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Original Article

Retrospective Investigation of Medication Interactions in Dental Patients

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ABSTRACT

The potential for drug-drug interactions (DDIs) in dental care is a growing concern, especially for patients managing multiple medications or chronic conditions. However, detailed real-world data on the frequency and clinical significance of DDIs in dental practice remain limited. The aim of this study was to quantify the occurrence, seriousness, and clinical importance of DDIs in dental patients, and to examine how age and existing comorbidities influence DDI risk. A retrospective analysis was performed on 105 adult dental patients, examining demographic characteristics, preexisting health conditions, dental treatments, and medication records. DDIs were identified using the DrugBank Drug Interaction Checker, which categorizes interactions as major, moderate, or minor. Among the patients, 45.7% had one or more preexisting medical conditions, with cardiovascular disorders being the most frequent (19.0%). Dental diagnoses most commonly involved apical lesions (47.6%), and extractions were the leading procedure (53.3%), indicating substantial exposure to pharmacologic therapy. Of 1,332 possible drug pairs, 542 interactions were detected: 2.3% classified as major, 25.0% as moderate, 13.4% as minor, and 59.3% showing no interaction. Notable high-risk DDIs included combinations of epinephrine with beta-blockers. Age-stratified analysis revealed that patients aged 31–60 years experienced 61.3% of major DDIs, while those ≥61 years accounted for 38.7%; no major interactions were identified in the 0–30 years group. The elevated DDI incidence in the 31–60 cohort may reflect more accurate reporting of their medications. This study provides valuable real-world insights into DDIs within dental settings, highlighting the importance of thorough medication review, systematic screening for interactions, and targeted strategies based on patient age and comorbidities to optimize safety.

Keywords: Drug-drug interactions, Dental medications, Real-world analysis, Patient safety, Age-related DDI risk

Introduction

The growing variety of pharmaceutical agents has led to an increase in patients taking multiple medications simultaneously, which raises the risk of drug-drug interactions (DDIs). Such interactions have become a notable concern in healthcare, particularly among older adults and those managing several chronic conditions [1]. Although dentists generally prescribe a narrower spectrum of drugs compared to other clinicians [2, 3], DDIs remain relevant, especially for patients receiving treatments for acute or chronic systemic diseases [4]. Interactions between drugs can diminish treatment effectiveness, heighten adverse effects, or complicate procedures, potentially affecting both oral health outcomes and overall patient safety.

Dental practice routinely involves the use of medications for local anesthesia, infection control, pain relief, and sedation. Common local anesthetics include lidocaine, mepivacaine, and articaine, delivered via topical or injectable forms [3, 5, 6]. These are frequently combined with vasoconstrictors, such as epinephrine, to prolong

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anesthetic effects and minimize intraoperative bleeding [5]. Antibiotics, like amoxicillin and clindamycin, may be administered prophylactically in select surgical procedures [7]. Amoxicillin can reduce the likelihood of implant failure [8], whereas clindamycin and metronidazole are effective for periodontal or postoperative infection management but require caution due to allergy risks and side effects [9, 10].

Postoperative pain management typically relies on NSAIDs, with acetaminophen as an alternative for those who cannot tolerate NSAIDs [11, 12]. Both NSAIDs and corticosteroids are used to control surgical inflammation [13, 14]. Severe pain may be addressed with opioids, such as codeine or tramadol, often combined with acetaminophen [11, 15]. Sedation techniques improve patient comfort and cooperation during procedures [16]. Oral benzodiazepines are effective for mild to moderate anxiety [17, 18], while nitrous oxide or intravenous agents like midazolam and propofol are applied for deeper sedation in complex cases [19-21].

To reduce the risks posed by drug-drug interactions (DDIs), dental clinicians must gather comprehensive information on all patient medications, including prescriptions, over-the-counter drugs, and herbal supplements. For patients with complex medical conditions, using DDI screening software and consulting the prescribing physician are strongly recommended. Despite the importance of DDIs in dental care, data on their prevalence and consequences are limited. The lack of standardized guidelines for detecting and managing these interactions may result in inconsistent prescribing practices and increased adverse outcomes. With polypharmacy becoming more common among older adults and patients with multiple chronic diseases, studying DDIs in dentistry is essential to safeguard patient health.

Most research has examined DDIs in broader medical contexts [1, 4, 22] or assessed adverse reactions of medications often used in dental treatment [3]. Some studies investigate interactions between dental drugs and other commonly prescribed medications [23], including herbal or dietary supplements [24]. Certain reports focus on drugs metabolized via cytochrome P450 pathways or specific classes, such as antithrombotics [25], oral anticoagulants [26], disease-modifying antirheumatic drugs [27], or antihypertensives [28]. Recent attention has also turned to potential interactions between remdesivir in COVID-19 patients and dental medications [29].

