

Drug Hypersensitivity Associated with Dental Treatments

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ABSTRACT

Objective: To characterize drug hypersensitivity associated with dental treatments. **Material and Methods:** Data from 5,302 dental patients extracted from the Faculty of Dental Medicine were used to investigate drug use history, drug hypersensitivity, and associations with oral health outcomes. The chi-square test was used, and values of $p \leq 0.05$ were considered statistically significant. **Results:** The frequency of patients' self-reported drug hypersensitivity was 26.42% ($n = 1,401$). The highest frequencies were for opioid/narcotic analgesics (20.84%, $n = 292$), antibiotics (18.13%, $n = 961$), and non-steroidal anti-inflammatory drugs (10.46%, $n = 141$). Most of the patients (68.65%, $n = 3,640$) reported using medications, mostly for cardiovascular disease (43.1%, $n = 1,569$), for psychiatric/neurological disorders (39.75%, $n = 1,447$), drugs that affect the endocrine system (32.55%, $n = 1,185$), and drugs for pain (24.92%, $n = 907$). Higher drug hypersensitivity frequencies were associated with older White female subjects ($p < 0.0001$). Associations were also identified between drug hypersensitivity and history of the following dental procedures: tooth extractions ($p = 0.003$), root canal treatment ($p = 0.0004$), prosthodontic treatments ($p < 0.0001$), and orthodontic treatments ($p = 0.007$). **Conclusion:** A high frequency of self-reported drug hypersensitivity in dental patients was found, with a higher occurrence in older White women and those with a history of more extensive and invasive dental care.

Keywords: Drug hypersensitivity; Drug-Related Side Effects and Adverse Reactions; Drug Reactions, Adverse; Dental Care.

Introduction

Drug hypersensitivity (DH) is defined as an undesirable effect resulting from drug use that may or may not involve the immune system [1]. Previous studies suggested that these events affect about 5 to 25% of the population and are influenced by factors such as sex, age, ethnicity, and history of drug use [2-4].

Diagnosis of DH, in general, involves laboratory tests, dermatological tests, drug provocation tests, and predictive analysis using pharmaco-genetic biomarkers, which are not as frequently conducted. Major clinical events are characterized by immediate reactions, including airway obstruction, hypotension, diarrhea, rash, pruritus, and commonly followed by small pustules, fever, fatigue, nausea, and abdominal pain [5]. This represents the greatest challenge when initiating drug therapy, which may also worsen the patient's health status who is often already weakened by the health problem motivating the search for care.

Dental treatment often involves the use of drugs to help restore the patient's health, to control trans and postoperative pain, or even to alleviate anxiety associated with treatment. Local anesthetics, analgesics, anti-inflammatory agents, antibiotics, and sedatives are frequently used [6,7]. However, to the best of our knowledge previous studies have never characterized demographic and risk factors related to dental prescription and DH. Thus, there is a need for more studies that elucidate these factors.

Our study characterizes DH occurrences in dental practice with the ultimate goal of contributing to future predictability analyses for the occurrence of new events. Further, we provide dental patient characteristics associated with drug hypersensitivity and we believe that our results will support future studies aiming to implement effective and safer dental treatment plans.

Material and Methods

Data Collection and Ethical Clearance

Medical and dental histories were obtained through the Dental Registry and DNA Repository project of the School of Dental Medicine, University of Pittsburgh, United States. The total cohort consisted of 6,690 subjects. After excluding individuals with incomplete data, 5,302 subjects were included in the analysis. The project was approved by the University of Pittsburgh Institutional Review Board.

Demographic data (age, sex, ethnicity, and education), oral health information history (experiences with dental procedures), drugs used, and self-reported drug hypersensitivity were collected. Figure 1 illustrates the main variables included.

