female gender and urban origin, and having SAH and type II Diabetes as main concomitant diseases.

In relation to the prescribed drugs, those more often prescribed for dental purposes were nimesulide and ibuprofen, among the non-steroidal anti-inflammatory drugs. Amoxicillin was the most prescribed antimicrobial.

The interactions verified relate to the NSAIDs or antimicrobials prescribed by dentists and drugs of continuous use,

such as antidepressants, antihypertensive drugs, contraceptives and anticonvulsants. The need for a careful analysis of dental prescriptions and a review of the concomitant therapy used by patients, reducing the risk of interactions, and consequently, preventing adverse reactions and preserving the patients' safety and the quality of pharmacotherapy, are observed.

However, this study provides important information on the pharmacology and pharmacovigilance of DIs in Dentistry, seeing as this topic is rarely discussed in detail during graduation.

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## Mini Curriculum and Author's Contribution

- Adriana Antônia da Cruz Furini – PharmD and PhD. Contribution: project's supervision, data analysis and writing of the manuscript.
- Juliana Mendes de Almeida Malagoli – Pharmd. Contribution: data collection and writing of the manuscript.
- Nayane Justi Dias – PharmD. Contribution: data collection and writing of the manuscript.
- Bruna Miranda Lima – PharmD. Contribution: data collection and writing of the manuscript.
- Manuela Manzano Bonjardin – PharmD. Contribution: data collection and writing of the manuscript.
- Ponatyellen Souza Machado – PharmD. Contribution: data collection and writing of the manuscript.
- Tiago Aparecido Maschio de Lima – PharmD and MSc. Contribution: writing of the manuscript and reviewing of references.

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