Few studies have leveraged real-world dental clinic data, which reflects the complexity of daily patient care. This gap limits understanding of DDI impacts, particularly among patients taking multiple drugs or with chronic conditions. For instance, Mohan *et al*. [30] summarized potential DDIs in dentistry but did not quantify real-world prevalence, while Goh *et al*. [31] developed digital decision-support tools without analyzing patient-level clinical outcomes. One retrospective analysis of emergency and dental clinic records reported that over half of patients had systemic diseases, with analgesics being the most common DDI source [32]. In patients aged 60 and older, approximately 10% experienced major DDIs according to drugs.com, though underreporting was not addressed [33]. A pilot study in 100 patients over 65 noted frequent discrepancies in medication records, showing the risks of incomplete histories [34]. However, these studies did not examine the clinical significance or severity of interactions.

To fill these gaps, this study aimed to: (i) quantify the prevalence of DDIs in dental patients with comorbidities; (ii) assess interaction severity for both dental and systemic medications; (iii) evaluate clinical relevance, with a focus on cardiovascular comorbidities; and (iv) provide evidence-based guidance for safer analgesic and anesthetic use in dental practice. We analyzed interactions between dental-specific drugs and other medications using the DrugBank Drug Interaction Checker [35]. This study represents the first investigation in a Romanian dental cohort providing real-world insights into DDI prevalence, severity, and clinical implications in dentistry.

Materials and Methods

Study design and ethical approval

We carried out a retrospective analysis of patient records from a private dental clinic in Timișoara spanning November to December 2024. Ethical clearance was obtained from the Scientific Research Ethics Committee at "Victor Babeș" University of Medicine and Pharmacy Timișoara (approval no. 60/2022).

The study focused on individuals whose medical documentation included at least two medications, allowing assessment of potential drug-drug interactions (DDIs). Eligible participants met the following criteria: (i) provided written informed consent (or parental consent for minors), (ii) were of any age (≥18 years or <18 years with parental approval), (iii) underwent dental procedures, and (iv) had records showing two or more drugs, whether prescribed for treatment, post-procedural management, or ongoing therapy. Patients were excluded if they (i) did not give consent, (ii) were under 18 without parental authorization, (iii) had incomplete medication information, or (iv) did not receive dental interventions during the study timeframe.

A total of 105 sequential patients who satisfied these requirements were recruited to reduce bias in selection. From each patient, data were collected on age, sex, dental diagnoses, procedures, medications related to interventions, and therapies for chronic or acute conditions. Additional information regarding comorbidities and concurrent medications was obtained from self-reported forms completed by patients. Throughout the study, all personal data were de-identified and managed in strict confidentiality to ensure privacy protection.

Assessment of drug interaction severity

Each patient's medications were analyzed for potential interactions using the DrugBank Drug Interaction Checker. This platform was chosen for multiple advantages: (i) it contains an extensive dataset with more than 1.3 million drug pairs, widely referenced in pharmacology research [6]; (ii) it is freely available for academic purposes, unlike subscription-only tools; (iii) the API allows automated analysis, minimizing human errors and enabling efficient processing of large datasets [36]; (iv) its version-controlled database permits tracking changes in interaction knowledge over time [37].

When evaluating drug pairs, interactions were classified into major, moderate, or minor, accompanied by brief explanations and references. If the checker returned "No interactions found", this does not guarantee absence of interaction and should be interpreted cautiously.

Data analysis

Initial summary statistics were applied to outline participant characteristics, medical backgrounds, dental treatments, prescribed drugs, and identified drug-drug interactions, including their severity and spread within the group.

To investigate how age and comorbidities influence interaction prevalence, inferential analyses were performed. The Chi-square test examined differences in major interaction frequencies among age groups (0–30, 31–60, ≥61 years), with significance at $p < 0.05$. The Kruskal-Wallis test compared total interaction counts across these age categories, while the Mann-Whitney U test assessed differences between patients with and without cardiovascular disease, also using $p < 0.05$ as the significance threshold.

This research involved 105 sequential patients managed over a two-month span at one dental clinic. As an exploratory real-world investigation, no prior formal sample size estimation was conducted. A retrospective power analysis was carried out to assess statistical robustness, and the findings guide sample size planning for subsequent studies aiming for 80% power at $\alpha = 0.05$, assuming equal group sizes and effect sizes observed in this dataset.

All analyses were implemented in Python 3.10 using the pandas and SciPy libraries for data management and statistical testing. Cross-checking results with additional interaction databases or literature was not performed, which is noted as a study limitation in Section 4.

Results and Discussion

Cohort demographics and preexisting conditions

The analyzed dataset comprised dental patients ranging from 6 - 78 years old, with a mean age of 43.2 ± 15.9 years. For comparative purposes, patients were stratified into three age groups: young, middle-aged, and older adults. **Table 1** outlines this classification and shows the corresponding distribution of drug-drug interactions (DDIs) across the age spectrum.

Among the participants, 48 individuals (45.7%) reported at least one underlying medical condition, including both chronic and acute illnesses, highlighting the heterogeneity in baseline health. **Table 1** details age categories, sex proportions, and specific disease types observed during dental evaluations, with all figures presented as counts and percentages.

Table 1. Demographics and reported health conditions of dental patients. Row 1: age classification; row 2: gender distribution; row 3: chronic and acute condition types.

