Review Article

An update on drug interactions involving anti-inflammatory and analgesic medications in oral and maxillofacial medicine: a narrative review

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Background and Objective: The management of pain has always been an integral aspect of the provision of high-quality dental care. Fortunately, the cornerstone dental pharmaceutical analgesics, such as non-steroidal anti-inflammatory drugs (NSAIDs), acetaminophen, and select opioids, have favorable drug profiles and are safe for use in healthy patients when prescribed according to dosage guidelines. Prudent clinicians must be aware of numerous crucial drug interactions associated with these common analgesics, as their severity can be influenced by the presence of various diseases. Particularly, with the increasing prevalence of polypharmacy and chronic diseases in the aging population, the risk of drug interactions is inherently higher, making it challenging to determine safe prescriptions. This article discusses the relevant drug interactions seen with the concomitant use of dental analgesics. Emphasis is placed on NSAIDs due to their common prescription and over-the-counter availability, non-addictive properties, and significant number and severity of interactions.

Methods: This narrative review utilized electronic databases including MEDLINE, PubMed, PubMed Central, Cochrane Library, and ScienceDirect as sources. Various study designs such as meta-analyses, systematic reviews, clinical trials, narrative reviews, case-control, cross-sectional, and case report studies were included. All articles were in English or translated to English.

Key Content and Findings: The search spanned from 1988 to 2021, with approximately 50% of the studies published between 2015 and 2021, and 25% published from 2018 to 2021. NSAIDs have been found to escalate lithium toxicity in a manner that is dependent on the dosage. It has been observed that no dosage of methotrexate appears to be clinically safe when used concurrently with NSAIDs. Acetaminophen, when combined with warfarin, causes an increase in international normalized ratio (INR) in a linear and dosage-dependent manner. Lastly, combining tramadol with serotonergic medications increases the risk of serotonin syndrome.

Conclusions: When developing pain management strategies, clinicians must consider the patient's pain level, comorbidities, current medications, and overall health. It is important to avoid prescribing NSAIDs to patients taking methotrexate, lithium, digoxin, and to those taking both a diuretic and an angiotensin converting enzyme inhibitor (ACEI) or angiotensin II receptor blocker. Alcoholics should not take acetaminophen without concurrent alcohol consumption, and certain opioids, namely meperidine, tramadol, and methadone, should not be used in combination with monoamine oxidase inhibitors or alcohol.

Keywords: Drug interactions; dentistry; analgesics; adverse effects; non-steroidal anti-inflammatory drugs (NSAIDs)

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Introduction

Background

Pain management is integral to ethical and judicious dental care. Sufficient intraoperative and postoperative analgesia can be accomplished with numerous medications, both individually and additively. As such, appropriate clinical judgement must consider the patient's degree of pain, comorbidities, current medication, and health status. To ensure the safe and efficacious prescription of anti-inflammatory and analgesic medications, a prudent clinician should be aware of pertinent potential adverse drug interactions. Put simply, drug interactions occur when the effect of one drug is altered by the concurrent consumption of another drug. Adverse outcomes occur for a variety of reasons, including when drugs have a similar mechanism of action, when the metabolism and excretion of one drug is delayed by the existence of the other drug resulting in heightened and prolonged blood concentrations, and when consumption of one drug affects a mechanism that protects against adverse effects caused by another drug (1).

Rationale and knowledge gap

The knowledge of adverse drug interactions will also allow clinicians to confidently prescribe medications necessary to combat moderate to severe pain. Currently there is limited data on the prevalence of adverse drug interactions involving analgesics prescribed by dentists, though this paper overviews multiple studies that indicate potential interactions with drugs commonly used in a dental setting. The last prominent review of this nature was written by Dr. Daniel Haas in 1999 (2). The utility of this review is the necessity for a contemporary update on the topic, utilizing novel literature amassed over the last 20 years, with a focus on the last 8 years.

Objectives

This literature review serves to identify common drug-drug and drug-alcohol interactions involving commonly prescribed and recommended anti-inflammatory and analgesic medications in oral and maxillofacial medicine. Included in this paper are succinct recommendations for avoiding potentially adverse effects from interactions, all of which are supported by contemporary literature. We present this article in accordance with the Narrative Review reporting checklist (available at https://fomm.amegroups.com/article/view/10.21037/fomm-22-70/rc).

Methods

Sources included in this narrative review were found from electronic databases, including MEDLINE, PubMed, PubMed Central, Cochrane Library, and ScienceDirect. Meta-analyses, systematic reviews, clinical trials, narrative reviews, case-control, cross-sectional, and case report study designs were included in this narrative review. The search period ranged from 1988 to 2021, with roughly 50% of included studies being published from 2015 to 2021, and 25% of included studies being published from 2018–2021. Please see *Table 1* below.

Non-steroidal anti-inflammatory drugs (NSAIDs)

NSAIDs have long been utilized in dentistry for their efficacious analgesic, antipyretic and anti-inflammatory properties (1). NSAIDs have numerous interactions with other medications that are pertinent in dentistry. In general, these interactions stem from the inhibition of prostaglandins (PGs) and thromboxane production, which directly or indirectly affect the mechanism of action of other medications (3). Additionally, NSAIDs are highly protein bound drugs that demonstrate the ability to displace other highly protein bound drugs (4). This resultantly affects the displaced drug's effective plasma concentration, and subsequently their volume of distribution (4). The drugs that interact with NSAIDs used in dentistry include most antihypertensives, lithium, anticoagulants, selective serotonin reuptake inhibitors (SSRIs), methotrexate,

Table 1 The search strategy summary

Items	Specification
Date of search	January 2022
Databases and other sources searched	MEDLINE, PubMed, PubMed Central, Cochrane Library and ScienceDirect
Search terms used	"Acetaminophen", "NSAIDs", "opioids", "toxicity", "drug interactions", "dentistry", "adverse effects", "analgesics"
Timeframe	1988–2021
Inclusion criteria	Human studies
	Meta-analyses, systematic reviews, clinical trials, narrative reviews, case-control, cross-sectional, and case reports were all included
	No language restrictions: all translated to English
Selection	Completed independently by Dunbar D

NSAIDs, non-steroidal anti-inflammatory drugs.

ethanol, digoxin, cyclosporin A (CSA), other NSAIDs, acetaminophen, some herbal medications, sulfonylureas (SUs), and carbonic anhydrase inhibitors.

