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Review

Pharmacological safety in dental practice: Drug–drug interactions, adverse drug reactions, and pharmacovigilance

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Abstract: *Background:* As the prevalence of systemic co-morbidities and polypharmacy increases among dental patients, the risk of clinically significant drug-drug interactions (DDIs) has become a critical concern in outpatient care. In this narrative review, we evaluated the pharmacological risks associated with the most common dental prescriptions, including analgesics, antimicrobials, and local anesthetics, in patients with underlying systemic conditions under long-term treatment. *Materials and methods:* A comprehensive literature search was conducted across PubMed, Scopus, and Google Scholar using MeSH terms related to "dental drug interactions", "pharmacovigilance in dentistry", and "adverse drug reactions". We synthesized data from clinical trials, systematic reviews, and pharmacological guidelines published over the last 16 years. *Results:* Analysis revealed that common dental therapeutics are not always "low-risk" interventions. Interactions can range from decreased treatment efficacy to potential severe complications. Furthermore, the review highlights the lower levels of pharmacovigilance and Adverse Drug Reaction reporting among dental professionals. *Conclusions:* The findings underscore significant "underlying risks" in routine dental practice. To ensure patient safety, dental practitioners must shift toward an evidence-based prescribing model that prioritizes pharmacological literacy, systematic pharmacovigilance, and proactive reporting of Adverse Drug Reactions (ADRs).

Keywords: drug-drug interactions (DDIs); dental pharmacology; pharmacovigilance; NSAIDs interactions; antibiotic interactions

1. Introduction

Patients with chronic diseases, which require long-term medication, have become more common in everyday dental practice in the last few years. Projections indicate a continued upward trend in pharmaceutical consumption [1]. Concurrently, the introduction of new drugs and the widespread practice of simultaneous multi-drug intake increases the risk of drug-drug interactions (DDIs). DDIs can be classified into three main categories: physical-chemical interactions, pharmacokinetic interactions, and pharmacodynamic interactions [2]. In addition to drug-specific properties, the manifestation of drug interactions is heavily influenced by patient-dependent variables. Factors such as advanced age, genetic predispositions, specifically polymorphisms in drug-metabolizing enzymes, comorbidities, and therapeutic adherence, play a critical role in pharmacological outcomes. Consequently, interactions described in the literature are often categorized as potential or theoretical; their actual clinical occurrence is variable and contingent upon the unique physiological profile of the individual patient [3].

Although in dental practice prescriptions consist of a narrow spectrum, the risk for potential interaction remains high. Clinical practice routinely involves the use of medications for local anesthesia, infection control, pain relief, and sedation. The most common drugs that dentists prescribe or administer include Nonsteroidal Anti- Inflammatory Drugs (NSAIDs), antibiotics and antifungals, and local anesthetics.

While pain remains the most common symptom referred by patients approaching the dental office, consequentially analgesics remain the most commonly prescribed, but it is worth noticing that analgesic drugs should be judiciously selected based on factors such as intensity of pain, medical status of the patient, pharmacokinetic and pharmacodynamic properties of the drug, the logistics, and the cost of obtaining the medicine [4]. However, literature shows that a very limited number of dental care professionals prescribe analgesics after thoroughly taking into consideration the drug properties and potential combinations [5]. It is important to note that several studies suggest that significant deficits in prescribing practices originate during the undergraduate dental education phase [6,7]. These gaps appear to persist into professional practice, with a particularly pronounced deficiency observed in the clinical management and prescription of analgesics [8]. The range of analgesics utilized in dental practice remains notably narrow and frequently fails to align with patient-specific clinical indications. Despite evolving guidelines, NSAIDs, particularly ibuprofen, continue to be prescribed for extended periods, often in direct conflict with established recommendations. Of significant concern is the observation that a substantial proportion of practitioners prescribe medications that are contraindicated for patients with high-risk systemic profiles [9].

Although therapeutic indications for the use of systemic antibiotics in dentistry are limited, and since most dental and periodontal diseases can be effectively managed by operative intervention and oral hygiene measures, antibiotics are among the most frequently prescribed pharmacological agents in dentistry, utilized for prophylactic measures and operative procedures. In industrialized nations, dental-related prescriptions account for approximately 10% of the total antibiotic volume [10–12]. While overall counts of antibiotic prescriptions fell by 41.6% between 2012 and 2021, the proportion of dental antibiotics' prescriptions increased [13].

Although antibiotics constitute a transformative milestone in medicine, the elevated risk associated with DDIs demands meticulous evaluation and a sophisticated understanding of patient-specific information to ensure safety. The high volume of antibiotic use in dentistry presents a

bifurcated clinical challenge. On one hand, practitioners must navigate the immediate pharmacological risk of DDIs, which necessitates a precise understanding of patient- specific data. On the other hand, the dental profession faces the systemic crisis of antimicrobial resistance driven by chronic overprescription [14–16].

The pharmacological management of pain in dentistry relies on two distinct classes of local anesthetics (LA), classified by their amide or ester linkages. Both groups function by reversibly binding to sodium channels to obstruct the influx of sodium ions into the neuronal cell. This suppression of depolarization effectively halts the transmission of pain signals, enabling the painless execution of operative procedures. Despite this shared mechanism, the choice between amides and esters is dictated by their differing metabolic profiles and durations of action [17].

Most local anesthetics commonly used in dental procedures belong to the amide group, such as lidocaine, articaine, mepivacaine, and bupivacaine [18]. Besides anesthetic agents, adrenaline is another LA cartridge component where clinically relevant interactions may be expected [19].