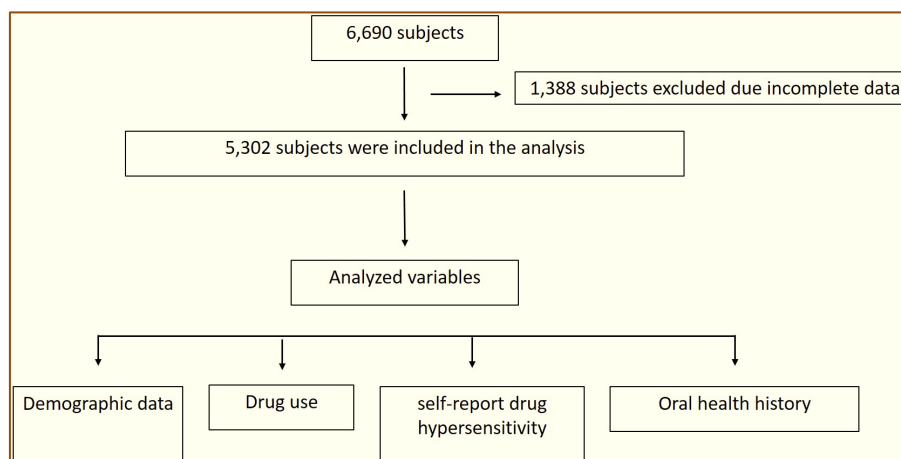


Figure 1. Main variables studied.

To analyze the drugs used, categorization was performed considering the most used drugs. For therapeutic purposes, the following categories were generated: drugs for psychiatric or neurological disorders, drugs for allergies, drugs for pain control, drugs for birth control, drugs for cardiovascular diseases, antimicrobials (antibiotics, antivirals and antifungals), drugs for gastric diseases (acid inhibitors), drugs that affect the endocrine system (steroidal and non-steroidal anti-inflammatory drugs, hormones, and drugs to treat diabetes), vitamins and supplements, as well as others drugs.

For the "other drugs" category, the following groups were considered: muscle relaxants, laxatives, bronchodilators, anticholesterol medications, anticancer, uric acid reducers, anticoagulants, antispasmodics, antiemetics, drugs for intestinal disorders, glaucoma, smoking cessation, nausea, vomiting, sexual dysfunction, pancreas disease, anemia, liver disease, bone disorders, and urinary disorders.

The self-reported drug hypersensitivity analysis considered the following categories: antibiotics (in general), penicillin, cephalosporin, sulfa drugs, macrolides, others antibiotics, NSAIDs (non-steroidal anti-inflammatory drugs), opioid/narcotic analgesics, local anesthetics, and others drugs (citalopram, promethazine, benzoyl, ketamine, metoclopramide, rufinamide, ranitidine, phenytoin, acetaminophen, lithium, diphenhydramine, lamotrigine, fenofibrate, heparin, haloperidol, sertraline, gabapentin, diltiazem, insulin, metformin, meperidine, terfenadine, atorvastatin, pseudoephedrine, enoxaparin, metoprolol, acetazolamide, loratadine, lisinopril, enalapril, quinidine, primidone, nitrofurantoin, linagliptin, and hydroxyzine.

Data Analysis

The data collected were analyzed using Jamovi software version 1.8 (<http://www.jamovi.org>). To verify the association between self-reported drug hypersensitivity and experiences with dental procedures, the chi-square test was used. Values of $p \leq 0.005$ were considered statistically significant.

Results

Our findings revealed that 26.42% (n=1,401) of the individuals analyzed reported a history of drug hypersensitivity (*versus* 73.58%; n= 3,901, who reported no hypersensitivity). Regarding antibiotics in general, it was found that 18.13% (n=913) reported hypersensitivity. In relation to the type of drug, the most frequent were opioid/narcotic analgesics (20.84%, n=292), antibiotics (18.13%, n=961), especially penicillin (11.81%, n=626), and non-steroidal anti-inflammatory drugs (10.46%, n=141). Table 1 summarizes the results for self-reported drug hypersensitivity.

Table 1. Drug hypersensitivity among dental patients.

Drugs	N Total		N Sample	
	N	%	N	%
Penicillin				
No	4676	88.19	775	55.32
Yes	626	11.81	626	44.68
Cephalosporin				
No	5251	99.04	1350	96.36
Yes	51	0.96	51	3.64
Sulfa drugs				
No	5018	94.64	1117	79.73
Yes	284	5.36	284	20.27
Macrolides				
No	5219	98.43	1318	94.08
Yes	83	1.57	83	5.92

Others Antibiotics				
No	5174	97.59	1273	90.86
Yes	128	2.41	128	9.14
NSAIDs				
No	5161	97.34	1260	89.94
Yes	141	2.66	141	10.06
Opioid/Narcotic Analgesic				
No	5010	94.49	1109	79.16
Yes	292	5.51	292	20.84
Others Drugs				
No	5060	95.44	1159	82.73
Yes	242	4.56	242	17.27
Local Anesthetic/Sulfites				
No	5276	99.02	1349	96.29
Yes	52	0.98	52	3.71

N Total: Number of individuals in the total sample; N Sample: Number of individuals in the sample that self-reported drug hypersensitivity.