NSAIDs and antihypertensives

To properly understand the interaction between NSAIDs and certain antihypertensive medications, we must investigate the impact of PGs on renal physiology. Of the many PGs, PGE_2 and prostacyclin (PGI_2), are the most pertinent to renal function, as they play an important compensatory role in patients with reduced renal perfusion (3). In fact, the compensatory nature of these PGs makes them invaluable for patients with diminished renal capacity, as seen in elderly, diabetic and hypertensive patients (5). Additionally, since hypertension and renal disease are mutually causal in nature, any patient taking antihypertensive medication should be assumed to be reliant on these PGs for renal homeostasis (5).

Prostacyclin and PGE_2 have intrinsic antihypertensive properties (6). Since both are potent vasodilators, their action on the afferent arterioles of the nephron causes an increase in renal blood flow and subsequently glomerular filtration rate (GFR) (7). PGE_2 also elicits a natriuretic effect at the thick ascending loop of Henle, likely through inhibition of the sodium-potassium-chloride ion cotransporter (NKCC-2) (3,6,8). Furthermore, both PGs are responsible for the COX-2 dependent paracrine-mediated activation of the renin-angiotensin-aldosterone system (RAAS) in response to low tubular sodium ion concentration (8-11). To elaborate, in the macula densa of the juxtaglomerular apparatus, when sodium levels are low or the NKCC-2 transporter is inhibited, COX-2 expression is elevated (6,11). COX-2 will then stimulate the production and release of prostacyclin and PGE_2—which will act on EP_2 and EP_4 receptors of the juxtaglomerular cells, thus stimulating renin release (11,12). Angiotensin converting enzyme inhibitors [ACEIs; e.g., captopril (gen.)/capoten (tr.), enalapril (gen.)/innovance (tr.)], angiotensin receptor blockers [ARBs; e.g., losartan (gen.)/cozaar (tr.), olmesartan (gen.)/olmetec (tr.)], and diuretics [furosemide (gen.)/Lasix (tr.)] all significantly increase the expression of COX-2 in this region (*Figure 1*), thus serving as the basis for the interaction (11). Beta blockers [atenolol (gen.)/tenormin (tr.), metropolol (gen.)/betaloc (tr.)] also stimulate prostacyclin production, though this is believed to occur in extrarenal blood vessels (13). Notably, antihypertensives with no mechanism related to PG function—such as calcium channel blockers like nifedipine [adalat (tr.)]—do not exhibit any worrisome interaction with NSAIDs. In fact, in a population of elderly patients, administration of indomethacin raised the blood pressure for patients taking ACEIs, and not to those taking amlodipine or felodipine (9). However, in patients reliant on COX-2 mediated regulatory mechanisms, the administration of NSAIDs is relatively contraindicated, as it will negate the beneficial antihypertensive effects of prostacyclin and PGE_2. This interaction does exhibit heterogeneity in its response, even in healthy patients. A longitudinal cohort study of patients with ankylosing spondylitis found that long-term continuous NSAID use was associated with a 12% increased risk for hypertension (14). Despite this, only 129 of the

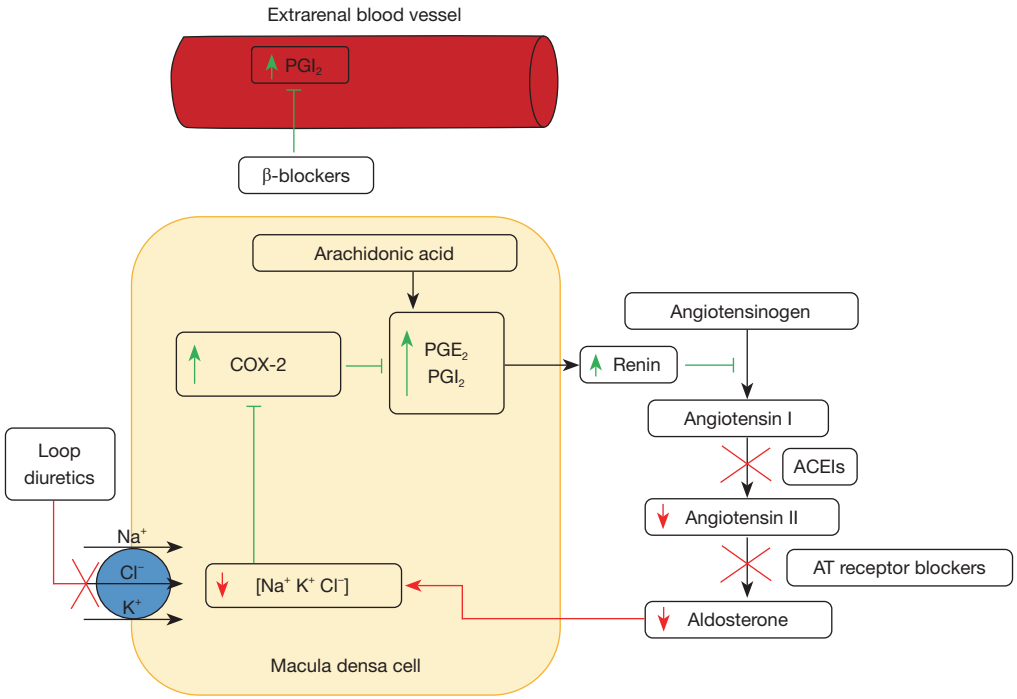

Figure 1 Macula densa cells located in the distal convoluted tubule of the nephron are an important part of the juxtaglomerular apparatus. The role of the macula densa is to monitor tubular [NaCl] with the goal of determining blood pressure dynamics via ion concentration. Importantly, [NaCl] in the macula densa can become reduced by ACEIs and ARBs due to reduced aldosterone production, and by diuretics via inhibition of the NKCC-2 cotransporter. If tubular [NaCl] is low, COX-2 expression increases, resulting in PGE_2 and prostacyclin production. These PGs are released from the cell and act on the nearby juxtaglomerular cells, triggering them to release renin. Without inhibition further on in the RAAS cascade, this renin production could act to increase blood pressure. However, if ACEIs or ARBs block the production or action of ATII, the potential hypertensive effects of these PGs are eliminated. In this case, the produced PGs are uninhibited in their vasodilatory and natriuretic properties, thus reducing blood pressure. Additionally, beta blockers stimulate the release of prostacyclin in extrarenal blood vessels, thereby contributing to the vasodilatory response. NaCl, sodium chloride; ACEIs, angiotensin converting enzyme inhibitors; ARBs, angiotensin receptors blockers; NKCC-2, sodium-potassium-chloride ion cotransporter; COX, cyclooxygenase; PGs, prostaglandins; PGE_2, prostaglandins E2; RAAS, renin-angiotensin-aldosterone system; ATII, alveolar type II epithelial cell; PGI_2, prostaglandins GI 2; AT, alveolar epithelial.