DDIs frequently arise between agents commonly prescribed in dental practice and medications utilized in the management of chronic systemic conditions [20]. These interactions may diminish therapeutic efficacy, escalate the risk of clinical complications, or exacerbate Adverse Drug Reactions (ADRs). Consequently, such pharmacological conflicts possess the potential to compromise the success of dental interventions and the stability of the patient's systemic health.

The rise of ADRs as a significant contributor to mortality underscores the urgent need for effective pharmacovigilance, the process of monitoring and preventing adverse drug effects. Pharmacovigilance is defined as the science and activities relating to the assessment, detection, and prevention of adverse effects of medications; it is an essential step in ensuring patient safety. As major prescribers of systemic medications, dentists play a vital role in this safety chain. Nevertheless, research highlights a pervasive under-reporting of ADRs by dental professionals, suggesting that the clinical potential for identifying and preventing drug-related harm is underutilized in the dental field [21,22].

Detailed real-world data on the frequency and clinical significance of DDIs in dental practice remain limited.

In this narrative review, we aim to identify the potential DDIs associated with common dental prescriptions while underscoring the critical necessity of comprehensive medical history-taking and pharmacological reconciliation. Furthermore, we seek to emphasize the pivotal role of pharmacovigilance and ADRs reporting within the dental community as essential components for optimizing patient safety and enhancing the quality of systemic healthcare.

2. Materials and methods

To achieve our objectives of this narrative review, a comprehensive literature search was conducted across several electronic databases, including PubMed/MEDLINE, Scopus, and Google Scholar. The search was performed for articles published between January 2010 and December 2025 to ensure contemporary relevance. The search strategy utilized a combination of Boolean operators and keywords, including: ("drug-drug interactions" OR "DDI") AND ("dental pharmacology" OR "dentistry") AND ("antibiotic resistance" OR "pharmacovigilance"). Articles were included if they met the following criteria: (1) peer-reviewed original research or clinical guidelines; (2) focus on interactions involving common dental prescriptions (analgesics, antibiotics, and local anesthetics); and (3) published in the English language. Exclusion criteria included conference abstracts and letters

to the editor. Based on the study's focus on conventional outpatient dental care, interactions involving herbal supplements, holistic remedies, and illicit or non-regulated substances were also excluded. Furthermore, opioid analgesics were excluded to reflect recent clinical shifts prioritizing non-narcotic alternatives in dentistry. The screening process involved a dual-stage review of titles and abstracts followed by a full-text analysis to assess clinical relevance. In addition to traditional databases, professional pharmacological repositories were consulted for real-world risk data, including DrugBank.com, the Specialist Pharmacy Service (sps.nhs.uk), and official regulatory updates from the U.S. Food and Drug Administration (fda.gov) with latest search performed on May 2026. Data were synthesized qualitatively to highlight potential and clinically established moderate and high risk DDIs. The results were categorized by drug class: analgesics, antibiotics, and local anesthetics and the potential severity of the ADRs.

3. Results

3.1. Analgesic interaction

Analgesics are the primary agents for managing acute odontogenic or postoperative pain. These medications are generally categorized into two major groups: non-opioids (including Acetaminophen and NSAIDs) and opioids [23].

Acetaminophen (Paracetamol) is among the most frequently prescribed analgesics in dentistry. Despite its long- term clinical use, its exact mechanism of action is not fully elucidated. Because it lacks significant inhibitory effects on peripheral cyclooxygenase (COX) activity, it is less likely than traditional NSAIDs (tNSAIDs) to induce gastrointestinal or cardiovascular adverse effects, and it does not affect platelet aggregation or bleeding time.

Acetaminophen and Carbamazepine: While acetaminophen is a preferred analgesic in dentistry due to its safety profile compared to NSAIDs, it is categorized by the European Association for the Study of the Liver (EASL) as a prototype for intrinsic, dose-dependent liver injury. A clinically significant interaction occurs with carbamazepine, a potent inducer of hepatic enzymes (notably CYP3A4 and CYP2E1). According to the EASL 2019 Clinical Practice Guidelines, concomitant use of such enzyme-inducers can modulate the toxic threshold of acetaminophen by accelerating the production of its reactive metabolite, *N-acetyl-p-benzoquinone imine* (NAPQI). In patients stabilized on carbamazepine, the metabolic shift toward this toxic pathway depletes glutathione stores more rapidly, lowering the threshold for hepatotoxicity. To mitigate the risk of acute liver failure, it is recommended that the total daily dose of acetaminophen be strictly limited to 2 g/day in these patients [24,25].

Acetaminophen and Warfarin: While generally safer than other NSAIDs for anticoagulated patients, acetaminophen can cause a dose-dependent increase in the International Normalized Ratio (INR). The interaction meets the criteria for causality (dose-response and biologic plausibility), likely due to the disruption of vitamin K-dependent clotting factor synthesis. The risk of a supratherapeutic INR is highest when cumulative doses reach $\geq$ 2 g/day for at least 3 consecutive days. Recommendations in clinical management include short term use (< 3 days), as it is generally safe and no additional monitoring is required, and if extended use is necessary, an INR test is recommended 3–5 days after the first dose. Acetaminophen use should be investigated as a potential contributing factor in patients with erratic INR levels [26,27].

NSAIDs and Anticoagulants: NSAIDs can cause synergistic anticoagulant effects, significantly

increasing the risk of hemorrhage. The concomitant use of NSAIDs and oral anticoagulants represents a critical “hidden danger” in dental practice, nearly doubling the risk of hospital-diagnosed bleeding (aHR 1.81). While the synergistic effect with Warfarin is well-documented (aHR 1.46), recent nationwide cohort data (2012–2022) reveals even higher risks for specific Direct Oral Anticoagulants (DOACs), including Edoxaban (aHR 2.87), Apixaban (aHR 2.15), and Rivaroxaban (aHR 2.05). This elevated risk is not localized to the gastrointestinal tract, but extends to the respiratory and urinary systems. To mitigate these risks, dental practitioners should prioritize Acetaminophen or strictly limit NSAID therapy to a maximum of 48 hours [28].