Category	Subcategory	Number of Patients (n)	Percentage (%)
Age (years)	0–30	27	25.7
	31–60	59	56.2
	≥61	19	18.1
Sex	Female	65	61.9

	Male	40	30.1
Preexisting Conditions	Cardiovascular disorders	20	19.0
	Respiratory diseases	8	7.6
	Blood-related conditions	7	6.7
	Psychiatric disorders	6	5.7
	Neurological disorders	6	5.7
	Diabetes mellitus	5	4.8
	Gastrointestinal disorders	4	3.8
	Urological disorders	3	2.8
	Dermatological disorders	2	1.9
	ENT disorders	1	0.9
	Systemic infections	1	0.9
	Allergic conditions	1	0.9

Dental diagnoses and treatments

Table 2 provides a summary of dental-related traits within the cohort. The initial pair of columns display the occurrence rates of different dental conditions, including the count of impacted patients and their respective percentages. Columns three and four outline the frequency of dental treatments conducted, offering a view into the extent of care delivered to the patient group.

Table 2. Distribution of dental diagnoses and treatments in the study cohort. Columns 1–2: types of diagnoses with patient counts and percentages; columns 3–4: procedures carried out with the respective patient numbers.

Dental Condition	Patients n (%)	Dental Procedure	Patients n (%)
Apical lesion	50	Tooth extraction	56
Abscess	19	Endodontic therapy	20
Pulpitis	16	Dental implant placement	13
Complete tooth loss (Edentulism)	13	Endodontic retreatment	8
Dental caries	7	Caries restoration	4
—	—	Surgical extraction	2
—	—	Endodontic microsurgery	2

Evaluation of drug-drug interactions

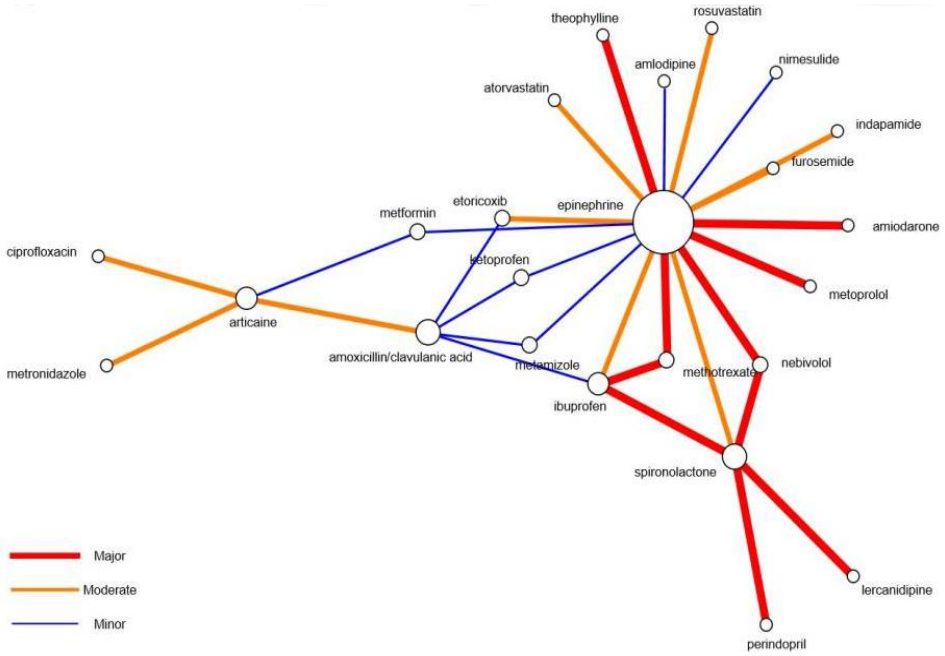
In our dental cohort, 1,332 unique pairs of medications were analyzed using the DrugBank Drug Interaction Checker, uncovering 542 interactions. The remaining combinations were reported as having no known interactions. **Table 3** summarizes the severity distribution: 25.0% of these interactions were classified as moderate, indicating that these drug pairs may necessitate careful monitoring, dose adjustment, or clinical supervision, though stopping either medication is not automatically required. Interactions deemed minor, comprising 13.4% of pairs, are generally of low clinical concern and usually require minimal intervention. Only 2.3% of the identified DDIs were major, representing high-risk combinations that could pose significant health threats, particularly for patients with complex medical backgrounds.

Table 3. Distribution of dental diagnoses and treatments in the study cohort. Columns 1–2: types of diagnoses with patient counts and percentages; columns 3–4: procedures carried out with the respective patient numbers.

Interaction Severity	Count (n)	Percentage (%)
Major	31	2.3
Moderate	333	25.0
Minor	178	13.4

No interactions	790	59.3

Figure 1 illustrates the ten most common DDIs detected among the 1,332 pairs. Interactions were ranked according to severity: major, moderate, and minor. A visual network was constructed using Mathematica 13.0, in which each node corresponds to a specific drug. Node size reflects the number of interactions the drug participates in, while the connecting lines indicate interaction pairs. Line thickness and color convey the severity: thick red for major DDIs, medium orange for moderate, and thin blue for minor interactions. This graphical representation highlights the drugs most frequently involved in DDIs and their relative importance in dental pharmacotherapy. Overall, our findings emphasize both the prevalence and diversity of drug interactions in dentistry, providing actionable insights into the combinations that warrant special clinical attention.