200 participants with normotensive baselines that were continuously taking NSAIDs developed hypertension at the 7-year follow-up (14).

Loop diuretics, including furosemide, primarily reduce blood pressure by reducing blood volume—this is accomplished through the inhibition of the NKCC-2 cotransporter, decreasing reabsorption of Na^+ and Cl^- and thereby increasing ion and water excretion in the urine (15). Inhibition of the NKCC-2 increases the expression of COX-2 in the macula densa (*Figure 1*), thus producing PGs to stimulate compensatory renin release (6,11). Specifically, prostacyclin secretion was demonstrated to be enhanced following administration of loop diuretics *in vivo* (16), and the use of the non-selective NSAID, indomethacin, blocked furosemide's vasodilatory effect (15). The significance of this secondary vasodilatory effect should not be underscored, since NSAIDs have been shown to reduce the response to loop-acting diuretics by as much as 20% (9).

ACEIs, including enalapril, primarily lower blood pressure by inhibiting the creation of angiotensin II—a potent vasoconstrictor and stimulator of antidiuretic hormone (ADH) and aldosterone. ARBs have a similar effect, except they prevent angiotensin II from binding to its receptors, rather than inhibit its production. When NSAIDs are used concurrently, the resultant inhibition of PG production causes a reduction in GFR and natriuresis

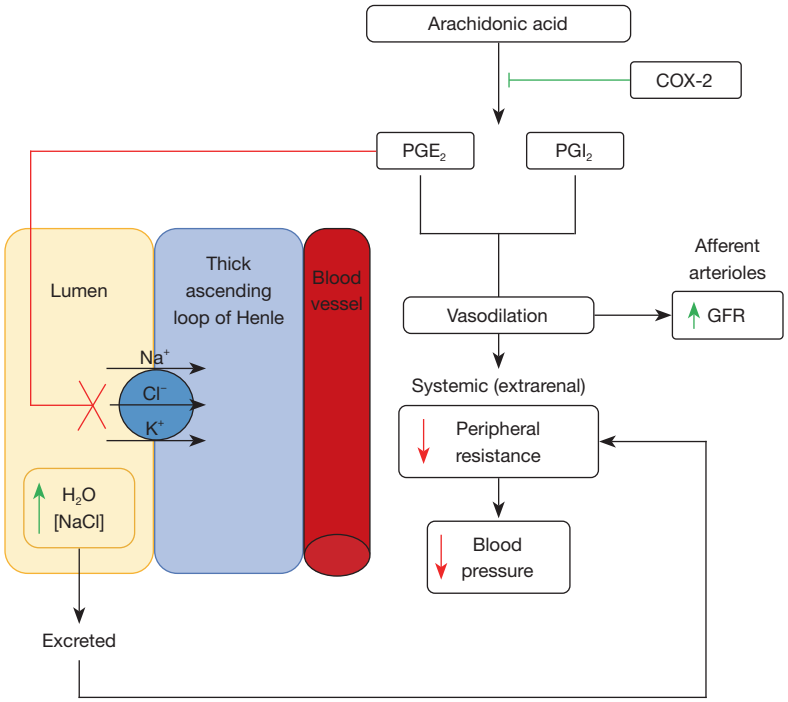

Figure 2 This diagram outlines some of the antihypertensive effects of renal PGs. Upon COX-2 expression, arachidonic acid is converted into PGE_2 and prostacyclin. PGE_2 inhibits the NKCC-2 cotransporter at the thick ascending loop of Henle, thus increasing the luminal H_2O and [NaCl], resulting in increased fluid excretion in the urine. Additionally, both PGE_2 and prostacyclin are vasodilators. When acting on extrarenal blood vessels, these PGs aid in decreasing peripheral resistance and thus decrease blood pressure. When acting on the afferent arteriole of a nephron, these PGs increase renal blood flow, and thereby increase GFR. When an NSAID is used, these effects are blocked; reabsorption of sodium ions increases water reabsorption and decreases fluid loss, peripheral resistance is not decreased, and GFR is reduced—especially in those with reduced renal perfusion. It is also important to mention that prostaglandin related renin production can also result in increased angiotensin II synthesis and activity (if uninhibited by ARBs or ACEIs), thus countering the systemic antihypertensive effect of prostaglandin mediated vasodilation. However, this hypertensive effect of prostaglandin synthesis helps increase renal perfusion, therefore aiding in afferent arteriole vasodilation in increasing GFR. Consequently, the effects of NSAIDs are not only influential in blood pressure modulation, but also in lithium excretion, which decreases with reduced GFR and increased tubular reabsorption. COX, cyclooxygenase; PGE_2, prostaglandins E2; PGI_2, prostaglandins GI2; GFR, glomerular filtration rate; NaCl, sodium chloride; PG, prostaglandins; NKCC-2, sodium-potassium-chloride ion cotransporter; NSAID, non-steroidal anti-inflammatory drug; ARBs, angiotensin receptors blockers; ACEIs, angiotensin converting enzyme inhibitors.

(*Figure 2*). The clinical manifestation is significant, as the hazard ratio for hypertension intensification was 4.09 and 3.62, respectively, for ACEIs and ARBs when combined with NSAIDs (17).

Importantly, there is a significantly increased risk of acute kidney injury (AKI) when combining NSAIDs with a diuretic and either an ARB or ACEI—dubbed the '*triple whammy*' (18). Notably, a retrospective cohort study involving almost 500,000 people using antihypertensive medications found that the triple whammy effect increased the risk of AKI by 31% (19). Furthermore, the effect was most profound during the first thirty days of concomitant use (18,19). This is extremely worrisome, since patients admitted to the hospital due to AKI that require dialysis have a mortality rate greater than 50% (19,20). Interestingly, double therapy between NSAIDs and ARBs or ACEIs did not result in significant renal injury. Thus, the vasoconstrictive effects of PG inhibition, in addition to the hypovolemic state caused by diuretics, results in a catastrophic reduction in GFR that precipitates the observed AKI (19). Crucially, NSAIDs, regardless of short duration, must be avoided in patients concurrently taking a

diuretic and an ARB or ACEI.

Beta blockers, such as propranolol, do not interact with NSAIDs in the same manner as the other antihypertensive medications. The literature indicates that beta blockers induce prostacyclin release in extrarenal blood vessels, thus leading to vasodilation (13). Unfortunately, the literature contains mixed results regarding this interaction. One study demonstrated that flurbiprofen attenuates the antihypertensive effect of propranolol, but another randomized controlled trial found no significant effect with prescription-strength ibuprofen (1,17). That said, the 3-week combination of ibuprofen, diuretics and β-blockers resulted in an increase in mean arterial pressure of 5.8 mmHg (17). While further research is needed, it would be wise to avoid or reduce the dosage of NSAIDs with beta-blockers, specifically in patients who have reduced renal perfusion.