NSAIDs and Angiotensin-converting enzyme (ACE) inhibitor/ angiotensin II receptor blockers (ARBs): The nephrotoxic potential of NSAIDs in patients using renin-angiotensin system (RAS) inhibitors (ACE inhibitors or ARBs) is driven by the inhibition of prostaglandin E2 (PGE2), which is vital for maintaining renal blood flow. While the ‘triple whammy’ combination (NSAID + RAS inhibitor + diuretic) is well-documented, in a 2013 study [29], by establishing its significant role in community-acquired acute kidney injury, subsequent data reveals that dual combinations are nearly as dangerous. Moreover, laboratory-based studies utilizing serum creatinine data indicate that the dual combination (NSAID + RAS inhibitor) carries an adjusted relative risk for AKI nearly identical to the triple therapy (aRR 1.60 vs. 1.64, respectively) [30]. The absolute risk is significantly higher in patients over 75 years of age, those with pre-existing renal impairment, or those using loop diuretics. These findings suggest that rather than a broad rule to avoid RAS blockers for any NSAID use exceeding five days, clinicians should adopt a risk-stratified approach, prioritizing Acetaminophen for high-risk individuals [27,30].

Lithium and NSAIDs: Lithium is a first-line maintenance therapy for bipolar disorder and a mood stabilizer [31]. NSAIDs are a major risk factor for these patients, because they reduce the renal clearance of lithium, leading to dangerously elevated blood levels of lithium. Mechanistically, NSAIDs inhibit prostaglandin synthesis, which decreases the glomerular filtration rate and subsequently reduces the kidney's ability to excrete lithium. Lithium toxicity is known to affect multiple organ systems, including the central nervous system. Common clinical signs of lithium poisoning include confusion, tremors, numbness in the hands, dysarthria (speech difficulty), agitation, and diarrhea. To mitigate these risks, it is recommended that lithium levels be checked every 4–5 days if an NSAID is initiated [32].

Oral Antidiabetics and NSAIDs: While Aspirin may potentiate the hypoglycemic effects of oral antidiabetic agents, this risk is generally moderate and mostly clinically significant in patients on therapies with a high baseline risk for glycemic instability [33,34]. Real-life clinical data from a 20-year cohort study indicates that patients on Metformin plus Sulfonylureas (SU) or Basal Insulin experience the highest rates of severe hypoglycemia requiring hospitalization [35]. Conversely, patients on newer combinations involving SGLT2 inhibitors or GLP-1 receptor agonists exhibit significantly lower risk profiles. Therefore, dental practitioners should exercise particular caution when prescribing high-dose aspirin to patients stabilized on Sulfonylureas, as this interaction may exacerbate an already high intrinsic risk of life-threatening hypoglycemic events [33,34].

Selective Serotonin Reuptake Inhibitor (SSRIs) and Serotonin and Norepinephrine Reuptake Inhibitor (SNRI) and NSAIDs: Concurrent intake increases the risk of Gastrointestinal bleeding [36]. SSRIs inhibit the reuptake of serotonin into platelets. Since platelets lack the machinery to synthesize their own serotonin, these stores are depleted, while NSAIDs deplete cytoprotective prostaglandins. This impairs platelet aggregation and limits the vasoconstriction usually triggered by serotonin release

during hemorrhage [37]. Extreme caution is required for high-risk profiles, including advanced age, male gender, and a history of peptic ulcer disease. To ensure patient safety, Acetaminophen should be prioritized as the first-line postoperative analgesic. However, if NSAID use is unavoidable, the concurrent prescription of a Proton Pump Inhibitor (PPI) is recommended to significantly reduce the incidence of major upper GI hemorrhaging [36]

Table 1. Summary of commonly reported DDIs between analgesics and other medication and their respective ADRs.

Interacting pairs	Mechanism of interaction	Clinical consequences	Management recommendations
Acetaminophen + Carbamazepine	Induction of hepatic enzymes (CYP3A4/2E1) accelerates production of reactive metabolite NAPQI.	Rapid glutathione depletion; increased risk of hepatotoxicity at lower thresholds.	Strictly limit total acetaminophen dose to ≤ 2 g/day.
Acetaminophen + Warfarin	Potential disruption of Vitamin K-dependent clotting factor synthesis (dose-dependent).	Increased INR levels and risk of supratherapeutic anticoagulation.	Safe for < 3 days; if used ≥ 3 days, check INR in 3–5 days.
NSAIDs + Anticoagulants (Warfarin/DOACs)	Synergistic impairment of platelet aggregation and gastric mucosal protection.	Doubled risk of hemorrhage; highest risk seen with Edoxaban (aHR 2.87) and Apixaban (aHR 2.15).	Prioritize acetaminophen; limit NSAID use to max 48 hours.
NSAIDs + ACE Inhibitors / ARBs	Inhibition of PGE2 reduces renal blood flow, causing efferent/afferent arteriole imbalance.	Elevated risk of Acute Kidney Injury (AKI); risk is nearly equal to the “triple whammy”.	Prioritize acetaminophen for patients > 75 years or those with renal impairment.
NSAIDs + Lithium	Inhibition of prostaglandin synthesis reduces glomerular filtration and lithium excretion.	Lithium toxicity: tremors, confusion, dysarthria, and agitation.	Monitor lithium levels every 4–5 days if NSAID is initiated.
Aspirin + Oral Antidiabetics (Sulfonylureas)	Potentiation of hypoglycemic effects in patients with high baseline glycemic instability.	Increased risk of severe hypoglycemia requiring hospitalization.	Exercise extreme caution; particularly in patients on Sulfonylureas or Basal Insulin.
NSAIDs + SSRIs / SNRIs	Combined depletion of platelet serotonin and gastric cytoprotective prostaglandins.	Impaired platelet aggregation; significantly increased risk of upper GI bleeding.	Prioritize acetaminophen; if NSAID is required, co-prescribe a Proton Pump Inhibitor (PPI).