Major	Moderate	Minor
epinephrine⟷nebivolol	amoxicillin/clavulanic acid⟷articaine	amoxicillin/clavulanic acid⟷ibuprofen
epinephrine⟷metoprolol	epinephrine⟷ibuprofen	epinephrine⟷ketoprofen
ibuprofen⟷spironolactone	articaine⟷metronidazole	epinephrine⟷metamizole
nebivolol⟷spironolactone	epinephrine⟷etoricoxib	amoxicillin/clavulanic acid⟷ketoprofen
perindopril⟷spironolactone	epinephrine⟷atorvastatin	amoxicillin/clavulanic acid⟷metamizole
lercanidipine⟷spironolactone	epinephrine⟷spironolactone	amoxicillin/clavulanic acid⟷etoricoxib
epinephrine⟷methotrexate	epinephrine⟷furosemide	articaine⟷metformin
ibuprofen⟷methotrexate	epinephrine⟷indapamide	epinephrine⟷metformin
epinephrine⟷theophylline	epinephrine⟷rosuvastatin	epinephrine⟷amlodipine
epinephrine⟷amiodarone	articaine⟷ciprofloxacin	epinephrine⟷nimesulide

Figure 1. Top ten drug-drug interactions in the dental cohort. The upper diagram depicts a network of the ten most frequent drug pairs at each severity level, visualized in Mathematica 13.0. Each circle represents a medication, labeled with its name, and the circle's size reflects the number of connections (interactions) it has with other drugs. Lines connecting the circles indicate interactions, with line thickness and color corresponding to severity: thick red lines signify major interactions, medium orange lines indicate moderate interactions, and thin blue lines represent minor interactions. The lower diagram lists the ten most common DDIs in the study population, categorized into major, moderate, and minor groups according to their frequency.

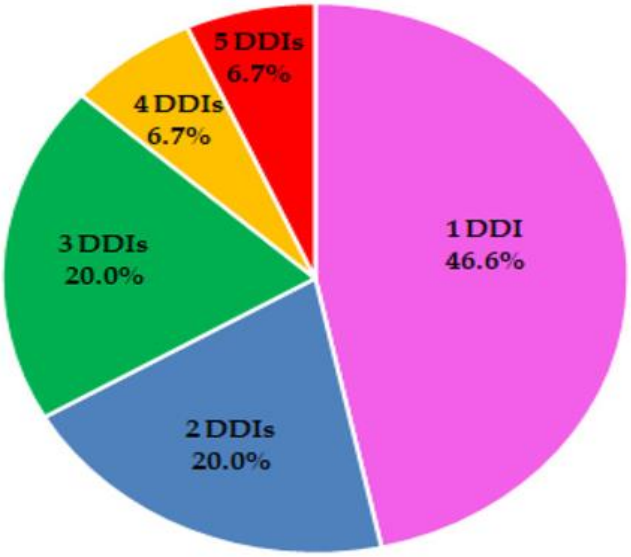


Figure 2. Major DDIs per patient. Among the 31 major interactions identified, 15 patients were affected. Specifically, 46.6% of these patients experienced one major DDI, 20.0% had two, 20.0% had three, 6.7% had four, and another 6.7% exhibited five major interactions. The pie chart illustrates these percentages, highlighting the distribution of multiple major DDIs across patients.

Table 4. Age-based breakdown of DDIs. This table presents the count of individuals in each age group—0–30, 31–60, and ≥61 years—alongside the frequencies and proportions of severe, moderate, and mild drug-drug interactions. It illustrates how the frequency and intensity of DDIs vary based on patient age.

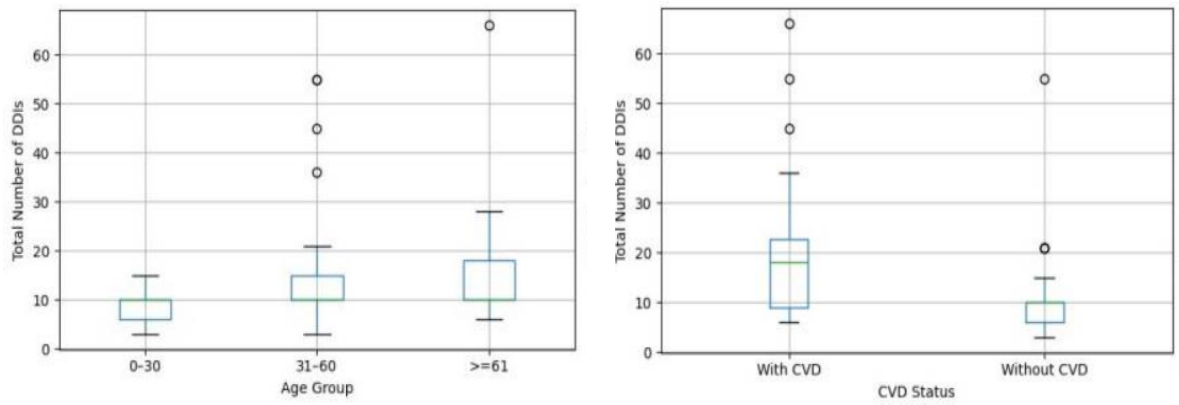
Patient Age (years)	Major DDIs, n (%)	Moderate DDIs, n (%)	Minor DDIs, n (%)
0–30	0	54 (16.2)	31 (17.4)
31–60	19 (61.3)	197 (59.2)	115 (64.6)
≥61	12 (38.7)	82 (24.6)	32 (18.0)

The frequency of drug-drug interactions (DDIs) was further analyzed based on patients' age categories and the existence of heart-related health conditions.