Most of the individuals included in the survey were chronic users of some type of drug (68.65%, n=3,640), with higher frequencies for drugs treating cardiovascular disease (43.10%, n=1,569), psychiatric/neurological disorders (39.75%, n=1,447), drugs that affect the endocrine system (32.55%, n=1,185), and drugs for pain (24.92%, n=907) (Table 2).

Table 2. Self-report frequency of drug use among dental patients.

Drugs	N Total		N Sample	
	N	%	N	%
Drugs for Psychiatric/Neurological Disorders				
No	3855	72.71	2193	60.25
Yes	1447	27.29	1447	39.75
Drugs for Allergy				
No	4990	94.12	3328	91.43
Yes	312	5.88	312	8.57
Drugs for Pain				
No	4395	82.89	2733	75.08
Yes	907	17.11	907	24.92
Drugs for Birth Control				
No	4968	93.70	3306	90.82
Yes	334	6.30	334	9.18
Drugs for Cardiovascular Diseases				
No	3733	70.41	2071	56.90
Yes	1569	29.59	1569	43.10
Antibiotics				
No	4905	92.51	3243	89.09
Yes	397	7.49	397	10.91
Gastric Diseases (acid inhibitors)				
No	4692	88.49	3030	83.24
Yes	610	11.51	610	16.76
Drugs that Affect the Endocrine System				
No	4117	77.65	2455	67.45
Yes	1185	22.35	1185	32.55
Vitamins and Supplements				
No	4344	81.93	2682	73.68
Yes	958	18.07	958	26.32
Others Drugs				
No	3842	72.46	2180	59.89
Yes	1460	27.54	1460	40.11

N Total: Number of individuals in the total sample; N Sample: Number of individuals who self-reported drug use in the sample.

Our data suggested that White women aged 60 years and over were associated with self-reported drug hypersensitivity ($p < 0.0001$). In addition, a higher self-reported drug hypersensitivity frequency was observed for individuals with a history of dental treatment in the areas of oral surgery, root canal treatment, prosthodontics, and orthodontics) (Table 3).

Table 3. Association between self-reported drug hypersensitivity and demographic data/oral health history.

Variables	Self-Reported Drug Hypersensitivity		Total	p-value*
	Yes N (%)	No N (%)		
Sex				
Male	480 (18.95)	2053 (81.05)	2,533	<0.0001
Female	921 (33.26)	1848 (66.74)	2,769	
Ethnicity				
White	1,095 (28.39)	2,762 (71.61)	3,857	<0.0001
Black	251 (22.43)	868 (77.57)	1,119	
Others	55 (16.87)	271 (83.13)	326	
Age				
18 to 29 year-old	316 (18.85)	1,360 (81.15)	1,676	<0.0001
30 to 59 year-old	677 (29.11)	1,649 (70.89)	2,326	
60 year or more	408 (31.38)	892 (68.62)	1,300	
Education Level				
Middle/High Education	779 (26.60)	2,150 (73.40)	2,929	0.83
Higher	597 (26.31)	1,672 (73.69)	2,269	
Other	25 (24.04)	79 (75.96)	104	
Dental Restorations				
Yes	1,116 (26.90)	3,033 (71.10)	4,149	0.14
No	285 (24.72)	868 (75.28)	1,153	
Oral Infections				
Yes	149 (28.38)	376 (71.62)	525	0.28
No	1,252 (26.21)	3,525 (73.79)	4,777	
Oral Surgery (most are tooth extractions)				
Yes	778 (28.17)	1,984 (71.83)	2,762	0.003
No	623 (24.53)	1,917 (75.47)	2,540	
Root Canal Treatment				
Yes	385 (30.20)	890 (69.80)	1,275	0.0004
No	1,016 (25.23)	3,011 (74.77)	4,027	
Periodontal Treatment				
Yes	650 (26.17)	1,834 (73.83)	2,484	0.69
No	751 (26.65)	2,067 (73.35)	2,818	
Prosthodontic Treatment				
Yes	813 (29.22)	1,969 (70.78)	2,782	<0.0001
No	588 (23.33)	1,932 (76.67)	2,520	
Orthodontic Treatment				
Yes	84 (20.79)	320 (79.21)	404	0.007
No	1,317 (26.89)	3,581 (73.11)	4898	

*Chi-square test.