3.2. Antibiotic interaction

Dentists prescribe medications for the management of several oral conditions, mainly orofacial infections. Antimicrobials prescribed by dentists belong to different classes and mechanisms of action. Potential DDIs have been reported.

Tetracyclines exhibit significant chelation when co-administered with polyvalent cations such as antacids (containing magnesium or aluminum), iron, and zinc. This process sequesters the drug in the gastrointestinal tract, significantly reducing systemic absorption and therapeutic efficacy; consequently, these agents should be administered several hours apart [38]. Doxycycline is a member of the tetracycline class frequently utilized for periodontal inflammation. Concomitant doxycycline therapy mildly increases the anticoagulant effect of warfarin. Rather than preemptive dose adjustment, a randomized controlled trial concluded that practitioners should prioritize prompt monitoring of the International Normalized Ratio (INR) following the initiation of doxycycline, enabling timely reactive adjustment if necessary; preemptive reduction may still be considered for patients with a prior history of doxycycline-associated excessive anticoagulation or those already at the upper end of their therapeutic range, in consultation with the prescribing physician or anticoagulation service [39,40]. Conversely, a clinically important interaction involves digoxin. Dental patients with a history of congestive heart failure or atrial fibrillation may be on a digoxin regimen. The interaction between digoxin and tetracycline antibiotics is a pharmacokinetic concern involving modulation of intestinal microflora. Approximately 10% of the population harbors substantial colonies of the anaerobic bacterium *Eggerthella lenta*, which facilitates pre-systemic conversion of digoxin into inactive reduction products. Administration of broad-spectrum tetracyclines can suppress this commensal flora, thereby reducing metabolic degradation of the glycoside and increasing its bioavailability and serum concentration. Given digoxin's narrow therapeutic index, this elevation in systemic exposure can precipitate toxicity, particularly in patients who harbor high colonic concentrations of the organism. Clinical manifestations of digoxin toxicity may include life-threatening cardiac arrhythmias, characteristic visual disturbances (e.g., xanthopsia), and gastrointestinal distress. Clinicians should therefore maintain close monitoring of serum digoxin levels, in consultation with the patient's prescribing physician, when tetracycline therapy is initiated or discontinued in patients on chronic digoxin treatment [41].

While pharmacological theory suggests that tetracyclines may reduce the efficacy of Oral Contraceptives (OCs) by disrupting enterohepatic recirculation, contemporary clinical evidence does not support a significant interaction for most of the population, and evidence-based recommendations have shifted. Non-rifamycin antibiotics, including tetracyclines, penicillins, and cephalosporins, are classified as Category 1 for combined oral contraceptives. This means there is no restriction on their use, as they do not significantly reduce contraceptive efficacy. Current national guidelines do not mandate the use of backup barrier methods for patients taking common antibiotics like tetracycline [42].

The concomitant administration of tetracyclines and methotrexate is generally discouraged due to the potential for increased methotrexate toxicity [43]. The interaction is multi-factorial, primarily involving the displacement of methotrexate from protein binding sites and competition for renal tubular secretion, which reduces its clearance. Furthermore, tetracyclines have been reported to interact with Lithium, with a possible side effect of increased levels of Lithium [44].

Macrolides: This class demonstrated the strongest association with Torsades de pointes (TdP)

and QT prolongation (QTP) in FDA Adverse Effect Reporting System (FAERS) pharmacovigilance data (class-level reporting odds ratio, ROR, of 14.32). Within this group, azithromycin, erythromycin, and clarithromycin ranked highest for reporting frequency, in that order, according to a pharmacovigilance study analyzing the FAERS database; the source reports this ranking qualitatively rather than as individual numeric RORs per drug [45]. Practitioners should adopt a risk-stratified approach to help mitigate cardiotoxicity and systemic metabolic complications. To reduce TdP risk, screening for risk factors is advisable before prescribing macrolides or fluoroquinolones, particularly for patients with unmodifiable risks (age > 65, female gender, congenital Long QT) or modifiable factors (electrolyte imbalances or concurrent long-term QT-prolonging medications). In higher-risk patients, an alternative antibiotic selected according to the clinical indication, spectrum requirements, allergy history, and antimicrobial stewardship principles, for example amoxicillin or clindamycin, where clinically appropriate, may be considered in place of higher-ROR agents such as azithromycin. While all macrolides can theoretically increase the anticoagulant effect of warfarin (raising the INR), they appear to do so through distinct pathways: a- Pharmacokinetic inhibition (clarithromycin and erythromycin): these agents are potent inhibitors of the CYP3A4 enzyme, and by blocking this pathway, they can allow warfarin levels to accumulate in the plasma, increasing the risk of over-anticoagulation. b- A proposed microbiome mechanism (azithromycin): Azithromycin is often considered comparatively safer because it does not significantly inhibit CYP450 enzymes; yet, INR elevation has been reported with its use. A proposed explanation is eradication of vitamin-K-producing intestinal flora (such as Bacteroides fragilis), although this remains a plausible rather than firmly established mechanism. Of particular concern are documented interactions between macrolides such as clarithromycin and agents such as pimozide (a typical antipsychotic used to control repeated movements in Tourette's disorder) [46] or cisapride (a gastrointestinal prokinetic drug) [47], which have been associated with fatal ventricular dysrhythmias due to excessive QT-interval prolongation. Erythromycin and clarithromycin have also been reported to reduce the clearance of Class IA antiarrhythmics such as quinidine and disopyramide, and this combination has been associated with life-threatening ventricular dysrhythmias and marked QT prolongation [48]. For potent CYP3A4 inhibitors like clarithromycin or erythromycin, combination with QT-prolonging substrates should generally be avoided; liver cirrhosis or active infection can further depress CYP activity, increasing susceptibility to these interactions [49,50]. Erythromycin has a documented interaction with theophylline, a bronchodilator used in the management of asthma and Chronic Obstructive Pulmonary Disease (COPD); the expected effect is increased theophylline levels, requiring monitoring and, if needed, dosage reduction under the guidance of the prescribing physician. Where clinically appropriate, an alternative macrolide with lower CYP-inhibitory potential, such as azithromycin, may be considered, based on indication and stewardship principles rather than as a default substitution [51–53]. Co-administration of methadone with macrolide antibiotics (specifically erythromycin and clarithromycin) has raised concern for a combined risk of opioid toxicity and cardiac arrhythmia, since these macrolides inhibit CYP3A4 (which can raise methadone serum levels), while both drug classes can prolong the QT interval. Given these risks, dental prescribers should consult the patient's opioid treatment program or prescribing physician before co-prescribing, and consider non-macrolide alternatives such as cephalosporins where clinically appropriate; azithromycin with close ECG monitoring may be a reasonable option in some cases, but any adjustment of the methadone dose should remain the responsibility of the prescribing physician or addiction medicine specialist [49,50].