Lithium and NSAIDs

Lithium has been the gold standard medication for treating bipolar affective disorders for over 50 years (21,22). Despite its benefits, lithium has a narrow therapeutic window—0.7 mmol/L wide—meaning relatively minor increases in plasma levels can result in significant adverse effects (22). Common sequalae include nausea, vomiting, diarrhea, tremors, and more rarely, sedation, ataxia, and cognitive impairment; significant toxicity can result in coma and death (23). Lithium is not metabolized and is eliminated almost completely by the kidney (21). Moreover, lithium's clearance is highly dependent on GFR and tubular reabsorption—which occurs in a very similar manner to sodium (21). This context is important when understanding the association between increased serum lithium levels and increasing age, decreasing sodium concentration, and decreasing GFR.

Diuretics, ACEIs, ARBs, and NSAIDs have all been associated with increased lithium plasma levels and lithium toxicity (21-24) Moreover, the magnitude of the observed increase is directly related to the degree of polypharmacy (22). According to a 2020 study investigating over 500 patients, those taking one, two or three of the aforementioned interacting drugs displayed 16.9%, 57.9%, and 62.5% higher lithium levels, respectively, when compared to controls (22). Crucially, the study also identified that only NSAIDs raised lithium serum levels independently of other contributing factors such as age, sex, renal function, and sodium concentration (22). The average increase in serum lithium concentration was 0.121 mmol/L ($P<0.0001$), which is ~17% of the therapeutic window, making it a significant interaction (22). Another cautionary finding of the study was that all NSAIDs, even low-dose acetylsalicylic acid (ASA), were associated with increased lithium levels (22). However, further research is needed to properly establish the relationship of low-dose ASA and elevated lithium concentration, as past research indicated only moderate to high dose NSAIDs were contributory (23).

A limitation of the 2020 study was that it was retrospective in nature, and thus cannot establish a causal link. That being said, there are a couple mechanisms that could explain NSAIDs association with increased lithium concentration. Firstly, reduced renal blood flow due to a blockade in the PG-mediated vasodilatory effect on the afferent arterioles—as outlined in *Figure 2*—will reduce GFR and subsequently diminish lithium excretion (22). Secondly, lithium reabsorption could take place via the same transporters as sodium, which is then modulated by PGE_2 (22).

While in the past, research was deemed insufficient to advise any clinical recommendations pertaining to NSAID administration with lithium users, recent research indicates otherwise. Although NSAIDs are generally prescribed for short periods in dentistry, one study found that the interaction occurs in the first days after coadministration (23). That said, the risk is heightened with higher doses and longer treatment regiments (23). Overall, it is most responsible that NSAID use should be avoided in patients taking lithium due to the concerning risk for toxicity. The avoidance of prescription is imperative when the patient has other associated risk factors, including increased age, diabetes, renal disease, and polypharmacy related to the 'triple whammy' antihypertensive medications.

NSAIDs and anticoagulants

Upper gastrointestinal (GI) bleeding is a significant adverse effect related to chronic NSAID use, especially in the elderly population (25). In fact, the risk for fatal peptic ulcers and associated bleeds increased three to five-fold in older adults chronically taking NSAIDs (25). In the United States alone, it is estimated that complications from NSAID-related peptic ulcers manifest in roughly 3,300 deaths annually (25). The mechanism of this serious adverse effect is multifactorial. First, NSAID inhibition of COX-1

in the GI tract diminishes the subsequent production of PGs, which serve an important cytoprotective role in the gastric mucosa. This results in dyspepsia, leading to an increased risk for peptic ulcer formation. Moreover, there is additional susceptibility to bleeding due to NSAIDs inhibition of COX-1 by-product, thromboxane—a PG that induces platelet formation (26). While non-specific NSAIDs like ibuprofen and naproxen caused the highest degree of gastric bleeding, selective COX-2 inhibitors still resulted more gastric bleeding than NSAID nonusers (27). A possible explanation for this observation could be related to COX-2 inhibitor-mediated alterations of gut microbiome or the generation of free radicals (28). Notably, rates of GI bleeds were significantly higher in patients taking aspirin, in comparison to ibuprofen (1). Regardless, the inherent risk of bleeding from NSAIDs makes it understandable that the risk for GI bleeding is further heightened in patients who concomitantly consumed oral anticoagulants, like Warfarin (27,29). In fact, the risk for major bleeding increases 2- to 4-fold in patients combining antiplatelet therapy with warfarin (27). New oral anticoagulants, like edoxaban, when taken with high dose ASA, low dose ASA or naproxen showed a 2-fold increase in bleeding time; this was an additive effect (30). That pharmacokinetic interactions were unaffected, and concomitant administration of edoxaban and ASA or Naproxen was well tolerated (30). Overall, some degree of caution should be taken before prescribing NSAIDs to patients taking new oral anticoagulants, and serious caution should be taken with patients taking vitamin K antagonist anticoagulants.

Oral anticoagulants represent one of the most encountered classes of drugs seen in patients in a dental practice, especially amongst the elderly population (27). Since the risk of significant upper GI ulceration and bleeding is heightened in elderly patients taking NSAIDs and anticoagulants, and that NSAIDs are easily available over the counter, it is prudent to consider modifications to therapy or the use of adjunctive medications in this population. Primarily, patient education regarding the risk for bleeding is imperative and should be the first step in this process. Secondly, if NSAIDs are necessary, a clinician should consider the use of a selective COX-2 inhibitor over a non-specific NSAID, with aspirin being the least attractive candidate. That said, since COX-2 inhibitors have their own cardiotoxic effects, it may be wise to choose for a semi-selective COX-2 inhibitor. Namely, drugs such as diclofenac—whose inhibition of COX-2 is three-fold of its inhibition of COX-1—would be a great alternative as it is associated with minimal GI toxicity and elicits less severe cardiotoxic effects than strongly selective COX-2 inhibitors (31). Further, the NSAID should be prescribed for the shortest duration possible, as the increased risk for bleeding can occur within the first month of chronic use (25). If the patient requires long-term anticoagulant-NSAID treatment, or if the patient has a history of or is at high risk for gastric ulcers, a proton pump inhibitor (PPI) or PG analogue can be prescribed. In support of these recommendations, a 2017 case-control study found that in comparison to those taking conventional NSAIDs, patients taking COX-2 NSAIDs with a PPI, patients taking COX-2 inhibitors alone, and patients taking conventional NSAIDs with a PPI, experience a risk reduction of GI perforation, ulcers, or bleeding of 49%, 34%, and 21%, respectively (28). Additionally, two systematic reviews determined that there is reduced risk of gastric ulcers between 74% and 91% in patients taking COX-2 inhibitors with a PPI compared to those taking conventional NSAIDs alone (32,33)—many observational studies also support these findings (28). Moreover, the daily prescription of 800 µg (200 µg QID) PG E1 analogue, misoprostol, in patients chronically consuming NSAIDS results in a 40% reduction in serious GI complications (4). While misoprostol must be avoided in the potentially pregnant population due to strong abortifacient effects, it can be a useful adjunct to NSAID therapy in patients that are elderly, have a history of GI ulceration and bleeding, are taking NSAIDs chronically, are undergoing anticoagulant therapy, or a combination of the listed risk factors.