Discussion

This study evaluated the self-reported frequency of drug hypersensitivity in dental patients and, therefore, embodies the idea that such events, whether involving an immune response or not, can be characterized as adverse drug events. Data used here refers to the use of drugs prescribed by the dentist or not and involves all classes of available drugs. This may help to explain the high self-reported drug hypersensitivity frequency observed. Similar results were obtained in a prior study performed using medical only electronic health records

of 411,543 patients in San Diego County, US [8]. In general, previous studies assessed the occurrence of DH for specific classes of drugs or adverse effects, often with laboratory confirmation [9,10].

High drug hypersensitivity frequencies were observed for antibiotics, especially beta-lactams and sulfa drugs, medications frequently prescribed by dentists, as most oral diseases are of infectious origin. Antibiotics are the most common cause of DH, which can include anaphylaxis, angioedema, orofacial angioedema, and adverse skin reactions such as flushing, itching, and hives [11,12]. The use of sulfonamide antibiotics is also responsible for a high frequency of self-reported DH [13], characterized by cutaneous reactions [14].

Inflammatory reactions during dental treatment are often managed with the use of pharmacological agents. Our results indicated that non-steroidal anti-inflammatory drugs (NSAIDs) are the therapeutic class with the second highest frequency of self-reported drug hypersensitivity. This result is similar to a previous study, with the main manifestations occurring in the respiratory tract, the skin (urticaria), or as a generalized effect (anaphylaxis) [15].

The self-reported frequency of drug hypersensitivity can be explained in part, by higher exposure than expected of the individuals included in the sample to drugs in general. In this study, we observed a high frequency of individuals using drugs for cardiovascular diseases, drugs that affect the endocrine system, drugs for psychiatric/neurological disorders, and for pain control. In general, these people use two or more drugs continuously. The American Heart Association, in conjunction with the National Institutes of Health, indicated that to avoid heart disease, blood pressure, obesity, and high blood cholesterol, lipids must be controlled [16]. Psychiatric disorders and abuse of opioid analgesics occur frequently in the US adult population, which also may explain the data observed in our study [17,18].

Our study indicated a higher frequency of self-reported drug hypersensitivity in White women aged 60 years and older. Similar data have been reported in previous studies [13,19]. To avoid undesirable effects from the use of medications, the identification of high-risk individuals is an important strategy since complications during dental treatment may even result in hospitalizations.

The higher frequency of drug hypersensitivity in women has been reported in other studies [20-22]. Although the role of sex as a factor in provoking drug hypersensitivity is not well understood, pharmacokinetic alterations might predict its higher occurrence in women, who generally present lower body weights and higher fat percentages but are prescribed the same dosages as the ones prescribed to men. Most of the research on this subject was conducted in male subjects, and the aforementioned factors, such as body weight directly affect drug absorption and distribution, which highlights the need for precision medicine efforts in the development of more inclusive clinical pharmacological studies [23].

Older adults tend to be more prone to drug hypersensitivity as well [24]. In addition to using drugs more often, older adults may present physiological changes involving reduced liver and kidney capacity, respectively, for metabolizing and eliminating drugs [25,26]. In addition, decreases in circulating plasma proteins, such as albumin, directly impact drug distribution, promoting exacerbation of pharmacological effects and/or the emergence of adverse effects [16].

In people with a history of dental treatments, our findings revealed a positive association between self-reported drug hypersensitivity and oral surgery (mostly for tooth extractions), root canal treatments, and prosthodontics. Dental procedures performed in these areas are invasive and often require drug therapy. In addition, most of the people treated in prosthodontics clinics are older adults.




Since this is the first report on this subject, our study warrants further investigations to test the hypothesis that the very drugs most often prescribed by dentists promote high frequencies of drug

hypersensitivity. However, our results reinforce the need for careful anamnesis and thorough medication history for prior occurrences of drug hypersensitivity. This would favor implementation of a safer and more effective dental treatment plans.