Clindamycin: The interaction between clindamycin and Vitamin K antagonists (such as warfarin,

acenocoumarol, and fluindione) is characterized by an increased risk of bleeding due to elevated coagulation levels (PT/INR). This interference primarily occurs because clindamycin disrupts the gut flora responsible for synthesizing Vitamin K, though a secondary pharmacokinetic interaction with warfarin metabolism may also play a minor role. Consequently, the European Medicines Agency (EMA) recommends frequent monitoring of INR levels in patients receiving this combination to prevent adverse bleeding events [54].

Fluoroquinolones: As a class, fluoroquinolones were significantly associated with TdP/QTP in FAERS pharmacovigilance data (class-level ROR 5.68); among individual agents, moxifloxacin, ofloxacin, ciprofloxacin, and levofloxacin ranked highest to lowest for reporting frequency [55], in that order, though the source reports this ranking qualitatively rather than as individual numeric RORs [45]. It is also important to underline the potential adverse effect of combining fluoroquinolones with systemic corticosteroids, which several case-control studies have linked to an increased risk of tendinitis and tendon rupture, particularly of the Achilles tendon [55–58]. Reported effect sizes vary considerably between studies, with adjusted odds ratios for fluoroquinolone use alone generally reported in the range of roughly 1.5–3, rising further with concomitant corticosteroid use, and the highest vulnerability has been reported in patients over 60 years of age and those with a low BMI (< 18.5 kg/m²). Given this variability between studies, precise numeric risk estimates should be interpreted with caution; clinically, this warrants caution and, where possible, avoidance of the combination, or prompt cessation of physical strain and antibiotic therapy at the first sign of tendon pain. Fluoroquinolones such as ciprofloxacin have also been reported to inhibit hepatic CYP450 metabolism; when combined with warfarin, this may delay warfarin clearance and increase INR, so the prescribing physician or anticoagulation service should be notified for closer INR monitoring whenever a fluoroquinolone is started in a patient on chronic anticoagulation. Co-administration of fluoroquinolones with other QT-prolonging agents such as pimozide should generally be avoided, given the additive risk of cardiac arrhythmia.

Metronidazole must be prescribed with caution for patients stabilized on warfarin, as this combination results in enhanced anticoagulant action and prolonged prothrombin time, significantly increasing the risk of life-threatening hemorrhage. To manage this interaction, patients require frequent monitoring of their prothrombin time and INR. Clinicians must also remain vigilant for physical signs of bleeding. Similarly, co-administration of metronidazole and lithium may result in elevated plasma levels and lithium toxicity, presenting as weakness, tremors, and confusion [59]. When combined with anticonvulsants such as phenytoin, the therapeutic efficacy of metronidazole may be compromised through accelerated elimination. Furthermore, the reduction in phenytoin clearance could potentially cause phenytoin toxicity characterized by ataxia, nystagmus, and drowsiness, emphasizing the need for close monitoring of serum drug levels to prevent adverse neurological effects associated with supratherapeutic concentrations [60], while the co-administration of metronidazole with phenobarbital causes a minor interaction that may accelerate metronidazole elimination, thereby decreasing its effectiveness [60].

Penicillins, the most prescribed antibiotic group in dental practice, have a theoretical antagonistic interaction with bacteriostatic agents such as erythromycin and tetracyclines, which classical pharmacology holds may reduce penicillin's bactericidal effect when taken concurrently; the clinical significance of this interaction remains debated in the modern literature. A separate, better-documented interaction is reported between oral β-lactam antibiotics, penicillin V, amoxicillin, ampicillin, and flucloxacillin, and probenecid (a gout medication), which reduces penicillin excretion and can increase