Analysis using the Chi-square test demonstrated notable differences in the occurrence of major DDIs among the age categories: no patients aged 0–30 experienced major DDIs, whereas 15.3% of those aged 31–60 and 31.6% of patients ≥61 years were affected. These results indicate a statistically significant link between age and major DDI prevalence (χ^2 (2, n = 105) = 9.19, p = 0.0101).

To assess total DDI counts, the Kruskal-Wallis test revealed significant variation across age groups (H(2) = 7.81, p = 0.0202). **Figure 3a** presents boxplots for each age group, showing that while the median total DDI count remained at 10 across all categories, older patients displayed a wider interquartile range, reflecting increased variability in interaction frequency.

Evaluation of individuals with and without cardiovascular disease (CVD) using the Mann–Whitney U test revealed a notably higher DDI burden among those with CVD (U = 490, p = 0.0033). **Figure 3b** illustrates this disparity through boxplots: individuals with CVD (n = 20) showed a median total DDI count of 18 (IQR 13.75), while those without CVD (n = 85) had a median of 10 (IQR 4).



a) b)

Figure 3. Spread of all drug-drug interactions (DDIs) within the research cohort.
a) Total DDIs by age group: 0–30 years (n = 27, median 10, IQR 4), 31–60 years (n = 59, median 10, IQR 5), ≥61 years (n = 19, median 10, IQR 8).
b) Overall DDIs based on cardiovascular disease (CVD) presence: with CVD (n = 20, median 18, IQR 13.75), no CVD (n = 85, median 10, IQR 4).

Drug-drug interactions (DDIs) occur when two or more medications are administered together, potentially altering their intended effects. These interactions may either amplify therapeutic outcomes or provoke unexpected adverse events. They can act synergistically, antagonistically, or additively, impacting both treatment efficacy and patient safety. With longer lifespans and an increasing number of patients taking multiple medications, exposure to DDIs has grown considerably [1, 4, 24, 33, 38]. Clinicians must exercise careful judgment to mitigate these risks and ensure safe care [32, 39].

Examination of comorbid conditions in our dental cohort **(Table 1)** shows a wide spectrum of health challenges. Cardiovascular diseases were most common, present in 19.0% of patients, reflecting patterns observed in other dental populations [2, 32, 33]. These patients are particularly vulnerable to DDIs due to frequent use of long-term medications, such as beta-blockers, which may interact with epinephrine-containing anesthetics or NSAIDs [40]. Respiratory (7.6%) and hematologic (6.7%) disorders followed in prevalence, highlighting systemic conditions that may influence responses to standard dental medications like analgesics and antibiotics. Psychiatric and neurological disorders each affected 5.71% of patients, while diabetes mellitus was observed in 4.76%. These findings underscore the complexity of coordinating dental treatment with ongoing pharmacotherapy [41]. Less common conditions included gastrointestinal (3.8%), urologic (2.85%), and dermatologic issues (1.9%). Single instances (0.95%, n = 1 each) of systemic infections, otolaryngological conditions, and allergies show that even rare disorders can complicate medication management. The overall distribution demonstrates the importance of using tools such as DrugBank's DDI checker to guide therapy adjustments in patients with complex health profiles.

Regarding dental diagnoses and procedures **(Table 2)**, apical lesions were most prevalent, affecting 47.6% of patients, in line with international prevalence data [42]. Abscesses (18.1%) and pulpitis (15.2%) were also frequent, indicating dependence on pharmacologic interventions, including anesthetics and pain management, which could interact with patients' systemic medications. Tooth extraction was the procedure performed most often (53.3%), reflecting the burden of severe dental disease requiring surgical or restorative care. Endodontic therapy occurred in 19.1% of cases, while dental implants were placed in 12.4% of patients, demonstrating a subset undergoing more complex procedures. Such interventions often involve prolonged or multiple drug regimens, highlighting the need for careful DDI monitoring to minimize adverse outcomes [43–49].

Clinical management strategies

The DrugBank DDI analysis of our dental patient cohort highlighted several critical interactions between drugs commonly used in dental care and those prescribed for chronic systemic conditions. Notably, epinephrine, a standard component in local anesthetics, frequently interacted with beta-blockers such as nebivolol, metoprolol, atenolol, bisoprolol, and carvedilol. These interactions can substantially elevate cardiovascular risk, especially in patients with preexisting hypertension or other cardiovascular disorders. Therefore, dental practitioners should administer epinephrine with extra caution in patients receiving such medications [5, 22, 23, 40, 50].