SSRIs and NSAIDs

In line with the previous interaction, SSRIs are associated with an increased risk of upper GI bleeds (34). While past conclusions from a relatively small number of studies indicated SSRIs were related to a substantial increased risk of upper GI bleeding, a 2014 meta-analysis determined that the true observed effect is rather small (34). However, the same meta-analysis—which included just under 400,000 individuals from fifteen case-control studies and four cohort studies—determined a significant increased risk of upper GI bleeding with the concurrent use of SSRIs and NSAIDs. The mechanism of this interaction could be explained by the potent inhibitory action that some SSRIs have on the CYP P450 enzymes that metabolize

Table 2 A summary of the key adverse drug interactions with NSAIDs in a dental setting

Drug	Interaction	Considerations and Recommendations
Antihypertensives (ACEIs, ARBs, diuretics, β-blockers)	Blockade of antihypertensive-induced prostaglandin production. Reduces GFR, increases blood pressure	Short-term (<4 days) combination if necessary. *Never give NSAID if taking both diuretic and either an ACEI or ARB*. Avoid in elderly. Monitor BP
Lithium	Increased serum lithium levels significantly, independent of other factors	*Avoid use*, especially in *elderly patient or patients* taking renal-affecting medications (antihypertensives)
Anticoagulants (Warfarin)	Increased risk for upper gastrointestinal bleeding. Risk ranking: aspirin > COX-1 > COX-2	*Avoid combination*. If necessary, use selective COX-2 inhibitor with gastroprotective medication (proton pump inhibitor or misoprostol in non-pregnant patients)
SSRIs	Increased risk for upper gastrointestinal bleeding	Short duration (*<4 days*) if healthy. Potentially avoid use or combine with gastroprotective medication in high-risk populations
Methotrexate	Increased risk for cytopenia and acute renal failure regardless of methotrexate dose. Aspirin does not interact; celecoxib has minimal clinical interaction	*Avoid use*. If necessary, consider use of aspirin or celecoxib in a reduced dose
Digoxin	Digoxin peak concentration increased; steady state not affected. Minimal observed affect on toxicity, though narrow therapeutic window concerning	Avoid long term combination. Avoid in patients with reduced renal perfusion. Monitor carefully
Ethanol	Synergistic increase in risk of upper GI bleeding. Aspirin most significant	Avoid combination, if possible. Otherwise, minimize dose and duration
HMs	Increased risk of bleeding	*Inquire about HMs*. Avoid combination of select HMs
Sulfonylureas	Aspirin potentiates hypoglycemia in long term combination	Avoid long term use. Monitor glucose levels
CAIs	Aspirin inhibits carbonic anhydrase II. CAIs increase aspirin half-life	Avoid combination, if possible
Aspirin	NSAIDs with Aspirin increases risk of thrombotic events	Avoid concurrent use, when possible. Take NSAID 8 hours prior or 30 min after aspirin

NSAIDs, non-steroidal anti-inflammatory drugs; ACEIs, angiotensin converting enzyme inhibitors; ARBs, angiotensin receptors blockers; SSRIs, selective serotonin reuptake inhibitors; CAIs, carbonic anhydrase inhibitors; GFR, glomerular filtration rate; COX, cyclooxygenase; GI, gastrointestinal; BP, blood pressure; HM, herbal medications.

NSAIDs (35). SSRIs also exhibit inherent antiplatelet properties, which is a product of the inhibition of serotonin-regulated expression of surface receptors required for platelet aggregation (36). To elaborate further on the severity of the interaction, patients taking both SSRIs and NSAIDs had an odds ratio of bleeding of 4.25 in comparison to controls (34). Additionally, in a low-risk population, the number needed to harm (NNH) was 3,177, while the NNH in a high-risk population was 881 (34). That said, a second meta-analysis utilizing an overlapping but not identical data set determined that the previously mentioned NNH of 881 may not accurately represent the highest risk group: those who have experienced a GI bleed within the last year (35). Therefore, a prudent clinician would consider modifying NSAID therapy by reducing the dose and duration or by adding an adjunctive gastroprotective medication for these patients, especially in the higher risk populations such as the elderly and those with a history of GI bleeding (35). Alternatively, for moderate to severe pain, acetaminophen in combination with an opioid can be used for pain management. Please see *Table 2* for a summary of the key drug interactions with NSAIDs.

Methotrexate and NSAIDs

Methotrexate is a chemotherapeutic and immunosuppressive medication, commonly prescribed for cancer therapy in higher doses (>1 g per dose) and rheumatoid arthritis

in lower doses (5–25 mg weekly) (37,38). Similar to the interaction between lithium and NSAIDs, NSAIDs affect methotrexate serum levels through the inhibition of the renal excretion of methotrexate. While methotrexate is partially metabolized in the liver, over 80% of the drug is excreted in the urine unmetabolized (39). The mechanism of interaction is multifactorial. In part, the interaction is a result of the blockade of the PG-mediated increase in GFR (*Figure 2*) and competition for protein binding sites (37). However, these play only a minor role in comparison to the primary pharmacokinetic source of the interaction: certain NSAIDs reduce the tubular secretion of methotrexate through competitive antagonism at the renal organic anion transporter 3 (OAT3) (37). Pharmacokinetic *in vitro* and *in vivo* studies determined that most NSAIDs demonstrated competition at OAT3 in a concentration-dependent manner; aspirin and acetaminophen did not show any inhibition (40). However, while celecoxib showed an interaction *in vitro*, *in vivo* studies showed it does not cause significant inhibitory effects at clinical doses (25). Other NSAIDs, including ibuprofen, naproxen, etoricoxib, and sulindac, have therapeutic concentrations which can cause significant renal effects on the tubular excretion of methotrexate (37,39,40).