penicillin exposure; the dentist's own penicillin dosing should therefore be adjusted with caution in these patients [61]. Other DDIs include the interaction between amoxicillin and methotrexate, which can reduce methotrexate clearance through competitive inhibition in the kidneys, although this effect is most clinically significant with high-dose oncological regimens rather than low-dose inflammatory treatments; for short courses (up to 10 days), penicillins may be used with caution alongside monitoring for methotrexate toxicity [62]. Most broad-spectrum penicillins can disrupt vitamin-K-producing gut flora; this reduction in available vitamin K can enhance warfarin's effect and increase the INR. Risk appears elevated in elderly patients and in those with active infection, as acute infection can independently increase the risk of excessive anticoagulation. Frequent INR monitoring, coordinated with the patient's prescribing physician or anticoagulation service, is advisable whenever antibiotic therapy is initiated or discontinued in patients on chronic warfarin therapy. Penicillins should not be treated as a monolithic group: Some agents (via effects on gut flora) may increase bleeding risk, while others, such as nafcillin and dicloxacillin, which act as hepatic enzyme inducers, have been associated with a decline in INR and reduced anticoagulant effect. In patients starting nafcillin, dicloxacillin, or other enzyme-inducing antibiotics, or conversely CYP450 inhibitors such as fluoroquinolones or macrolides, the prescribing physician or anticoagulation service should be notified so that INR monitoring can be intensified and the warfarin dose adjusted, if indicated; dose changes should not be made unilaterally by the dental prescriber [40].

Table 2. Summary of commonly reported DDIs between antibiotics and other medication and their respective ADRs.

Interacting pairs	Mechanism of interaction	Clinical consequences	Management recommendations
Tetracyclines + Polyvalent Cations (Antacids, Fe, Zn)	Chelation in the GI tract, sequestering the drug.	Significantly reduced systemic absorption and therapeutic failure.	Administer agents several hours apart.
Tetracyclines + Digoxin	Eradication of E. lentum microflora, reducing pre-systemic metabolism.	Marked elevation in bioavailability; Digoxin toxicity (arrhythmias, xanthopsia).	Rigorous serum digoxin monitoring and precise dose titration.
Tetracyclines + Warfarin	Mild microbiome-mediated enhancement of anticoagulation.	Potential for elevated INR and bleeding.	Prioritize prompt INR monitoring following initiation.
Macrolides + QT-Prolonging Drugs (e.g., Pimozide)	Additive or synergistic delay in cardiac repolarization.	Highest reporting frequency for Torsades de Pointes (TdP) among macrolides in FAERS pharmacovigilance data; azithromycin ranked highest.	Use with caution in high-risk patients; an alternative agent may be considered based on indication, allergy history, and stewardship principles (e.g., amoxicillin or clindamycin where appropriate).

Continued on next page

Interacting pairs	Mechanism of interaction	Clinical consequences	Management recommendations
Macrolides + Warfarin	1) CYP3A4 inhibition (Clarithro/Erythro) or 2) Gut flora disruption (Azithro).	Accumulation of warfarin; significant risk of over-anticoagulation.	Frequent INR monitoring; notify prescribing physician/anticoagulation service for possible dose adjustment.
Macrolides + Theophylline	Inhibition of CYP enzymes responsible for theophylline metabolism.	Increased serum theophylline; risk of toxicity.	Monitor theophylline levels; dosage reduction or an alternative macrolide (e.g., azithromycin) may be considered by the prescribing physician.
Fluoroquinolones + Corticosteroids	Potent synergistic effect on connective tissue metabolism.	Substantially increased risk of Achilles tendon rupture; reported odds ratios vary between studies and are generally higher with corticosteroid co-use.	Avoid combination; immediate cessation if tendon pain occurs.
Fluoroquinolones + Warfarin	Reported inhibition of hepatic CYP450 metabolism (e.g., ciprofloxacin).	Possible delay in warfarin clearance; INR elevation and bleeding risk.	Frequent INR monitoring; notify prescribing physician/anticoagulation service for possible dose adjustment.
Metronidazole + Warfarin	Enhanced anticoagulant action and prolonged prothrombin time.	Life-threatening hemorrhage.	Frequent INR/Prothrombin time monitoring; check for physical signs of bleeding.
Metronidazole + Lithium	Reduced renal clearance of lithium.	Lithium toxicity (weakness, tremors, confusion).	Monitor serum lithium levels closely.
Metronidazole + Phenytoin	Accelerated metronidazole elimination and reduced phenytoin clearance.	Reduced antibiotic efficacy and phenytoin toxicity (ataxia, nystagmus).	Monitor serum drug levels; adjust dosages accordingly.
Penicillins + Methotrexate (MTX)	Competitive inhibition of renal tubular secretion.	Reduced MTX clearance; potential for MTX toxicity (pancytopenia).	Monitor for toxicity (sore throat, ulcers) even during short 10-day courses.
Penicillins + Probenecid	Inhibition of renal penicillin excretion.	Elevated and prolonged penicillin serum levels.	Useful for “boosting” but requires careful dosage adjustment.
Penicillins (Nafcillin/Dicloxacillin) + Warfarin	Hepatic enzyme induction (CYP450).	Decline in INR; increased risk of thromboembolism.	Notify prescribing physician/anticoagulation service; anticipate possible need for a warfarin dose increase, guided by INR monitoring.