Conclusion

A high frequency of self-reported drug hypersensitivity in dental patients was found, with a higher occurrence in older White women and those with a history of more extensive and invasive dental care.

Authors' Contributions

RDC		https://orcid.org/0000-0001-7986-7376	Conceptualization, Methodology, Formal Analysis, Investigation, Writing - Original Draft, Writing - Review and Editing and Funding Acquisition.
MB		https://orcid.org/0000-0001-9397-3167	Methodology, Formal Analysis, Investigation, Data Curation and Writing - Review and Editing.
ARV		https://orcid.org/0000-0003-3392-6881	Conceptualization, Methodology, Formal Analysis, Investigation, Writing - Review and Editing, Supervision and Project Administration.
All authors declare that they contributed to critical review of intellectual content and approval of the final version to be published.			

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Conflict of Interest

The authors declare no conflicts of interest.

Data Availability

The data used to support the findings of this study can be made available upon request to the corresponding author.

References

- [1] Dykewicz MS, Lam JK. Drug hypersensitivity reactions. *Med Clin North Am* 2020; 104(1):109-128. <https://doi.org/10.1016/j.mcna.2019.09.003>
- [2] Kvedariene V, Sitkauskiene B, Tamasauskiene L, Rudzeviciene O, Kasiulevicius V, Nekrosyte G, et al. Prevalence of self-reported drug hypersensitivity reactions among Lithuanian children and adults. *Allergol Immunopathol* 2019; 47(1):32-37. <https://doi.org/10.1016/j.aller.2018.05.006>
- [3] Rubio M, Bousquet P-J, Gomes E, Romano A, Demoly P. Results of drug hypersensitivity evaluations in a large group of children and adults. *Clin Exp Allergy* 2012; 42(1):123-130. <https://doi.org/10.1111/j.1365-2222.2011.03887.x>
- [4] Sousa-Pinto B, Fonseca JA, Gomes ER. Frequency of self-reported drug allergy: A systematic review and meta-analysis with meta-regression. *Ann Allergy Asthma Immunol* 2017; 119(4):362-373. <https://doi.org/10.1016/j.anaai.2017.07.009>
- [5] Böhm R, Proksch E, Schwarz T, Cascorbi I. Drug hypersensitivity: Diagnosis, genetics, and prevention. *Dtsch Arztebl Int* 2018; 115(1): 29-30. <https://doi.org/10.3238/arztebl.2018.0501>
- [6] Becker DE Adverse drug reactions in dental practice. *Anesth Prog* 2014; 61 (1):26-34. <https://doi.org/10.2344/0003-3006-61.1.26>
- [7] Stein K, Farmer J, Singhal S, Marra F, Sutherland S, Quiñonez C. The use and misuse of antibiotics in dentistry: A scoping review. *J Am Dent Assoc* 2018; 149(10):869-884. <https://doi.org/10.1016/j.adaj.2018.05.034>
- [8] Macy E, Poon K-YT. Self-reported antibiotic allergy incidence and prevalence: Age and sex effects. *Am J Med* 2009; 122(8):778-e1-7. <https://doi.org/10.1016/j.amjmed.2009.01.034>
- [9] Duong TA, Valeyrie-Allanore L, Wolkenstein P, Chosidow O. Severe cutaneous adverse reactions to drugs. *Lancet* 2017; 390(10106):1996-2011. [https://doi.org/10.1016/S0140-6736\(16\)30378-6](https://doi.org/10.1016/S0140-6736(16)30378-6)
- [10] Guvenir H, Misirlioglu ED, Capanoglu M, Buyuktiryaki B, Onay ZR, Ginis T, et al. The frequency of nonsteroidal anti-inflammatory drug hypersensitivity in children with asthma. *Int Arch Allergy Immunol* 2018; 176(1):26-32. <https://doi.org/10.1159/000487305>
- [11] Khan DA, Banerji A, Bernstein JA, Bilgicir B, Blumenthal K, Castells M, et al. Cephalosporin allergy: Current understanding and future challenges. *J Allergy Clin Immunol Pract* 2019; 7(7):2105-2114. <https://doi.org/10.1016/j.jaip.2019.06.001>
- [12] Blumenthal KG, Peter JG, Trubiano JA, Phillips EJ. Antibiotic allergy. *Lancet* 2019; 393(10167):183-198. [https://doi.org/10.1016/S0140-6736\(18\)32218-9](https://doi.org/10.1016/S0140-6736(18)32218-9)