In the past, it was believed that the interaction between NSAIDs and methotrexate was only significant with high doses of methotrexate—which was associated with severe interactions, including renal failure and pancytopenia (2). Contrastingly, past literature also suggested that no modifications to NSAID consumption was necessary in patients taking low dose methotrexate for rheumatoid arthritis or psoriasis (7). This recommendation may require reconsideration as there have been conflicting results in case reports and pharmacokinetic studies (39). Furthermore, a 2018 prospective cohort study—which analyzed over 40,000 Danish citizens taking low-dose methotrexate either alone or in combination with NSAIDs for rheumatoid arthritis—found that compared to patients not taking NSAIDs, those taking NSAIDs and low-dose methotrexate concomitantly were associated with a 40% increased risk of any serious adverse event, including a 35% increase for cytopenia and 104% increase for acute renal failure (39). While more research may be needed in the future, this study demonstrated stronger evidence than past conflicting studies, as this study had a large sample size, assessed the concomitant use from the beginning of treatment, and controlled for confounders with rigorous exclusion criteria and adjusted statistics (39). Thus, the recommendation for avoidance of co-prescription of NSAIDs with methotrexate should potentially be advised regardless of methotrexate dose.

NSAIDs and ethanol

Alcohol consumption alone has been associated with an increased risk for upper GI bleeding, particularly as a secondary result of gastric peptic ulcers (41). The risk of GI bleeding increases in a linear relationship with alcohol consumption (41). In fact, the multivariable relative risk of men who consume two alcoholic drinks (30 g) daily is 1.43 compared to non-consumers, even after adjusting for other contributory factors such as anticoagulant therapy, SSRIs, and comorbid diseases (41). The impetus of this association could be related to several alcohol-mediated gastrodestructive effects, including exfoliation of gastric epithelium, hemorrhagic damage of the microvasculature, and necrosis of deep tissue layers (41,42). The mechanism causing these effects could be derived from an overproduction of oxygen free radicals and decreased protective PG synthesis (41,42). Since both alcohol and NSAIDs independently increase the risk of upper GI bleeding, it is unsurprising that taking both drugs concomitantly heightens the risk for bleeding even further. However, this effect is synergistic, meaning the risk with combination of both drugs is more than the multiplication of the risks of bleeding with each drug taken on their own (1,43). Notably, the most significant increase occurred with the combination of aspirin and alcohol (43). Thus, it is advisable to avoid the combination of NSAIDs, especially aspirin, with daily alcohol intake; patient education should be the primary focus since both drugs are available without prescription.

NSAIDs and digoxin

Digoxin is a cardiac glycoside that is commonly used to treat many cardiac issues, including atrial fibrillation, congestive heart failure, and select cardiac arrhythmias (44). In congruence with lithium, digoxin is excreted primarily by the kidneys and has a narrow therapeutic window (2). Thus, NSAIDs can potentially affect digoxin clearance through its negative effect on renal function, with special consideration for those with reduced liver and kidney function, such as the elderly population (44,45). NSAIDs

have been associated with increased plasma digoxin levels (45). In fact, concomitant consumption of digoxin with 120 mg of etoricoxib increased peak digoxin concentration by 33%, though digoxin plasma steady state was not affected (46). The latter point is important since digoxin toxicity is associated with increased steady state, not peak levels (46). Therefore, in an otherwise healthy patient, NSAIDs should not clinically affect digoxin toxicity, though caution and monitoring are recommended. In patients with reduced renal perfusion, as seen in the elderly, diabetics, and hypertensive patients taking one or more antihypertensive medications, NSAID prescription should be avoided.

NSAIDs and cyclosporin

CSA is an immunosuppressive medication used for autoimmune disorders and transplant rejection therapy. CSA, despite its utility, has several established nephrotoxic, neurotoxic, and cardiotoxic effects (47). Past literature provided evidence that non-selective NSAIDs, including sulindac, naproxen, diclofenac, and indomethacin, caused additive renal deterioration and an increased risk of hypertension when combined with CSA (47,48). Recent literature agrees with this observation but determined that selective COX-2 inhibitors did not cause increased risk of impaired renal function if concurrently consumed with CSA (47). However, the severity and conclusiveness of the interaction, as well as the identification of robust explanatory mechanisms, still require further research. Thus, no concrete recommendations can be provided, but it is advisable to monitor for symptoms of toxicity with concurrent use.

NSAIDs and other NSAIDs or acetaminophen

Despite their positive utility, NSAIDs can be nephrotoxic, cardiotoxic, and gastrotoxic, especially when they are combined with other NSAIDs, used chronically, taken in high doses, and used by vulnerable patient populations. Specifically, NSAID-mediated COX-2 inhibition in the kidney blocks the important previously mentioned effects of renal PGs, especially in patients with reduced renal perfusion (3). Additionally, COX-1 inhibition significantly increases the risk of fatal GI hemorrhages, normally following peptic ulcer formation (26). Moreover, chronic COX-2 inhibition has been associated with an increased risk for myocardial infarcts (49). Since all these outcomes are dependent on dose, it is intuitive that avoidance of high doses, whether due to one NSAID or the combination of multiple NSAIDs, should be avoided, especially with chronic use. Due to their identical mechanism of action, combining NSAIDs does not increase efficacy, and only serves to increase risk for toxicity. It is therefore unsurprising that the coprescription of NSAIDs is not recommended and minimizing duration of use is of equal importance.

Coadministration of NSAIDs with aspirin results in competitive antagonism at the acetylation site of COX-1 on platelets (1). The reversible binding of non-selective NSAIDs inhibits the irreversible action of aspirin. This potentially allows for platelet aggregation, leading to an unwanted thrombotic event (1). This interaction is significant, as a case-control study found that coadministration of ibuprofen with prophylactic aspirin (combined at least 4 times a week) doubled the risk for a myocardial infarction compared to patients that did not take ibuprofen (1). However, other studies indicate the opposite effect is true. The Food and Drug Administration (FDA) recommends that ibuprofen should be taken either more than 8 hours prior to or at least 30 minutes following the consumption of immediate-release aspirin to reduce the risk of a thrombotic myocardial event (50). Aspirin and acetaminophen should not be coprescribed chronically, though they should not pose any significant problems if the duration is less than 5 days—as seen in dentistry (2).