3.3. Interactions of local anesthesia

In the dental setting, the selection of a local anesthetic must be guided by the patient's systemic health and potential DDIs, particularly concerning hepatic metabolism and cardiovascular stability. Many of the interactions described below are pharmacologically plausible and are supported mainly by case reports, product labeling, or theoretical reasoning about hepatic enzyme inhibition; clinically significant toxicity at the low, intermittent doses used in routine dental anesthesia appears to be uncommon, and this distinction is worth keeping in mind alongside the mechanistic descriptions that follow. Lidocaine requires caution in patients taking non-selective beta-blockers [63] or cimetidine [64], both of which have been reported to reduce its hepatic clearance and could theoretically increase the risk of Local Anesthetic Systemic Toxicity (LAST), although this appears to be an uncommon event at standard dental cartridge doses. Articaine is unique in that it also contains an ester group, enabling it to be metabolized primarily by plasma esterases rather than solely by the liver (CYP enzymes); it is therefore often preferred for patients with hepatic dysfunction [65]. It should be avoided in patients with documented sulfite allergies, as it contains metabisulfite as a preservative. Co-administration of articaine with other oxidizing agents that can also induce methemoglobinemia, such as other local anesthetics, antimalarials (e.g., primaquine, tafenoquine), nitrates and nitrites, dapsone, flutamide, and rasburicase, may increase the risk of methemoglobinemia, a condition in which the blood's oxygen-carrying capacity is reduced [66,67]. Bupivacaine is a long-acting anesthetic metabolized in part by CYP3A4; a theoretical interaction with strong CYP3A4 inhibitors such as erythromycin or clarithromycin has been proposed, though this is not well documented clinically. Beta-blockers have also been proposed to increase the risk of bupivacaine-induced side effects, potentially via hepatic enzyme inhibition (e.g., propranolol) and/or additive negative inotropic effects on the heart, with patients with heart failure potentially at greater risk; the supporting data are conflicting and limited. Ophthalmic beta-blocker formulations may also interact, as they are systemically absorbed and can produce clinically significant systemic effects even at low or undetectable plasma levels; this is considered a moderate risk, and caution is recommended if multiple doses of bupivacaine are administered in a patient using a beta-blocker, whether systemic or ophthalmic [68]. Monitoring for drowsiness, mental status changes, convulsions, ECG changes, and hypotension is advisable during concurrent therapy. Prilocaine (Citanest) carries a distinct, clinically documented risk of methemoglobinemia: Prilocaine is metabolized to o-toluidine, which oxidizes hemoglobin to methemoglobin, and this risk is amplified when combined with other oxidizing agents such as acetaminophen (paracetamol), sulfonamides, or nitrites [66]. Prilocaine should generally be avoided, or used with particular caution and monitoring, in patients with anemia, respiratory failure, or those on high-dose oxidizing therapies. Other clinically significant risks in dental anesthesia involve local anesthetic formulations containing epinephrine, in patients on specific cardiovascular or psychotropic medications. A primary concern involves patients managed with non-selective beta-blockers: Blockade of β2-mediated vasodilation can enable the α-adrenergic effects of epinephrine to act relatively unopposed, potentially precipitating a hypertensive episode and reflex bradycardia. A cautious approach is advisable, including vital sign monitoring for several minutes post-injection; if hemodynamic stability is confirmed, treatment may proceed within conservative dosage limits, current recommendations suggest a maximum of about two cartridges of 1:100,000 epinephrine (approximately 0.036 mg) in these patients [69–71]. A further documented interaction is seen when epinephrine-containing local anesthesia is administered to patients taking tricyclic antidepressants,

where concurrent use can potentiate sympathomimetic effects and increase the risk of acute hypertension; a lower dose of epinephrine-containing anesthetic is recommended [72]. Patients on first- or second-generation (atypical) antipsychotics are susceptible to a phenomenon known as 'epinephrine reversal': Because these agents have α1-adrenergic blocking properties, epinephrine's α-mediated vasoconstriction can be competitively inhibited, leaving β2-mediated vasodilation relatively unopposed. This has been reported to precipitate paradoxical hypotension [73]. To reduce this risk, clinicians are advised to use the minimum effective concentration of epinephrine or, where appropriate, a vasoconstrictor-free alternative such as 3% mepivacaine plain. All these interactions are summarized in Table 3.

Table 3. Summary of commonly reported DDIs between local anaesthetics (including epinephrine-containing formulations) and other medications and their respective ADRs.

Interacting pairs	Mechanism of interaction	Clinical consequences	Management recommendations
Lidocaine + Non-selective Beta-blockers / Cimetidine	Reduced hepatic clearance of lidocaine (by 30–50%).	Increased risk of Local Anesthetic Systemic Toxicity (LAST).	Exercise caution; monitor for signs of CNS or cardiac toxicity.
Bupivacaine + Erythromycin / Clarithromycin	Theoretical inhibition of CYP3A4-mediated bupivacaine metabolism (limited clinical data).	Elevated anesthetic levels; potential for prolonged systemic exposure.	Monitor patient closely or select an alternative anesthetic.
Prilocaine + "Oxidizing Agents" (Acetaminophen, Sulfonamides)	Metabolism into o-toluidine oxidizes hemoglobin to methemoglobin.	Induction of methemoglobinemia (reduced blood oxygen-carrying capacity).	Avoid in patients with anemia, respiratory failure, or those on high-dose oxidizing therapy.
Epinephrine + Non-selective Beta-blockers	Blockade of β2-vasodilation allows unopposed α-adrenergic vasoconstriction.	Risk of hypertensive crisis and reflex bradycardia.	Limit dose to max 2 cartridges (1:100,000); monitor vitals for 5 minutes post-injection.
Epinephrine + Tricyclic Antidepressants (TCAs)	Potentiation of sympathomimetic effects.	Significantly increased risk of acute hypertension.	Use the lowest effective dose of epinephrine-containing anesthetic.
Epinephrine + Antipsychotics (e.g., Phenothiazines)	"Epinephrine Reversal": α1-blockade leaves β2-vasodilation unopposed.	Paradoxical hypotension has been reported.	Use minimum epinephrine concentration or vasoconstrictor-free 3% mepivacaine.