It is recommended to apply the lowest effective dose of epinephrine, tailored to each patient's cardiovascular profile, as even minimal quantities can have measurable systemic effects. Research by Guimaraes *et al*. indicates that local epinephrine injections can produce transient but clinically relevant systemic effects, particularly in patients on beta-blockers, due to its vasoconstrictive action [50]. Approximately 20% of intraoral injections may temporarily increase systemic adrenaline, potentially causing complications such as arrhythmias, ischemic episodes, tremors, glycemic fluctuations, or enhancement of other drug interactions. Both direct adrenergic receptor stimulation and indirect electrolyte changes, like potassium imbalance, contribute to these effects [51]. Additionally, the psychological stress of dental injections can mimic these cardiovascular responses, meaning some observed reactions may be anxiety-driven rather than pharmacologically induced [51].

To mitigate these risks, mepivacaine offers a safer alternative for local anesthesia. While it exhibits mild vasoconstriction, it avoids the strong sympathomimetic activity of epinephrine, making it suitable for patients on beta-blockers [52, 53]. For procedures requiring prolonged anesthetic effect, phenylephrine can serve as an alternative vasoconstrictor. As a selective alpha-1 adrenergic agonist, phenylephrine prolongs anesthesia without stimulating beta receptors, reducing the likelihood of tachycardia or other cardiovascular responses. Combined with lidocaine, phenylephrine effectively extends anesthesia duration and is appropriate when epinephrine is contraindicated [54].

Other drugs, including amiodarone and theophylline, metabolized by CYP3A4 and with narrow therapeutic ranges, are sensitive to epinephrine's inhibitory effects on this enzyme. Co-administration may elevate serum drug levels, heightening therapeutic effects and cardiovascular toxicity [6, 55, 56]. Accordingly, preoperative assessment and medication review are essential for patients on CYP3A4-sensitive agents, especially those with cardiovascular diseases. In such cases, using plain mepivacaine without vasoconstrictors provides a safer approach [57].

Ibuprofen, a common analgesic in dental care, can reduce kidney function, leading to higher potassium levels. When administered alongside spironolactone, the risk of hyperkalemia rises, posing serious cardiovascular threats [58, 59]. In such cases, clinicians should either avoid ibuprofen or use it with extreme caution, opting for alternatives like acetaminophen/paracetamol to minimize interaction risks [6].

The combination of ibuprofen and methotrexate may lead to methotrexate buildup and heightened toxicity due to reduced kidney function [6]. Thus, NSAIDs should be steered clear of in patients undergoing methotrexate treatment, while tramadol offers a safer alternative with minimal interaction risks [6]. Pain management must be tailored to each patient, and those on high-dose methotrexate may need to consult a rheumatology or oncology specialist before using any NSAIDs.

Individuals prescribed spironolactone alongside ACE inhibitors (such as perindopril or zofenopril) or angiotensin II receptor antagonists (e.g., candesartan cilexetil) have an increased risk of hyperkalemia. High-dose ibuprofen should be avoided in these situations. If NSAIDs are required, the smallest effective dose for the briefest period is recommended, with close observation of kidney function and blood potassium levels [40].

To manage epinephrine-related drug interactions in dental procedures, a decision-making framework is proposed **(Figure 4)**. This approach evaluates a patient's cardiovascular health and current medications to determine the most appropriate dosing strategy. Risk categories are defined based on known interactions with epinephrine, including beta-blockers, tricyclic antidepressants (TCAs), and MAO inhibitors (MAOIs). Recommendations range from normal dosing to reduced dosing or complete avoidance in high-risk cases. The algorithm emphasizes the importance of enhanced monitoring, specialist consultation when required, and thorough documentation of all decisions made post-treatment.