NSAIDs and herbal medications

Non-selective NSAIDs—especially aspirin due to its irreversible action at COX-1—have the potential to interact with herbal medications that are known to affect platelet aggregation (ginkgo, garlic, ginger, ginseng, turmeric, meadowsweet, bilberry, dong quai, and willow) and vitamin K synthesis (chamomile, motherwort, horse chestnut, fenugreek and red clover) (51). The mechanism of interaction can be related to the inhibition of platelet activating factor (ginkgo), reduced thromboxane production (ginger, ginseng, dong quai, feverfew, turmeric), anthocyanin-mediated platelet inhibition (bilberry), or through salicylate-derived COX-1 inhibition (meadowsweet, willow) (7,51). Additionally, herbal medications that contain coumarin derivatives—chamomile, motherwort, and red clover—have anticoagulant properties through vitamin K antagonism (51). While some of these medications have

in vitro evidence supporting the interaction, conclusive clinical evidence has not been established; many drugs have no clinical examples of an interaction and other are limited to the occasional case report (51). Despite the necessity for future research, there are reasons for clinicians to be concerned about this potential interaction. Firstly, over 50% of patients seen in health care are taking complementary or alternative medicine (CAM), including the previously mentioned herbal medicines (7,23). Despite the high prevalence, only 30–40% of patients admit to their provider that they take CAM, though this statistic varies by the study (51,52). Additionally, since herbal medications do not require regulatory approval or premarketing research, the safety and efficacy of the product is uncertain. Moreover, lack of rigorous standardization and potential contamination make it questionable to how much of an active or secondary ingredient exists in an equivalent amount of a CAM (51). Between the lack of research, regulation, consistency and admittance of use, and the prevalence of usage in the average patient population, clinicians should be cautious when prescribing or advising NSAID use with the previously mentioned herbal medications. Importantly, clinicians should inquire with their patients about their use of herbal medications, and offer guidance regarding the potential risk of bleeding, especially in the elderly population.

Aspirin and oral hypoglycemics

SUs, such as glipizide, glimepiride, and glibenclamide, are a group of oral hypoglycemic medication that are commonly prescribed for the treatment of type II diabetes mellitus (53). Past literature has indicated that aspirin potentiates the hypoglycemic effect of SUs when taken concomitantly (53). This effect could be explained by several salicylate actions, including its inhibition of hepatic glucose production and strengthening of insulin action through kinase inhibition (54). Additionally, since SUs like glimepiride are more than 99% protein bound in plasma, and salicylates like aspirin displace highly protein bound drugs, aspirin possibly increases SU concentration directly through displacement, and consequently increases SUs volume of distribution (54). The severity of this interaction still requires further investigation. However, a 2014 study found that low dose aspirin monotherapy did not statistically significantly increase fasting blood glucose in rats until more than 15 days of concomitant use with glimepiride (54). Resultantly, it is prudent that clinicians ensure patients avoid long-term use of aspirin in patients taking SUs, and to monitor glucose levels closely if the drugs are taken together for any period.

Aspirin and carbonic anhydrase inhibitors

Carbonic anhydrase inhibitors, such as acetazolamide, are useful in the treatment of glaucoma, altitude sickness, and epilepsy (55). Past literature indicated that aspirin displaces acetazolamide from plasma proteins and inhibits renal clearance (2). Recent literature has not investigated these specific interactions, though other notable interactions have been identified. Importantly, aspirin has a short half-life of ~15 minutes due to its degradation into salicylic acid by a previously unknown carboxylesterase (55). However, a 2020 study concluded that carbonic anhydrase II (CAII) is this carboxylesterase, and that the salicylic acid by-product in turn inhibits CAII (55). Therefore, through this mechanism, aspirin can both potentiate the effect of carbonic anhydrase inhibitors, and carbonic anhydrase inhibitors can theoretically prolong the half-life of aspirin (55) This might be useful for the potential prospective coprescription of both drugs to minimize dosage. However, until this is further researched, it is best that clinicians avoid prescribing aspirin to patients on carbonic anhydrase inhibitors, as there are a multitude of interactions that could result in toxicity of either drug.

Clinical implications

In summary, the majority of the outlined interactions are useful to avoid medical emergencies and potentially negative health outcomes. Namely, NSAID prescription should be avoided in patients taking methotrexate, digoxin (long-term), or lithium, as they are at risk of life-threatening toxicity. That said, other interactions are not necessarily life threatening, but can impact the delivery of dental care. Patients that are taking an SSRI, an anticoagulant—especially vitamin K antagonists—, or certain herbal medications, will have an increased risk of intraoperative bleeding if they consume an NSAID preoperatively for pain management. In these cases, hemostatic measures should be considered, especially during surgical procedures like periodontal surgeries, wisdom tooth extraction, and apical surgery.

Acetaminophen

Acetaminophen (Tylenol or paracetamol) is one of the most common over the counter medications and is often

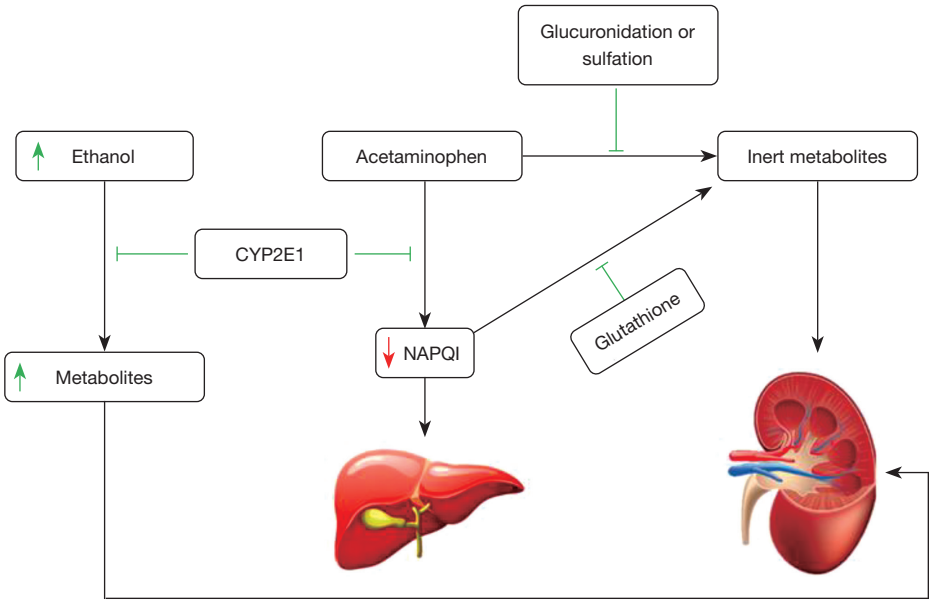

Figure 3 Ethanol outcompetes acetaminophen for CYP2E1, thus increasing acetaldehyde and acetate production and reducing NAPQI production. Rather, acetaminophen is conjugated by glucuronidation or sulfation. This phenomenon protects against hepatotoxicity. CYP2E1, cytochrome P450 2E1; NAPQI, N-acetyl-p-benzoquinone imine.

taken with other drugs such as NSAIDs and opioids (16). In dentistry, acetaminophen is a commonly utilized drug for the management of mild to moderate post-operative pain in all age groups due to its favourable risk-benefit ratio (56). Specifically, acetaminophen has potent analgesic and antipyretic properties, but does not cause the gastrotoxic and nephrotoxic effects seen in NSAIDs and salicylates (57). Additionally, compared to NSAIDs, the interactions between acetaminophen and other drugs are generally not impactful in a dental context, so long as dose regiments do not exceed the established guidelines. That said, it is important for clinicians to advise patients of not only the daily maximum of acetaminophen (4 g), but also of drugs that contain acetaminophen, as to avoid accidental overdose.