3.4. Pharmacovigilance and ADRs

Studies have shown that dentists have a lower level of pharmacovigilance compared to other healthcare professionals [74]. Global data indicate that the widespread under-reporting of adverse events is mainly due to a lack of institutional knowledge about standardized protocols. The efficacy of drug safety surveillance is fundamentally limited by the underreporting of ADRs. Systematic reviews [74,75]

indicate that sociodemographic factors have negligible influence compared to specific professional knowledge gaps and psychological attitudes, often categorized as Inman's "seven deadly sins" of reporting. The most prevalent barrier is ignorance, with up to 95% of studies showing clinicians incorrectly believe that only serious or proven ADRs require reporting. This is exacerbated by lethargy (77–84.6%), involving procrastination or perceived lack of time, and complacency (46–47%), the false belief that only safe drugs are permitted on the market. Psychological obstacles such as diffidence (fear of appearing unprofessional; 44.6–72%) and insecurity (difficulty in establishing causality; 33–67%) further suppress reporting rates [75,76]. Emerging factors like the non-obligatory nature of reporting and confidentiality concerns also contribute to the deficit. Despite these being modifiable factors, these attitudes have remained largely static over the last decade, highlighting the urgent need for targeted educational interventions and improved feedback to clinicians. Additionally, bureaucratic hurdles and the perceived administrative burden of documentation serve as major deterrents. These issues are worsened by a general lack of pharmacovigilance literacy, where practitioners may not recognize the clinical and public health importance of reporting spontaneous ADRs [77,78].

4. Discussion

In this review, we demonstrate that the most common dental prescriptions are not always "low-risk" in the context of systemic co-morbidities and multi-drug use. The pharmacological profile of the modern dental patient suggests a significant, often overlooked, vulnerability in outpatient care.

The potential DDIs identified represent a spectrum of clinical risks. These risks can range from increased/decreased potency or longevity of certain drugs to serious emergencies, including malignant arrhythmias (QT prolongation), difficult to control hemorrhage, or hypertensive crises [24,27,28,41]. A study reported that the most prevalent drug interaction severity was grade 2: requiring monitoring or use with caution [79].

An important finding emerging from this review is the "Reporting Paradox." Despite dentists being responsible for approximately 10% of global antibiotic prescriptions, their contribution to Pharmacovigilance databases remains disproportionately low [10,11]. This study reveals that this is rarely due to a lack of adverse events, but rather a lack of pharmacovigilance literacy [74].

The low levels of reporting suggest that the dental community is a "blind spot" in global drug safety monitoring [74,77]. When dentists fail to report an ADR, it delays the identification of rare signals and prevents the updating of safety guidelines that protect the wider medical community. Serious and life-threatening drug interactions are not common, but underreporting limits and delays initiatives that could reduce the harmful effects of medications, many of which are potentially predictable and preventable.

4.1. Limitations

Despite the clinical relevance of the interactions discussed, this review has several limitations that should be acknowledged. First, as a narrative review, it lacks the formal systematic methodology and quantitative synthesis (meta-analysis) typical of systematic reviews, which may introduce selection bias.

Furthermore, this review is strictly limited to interactions between agents prescribed within dental practice and pharmacological therapies utilized by physicians for the management of chronic systemic conditions.

Notably, this analysis does not encompass potential interactions involving herbal supplements or holistic remedies. Furthermore, interactions involving opioid analgesics were excluded from this paper, reflecting recent clinical shifts that discourage the use of opioids in favor of non-narcotic alternatives for the management of dental pain. (Only potential interactions of methadone when used in treating addiction were mentioned.)

We do not address potential DDIs in patients utilizing illicit or non-regulated substances. Although the management of such patients requires specialized anesthetic and analgesic considerations, our primary objective of this study was to delineate interactions between conventional dental prescriptions and physician-managed systemic therapies.

4.2. Future outcomes

Data indicate a concerning global lack of attention to DDIs and pharmacovigilance. To address this, future efforts must focus on bridging the gap between pharmacological theory and clinical application. Increasing the prominence of these topics in professional discussions is essential. Furthermore, to ensure long-term patient safety, comprehensive training on drug interactions and adverse reporting must be embedded within the dental education system.

5. Conclusions

DDIs are present in dental settings, although dental practitioners operate within a relatively limited formulary, and this focused selection requires careful prescribing practices and monitoring. Common therapeutic agents used in dentistry exhibit diverse DDI profiles that must be meticulously evaluated prior to prescription. Most adverse interactions are preventable through comprehensive anamnesis and the proactive identification of patient-specific risk factors. To mitigate the risks identified in this review, we recommend that dental practitioners integrate clinical decision support tools into their daily workflow. Utilizing evidence-based platforms such as Lexicomp Online for Dentistry, Micromedex, and the NHS Specialist Pharmacy Service (SPS), Drugs.com enables real-time verification of DDIs at the point of care. Ultimately, the prescribing dentist bears responsibility for DDI screening. Moreover, adoption of helpful digital resources, alongside a heightened commitment to pharmacovigilance, is essential. Maintaining clinical safety requires continuous engagement with evolving pharmacological concepts and a robust commitment to pharmacovigilance; by prioritizing the reporting of ADRs, dental professionals can significantly enhance the collective understanding of drug safety. Moving forward, it is essential to implement targeted educational frameworks and clinical training focused on DDIs.

Use of AI tools declaration

The authors declare that no Generative-AI tools were used in the writing or creation of this manuscript.

Authors' contribution

A.S. and Adela A. conceptualized the scope and framework of the narrative review. A.S., A.K., and N.S. performed the systematic literature search, article screening, and data extraction. A.S. and

S.P. drafted the original manuscript, while E.H. and Adem A. critically revised the draft for important intellectual and scientific content. All authors participated in final editing, read, and approved the submitted version of the manuscript.

Conflict of interest

The authors declare no conflict of interest.

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