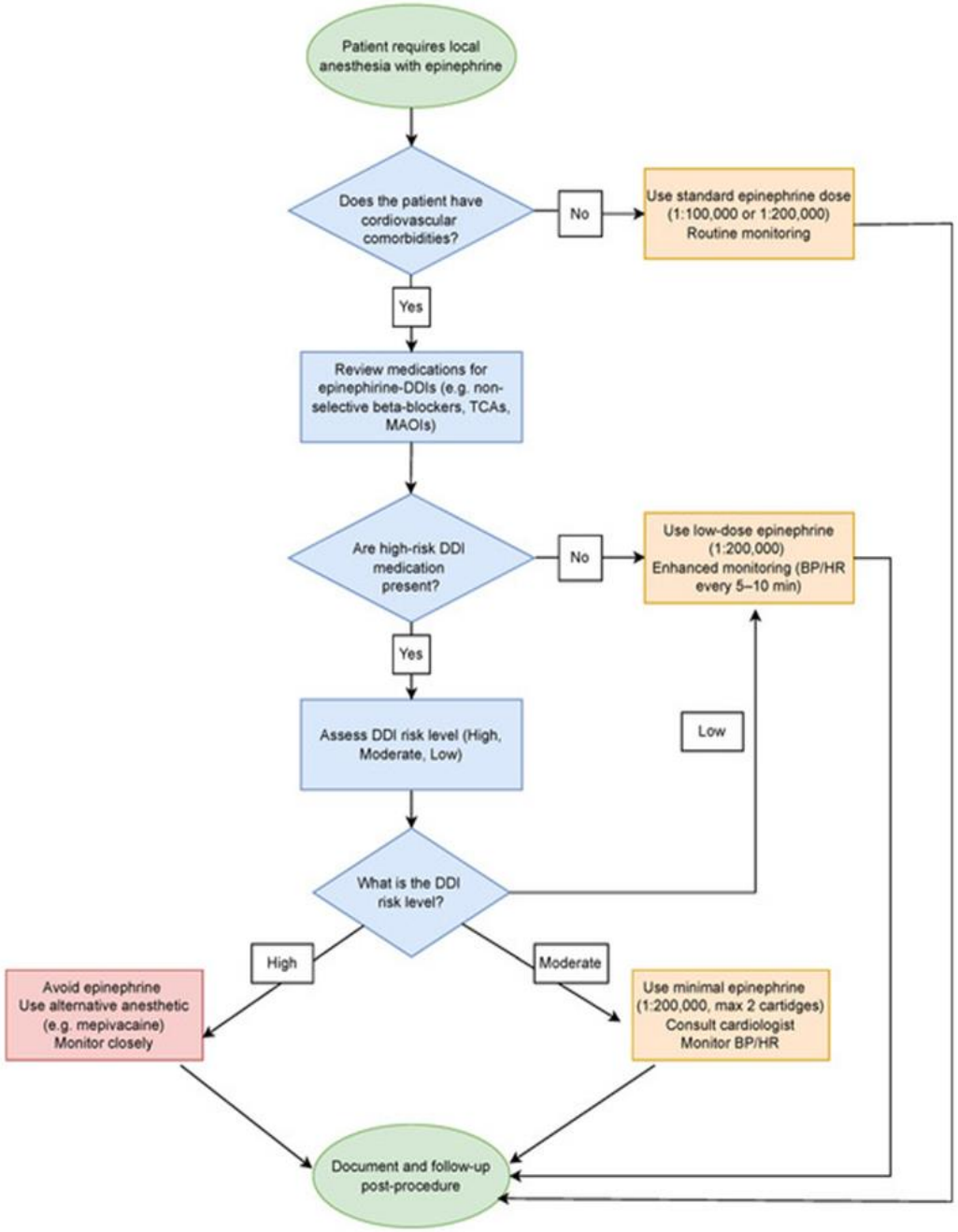


Figure 4. Flowchart for epinephrine administration considering potential drug-drug interactions. This visual tool organizes patients by cardiovascular risk and concurrent medications, providing stepwise guidance for safe epinephrine use. It underlines the need for vigilant observation, interdisciplinary advice, and recording of all management steps after the procedure.

Age and cardiovascular disease effects on major DDIs

Examination of significant drug-drug interactions (DDIs) within our dental patient group **(Figure 2)** indicated that approximately half of the participants encountered one high-risk interaction, while the rest experienced two or more major DDIs, increasing their risk of negative effects like heart-related issues or heightened drug toxicity. Specifically, 13.4% of participants had four to five significant DDIs, highlighting the difficulties of managing multiple medications in people with substantial health conditions. This corresponds with the 19.0% prevalence of cardiovascular disease (CVD) in the study group, in line with other dental patient populations where interactions with common cardiovascular medications, such as beta-blockers, are often noted. Therefore, routine DDI assessment using platforms like the DrugBank tool is critical to assist clinicians in safely modifying treatment strategies.

When stratified by age **(Table 4)**, the 0–30 years group had no major DDIs, likely reflecting their generally healthier profiles, minimal chronic disease, and limited exposure to systemic medications. Typical dental care in this group, such as caries management or routine preventive procedures, generally involves simpler pharmacotherapy, minimizing the risk for serious DDIs.

For patients aged 31–60 years, the prevalence of major DDIs reached 61.3%, suggesting that middle-aged adults face a combination of emerging chronic illnesses and active lifestyles that increase exposure to interacting medications. Dental drugs administered alongside newly initiated treatments for conditions like hypertension or other systemic disorders may elevate DDI risk.

Interestingly, the ≥61 years group experienced 38.7% of major DDIs, lower than the middle-aged group despite older adults typically being at higher risk due to polypharmacy. This reduction could reflect cautious prescribing habits, more thorough medication reconciliation, or pharmacokinetic changes in older patients affecting drug absorption, metabolism, or excretion.

Another contributing factor to the lower observed DDI prevalence among older adults is underreporting or incomplete medication documentation. Studies such as Abeleira-Pazos *et al*. found that older patients often provide incomplete drug histories due to memory limitations or complex regimens [34]. Similarly, Drenth-van Maanen *et al*. demonstrated that nearly all participants had inconsistencies in their medication records, with missing information about nonprescription drugs accounting for almost half of potential DDI consequences [60]. These findings underscore the importance of a comprehensive medication review—including prescription, over-the-counter, and herbal products—to accurately identify DDI risks in dental practice.