- [13] Vardakas KZ, Kalimeris GD, Triarides NA, Falagas ME. An update on adverse drug reactions related to β -Lactam antibiotics. *Expert Opin Drug Saf* 2018; 17(5):499-508. <https://doi.org/10.1080/14740338.2018.1462334>
- [14] Dibbern Jr DA, Montanaro A. Allergies to sulfonamide antibiotics and sulfur-containing drugs. *Allergy Asthma Immunol* 2008; 100(2):91-101. [https://doi.org/10.1016/S1081-1206\(10\)60415-2](https://doi.org/10.1016/S1081-1206(10)60415-2)
- [15] Sánchez-Borges M, Caballero-Fonseca F, Capriles-Hulett A, González-Aveledo L. Hypersensitivity reactions to nonsteroidal anti-inflammatory drugs: An update. *Pharmaceuticals* 2010; 3(1):10-18. <https://doi.org/10.3390/ph3010010>
- [16] Virani SS, Alonso A, Benjamin EJ, Bittencourt MS, Callaway CW, Carson AP, et al. Heart disease and stroke statistics—2020 update: A report from the American Heart Association. *Circulation* 2020; 141(9):e139-596. <https://doi.org/10.1161/CIR.0000000000000757>
- [17] Hasin DS, Sarvet AL, Meyers JL, Saha TD, Ruan WJ, Stohl M, et al. Epidemiology of adult DSM-5 major depressive disorder and its specifiers in the United States. *JAMA Psychiatry* 2018; 75(4):336-346. <https://doi.org/10.1001/jamapsychiatry.2017.4602>
- [18] Vadivelu N, Kai AM, Kodumudi V, Sramcik J, Kaye AD. The opioid crisis: A comprehensive overview. *Curr Pain and Headache Rep* 2018; 22(3):1-6. <https://doi.org/10.1007/s11916-018-0670-z>
- [19] Gomes E, Cardoso MF, Praca F, Gomes L, Mariño E, Demoly P. Self-reported drug allergy in a general adult Portuguese population. *Clin Exp Allergy* 2004; 34(10):1597-1601. <https://doi.org/10.1111/j.1365-2222.2004.02070.x>
- [20] Greil W, Zhang X, Stassen H, Grohmann R, Bridler R, Hasler G, et al. Cutaneous adverse drug reactions to psychotropic drugs and their risk factors – A case-control study. *Eur Neuropsychopharmacol* 2019; 29(1):111-121. <https://doi.org/10.1016/j.euroneuro.2018.10.010>
- [21] Tharpe N. Adverse drug reactions in women's health care. *J Midwifery Women's Health* 2011; 56(3):205-213. <https://doi.org/10.1111/j.1542-2011.2010.00050.x>
- [22] Nakagawa K, Kajiwara A. Female sex as a risk factor for adverse drug reactions. *Nihon Rinsho* 2015; 73(4):581-585.
- [23] Zucker I, Prendergast BJ. Sex differences in pharmacokinetics predict adverse drug reactions in women. *Biol Sex Differ* 2020; 11(1):1-14. <https://doi.org/10.1186/s13293-020-00308-5>
- [24] Oscanoa TJ, Lizaraso F, Carvajal A. Hospital admissions due to adverse drug reactions in the elderly. A meta-analysis. *Eur J Clin Pharmacol* 2017; 73(3):759-770. <https://doi.org/10.1007/s00228-017-2225-3>
- [25] Dong MH, Bettencourt R, Barrett-Connor E, Loomba R. Alanine aminotransferase decreases with age: The Rancho Bernardo Study. *PloS One* 2010; 5(12):e14254. <https://doi.org/10.1371/journal.pone.0014254>
- [26] Waring RH, Harris RM, Mitchell SC. Drug metabolism in the elderly: A multifactorial problem? *Maturitas* 2017; 100:27-32. <https://doi.org/10.1016/j.maturitas.2017.03.004>