Bennie *et al*. observed that in several European countries, more than 50% of older adults were prescribed five or more medications within a six-month period, reflecting widespread polypharmacy and a higher likelihood of drug-drug interactions. This study also highlighted frequent prescriptions of potentially inappropriate medications—such as proton pump inhibitors and benzodiazepines—indicating that incomplete drug records may conceal actual DDI prevalence [61]. In dental practice, conservative prescribing, particularly in frail patients, likely reduces observed interaction rates by favoring drugs with lower potential for adverse interactions.

In our cohort, the middle-aged group (31–60 years) accounted for 61.3% of patients with major DDIs, indicating that most affected individuals fall into this category. However, when analyzing the entire cohort, patients aged ≥61 years exhibited a 31.6% prevalence of major DDIs, which exceeded the 15.3% observed in the 31–60 group. The difference across age groups was statistically significant ($\chi 2$ (2, n = 105) = 9.19, p = 0.0101).

Figure 3 displays total DDI counts according to age and CVD status. Panel (a) shows that older patients (≥61) had a lower median total of DDIs than younger cohorts (0–30 and 31–60), suggesting either more cautious prescribing or incomplete drug documentation. Panel (b) demonstrates that patients with cardiovascular comorbidities experienced a higher median total of DDIs (18) compared with those without CVD (10), highlighting their elevated risk. Due to the limited sample, especially in the elderly, these subgroup observations should be interpreted cautiously.

The age distribution of major DDIs emphasizes the necessity of systematic medication review in dental care. Individuals 0–30 years old showed no major DDIs, consistent with lower rates of chronic illness and polypharmacy. Patients aged 31–60 faced the highest number of interactions, likely reflecting the onset of chronic conditions combined with ongoing dental treatments. The older group (≥61) displayed fewer major DDIs than expected, possibly due to conservative prescribing, pharmacokinetic differences, or underreported medication histories. Despite this, older adults remain highly vulnerable to clinically significant DDIs, warranting routine DDI screening and collaboration with physicians and pharmacists.

A retrospective power analysis verified that the chi-square test for age categories reached approximately 78% power (Cramér's V ≈ 0.296), adequate for identifying age-related variations in major DDI prevalence. Comparisons based on CVD status were less conclusive, with only ≈40% power despite a medium effect size (Cohen's h = 0.39). These results suggest that future research should aim for about 100 participants per group to attain 80% statistical power, facilitating the creation of predictive models for high-risk patients and enhanced clinical decision-support tools in dental practice.

Study limitations

This investigation is subject to several constraints:

(i) The relatively small sample size (n = 105), based on consecutive patients recruited within a two-month period, limits statistical power and restricts the generalizability of the outcomes [62]. Because the project was designed as an exploratory assessment of routine dental practice, no formal a priori sample size calculation was carried out.

(ii) The reliability of patient-reported data remains uncertain. Some individuals may have provided incomplete or rushed responses on intake forms, lacked full awareness of their medications, or deliberately withheld sensitive medical details (e.g., psychiatric illnesses or tuberculosis) [63].
(iii) Interaction detection relied exclusively on the DrugBank DDI checker. Employing additional databases or validation tools could improve consistency, facilitate cross-verification of results, and enhance the accuracy of clinical decision-making [36].

Conclusion

In this cohort of 105 dental patients, we observed a considerable number of potential drug–drug interactions (542 across 1332 medication pairs). Within these, 31 major DDIs were identified in 15 individuals, showing a clear age-related pattern: no cases in the 0–30 group, the highest proportion in the 31–60 group, and a smaller share among those ≥61 years. Statistical testing indicated meaningful differences in overall interaction counts across age strata, with older patients displaying a broader interquartile spread. Patients with cardiovascular disease (CVD) carried a significantly heavier interaction load compared with those without CVD, highlighting their greater pharmacological vulnerability.
Particularly concerning were combinations involving epinephrine and beta-blockers, relevant in routine interventions such as extractions. By applying real-world data and the DrugBank platform, this study addresses a gap in existing research on dental DDIs and underscores their age-specific distribution. Our findings support the systematic use of DDI screening in dental care, especially for older adults (≥61 years), who may benefit from adjusted pharmacotherapy (e.g., reduced epinephrine dosage) to minimize risk. The age-related clustering of major DDIs represents a central conclusion, reinforcing the need for targeted surveillance.
Dentists are advised to routinely review medication histories, apply validated interaction-checking tools, and coordinate treatment planning with physicians and pharmacists, particularly since nearly half of the patients (45.7%) presented with one or more comorbid conditions.
Looking ahead, the next phase of this research should involve a larger, multicenter cohort, which would improve the reliability of results, strengthen statistical validity, allow broader applicability, and help confirm the observed age-related interaction patterns. Future projects should also incorporate a priori sample size estimation to enable hypothesis-driven testing and provide a clearer evaluation of the link between cardiovascular disease (CVD) and drug–drug interactions (DDIs). Based on retrospective calculations from the present dataset, a sample of about 200 participants would likely be sufficient to reveal significant differences in the frequency of major DDIs between patients with and without CVD. Moreover, upcoming investigations should prioritize the creation of risk-prediction tools for vulnerable patients and the refinement of decision-support systems to assist dental practitioners.

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