Metabolism and toxicity

Roughly 95% of consumed acetaminophen will be metabolized in the liver by phase II reactions, such as glucuronidation and sulfation (*Figure 3*) (56). The subsequent conjugated metabolites do not pose any toxic threats and are eliminated from the body by the kidney. The remaining 5% of acetaminophen is metabolized by phase I oxidation reactions, primarily involving the cytochrome P450 enzyme, CYP2E1 (57). The product of this reaction is N-acetyl-p-benzoquinone imine (NAPQI), a toxic metabolite capable of significant irreversible hepatotoxicity if allowed to accumulate (56). This hepatotoxicity can manifest in significant cell death, resulting in acute liver failure in as little as 24–36 hours post toxic ingestion (57). However, in a healthy individual, this hepatotoxicity is avoided as NAPQI is conjugated safely by glutathione. Since NAPQI can only cause damage in the absence of glutathione, the glutathione replenishing drug, N-acetylcysteine (NAC), can be administered as an antidote in cases of severe acetaminophen toxicity (57).

Acetaminophen and ethanol

The interaction between ethanol and acetaminophen is outlined in *Figure 3*. The primary basis for the interaction is that ethanol is also oxidized by CYP2E1. Beneficially, ethanol will compete for binding sites of CYP2E1, thereby reducing the amount of acetaminophen oxidation, which consequently diminishes toxic NAPQI production (58). The remaining acetaminophen will be conjugated through phase II reactions and safely excreted by the kidney. Therefore, in both alcoholics and healthy individuals, acetaminophen ingestion is safer when consumed with alcohol than without.

In chronic alcohol consumption, or alcoholism, the

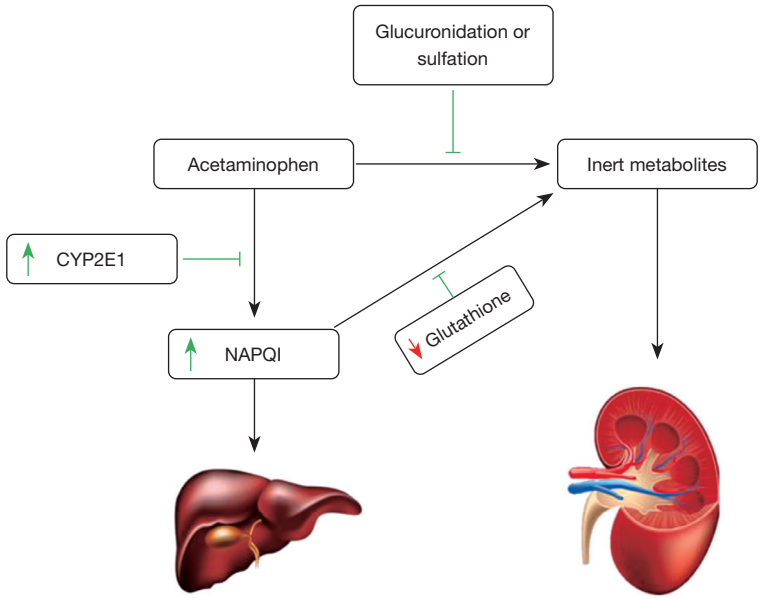

Figure 4 In alcoholism, CYP2E1 expression is increased and glutathione is decreased. Without ethanol present, acetaminophen is oxidized to NAPQI in higher proportions than normal, and there is less glutathione to conjugate the toxic metabolite. The rise in NAPQI has significant hepatotoxic effects; acute renal failure with the potential need for a liver transplant is a real possibility. CYP2E1, cytochrome P450 2E1; NAPQI, N-acetyl-p-benzoquinone imine.

potential for acetaminophen toxicity heightens. While ethanol competitively antagonizes acetaminophen at CYP2E1, it also induced CYP2E1 expression (58). Additionally, glutathione levels are reduced in alcoholism (59). Therefore, chronic alcohol intake both increases CYP2E1 and reduces glutathione. When an alcoholic consumes acetaminophen and ethanol concurrently, the non-hepatotoxic result is the same as before (*Figure 3*). However, if an alcoholic consumes acetaminophen without ethanol, CYP2E1 is both increased in amount and uninhibited, resulting in a significant increase in NAPQI (*Figure 4*). This toxic effect is even further enhanced by the diminished glutathione levels. Therefore, if an alcoholic must take acetaminophen, they should always concomitantly consume ethanol as well. In line with the label of Tylenol, it is best practice to consult with your primary care physician prior if one plans to consumer at least three alcoholic beverages per day while consuming acetaminophen.

While the exact risk of NAPQI toxicity is variable based on factors such as age, dose and duration of alcohol intake, dose of acetaminophen, and timing between consumption, clinician should exercise caution. As such, alcoholic patients should be encouraged to never consume acetaminophen without their regular ethanol intake, and the dose of acetaminophen should be reduced below the 4-gram daily maximum of a healthy patient. Please see *Table 3* for a summary of key adverse reactions with acetaminophen.

Acetaminophen and other drugs

While acetaminophen has some interactions with other medications, they are mostly not applicable in the dental setting. Specifically, phenytoin, phenobarbital, and cannabinoids all inhibit the enzyme uridine 5'-diphospho-glucuronosyltransferase (UGT), thus decreasing acetaminophen glucuronidation (60,61). Notably, a recent meta-analysis found that acetaminophen potentiates warfarin in a dose-dependent manner (20). The study found that the concurrent use of acetaminophen and warfarin resulted in a statistically significant increase in INR of 0.17 for each daily gram of acetaminophen ingested (20). While this increase may not appear significant, it is best that clinicians avoid the concurrent use of warfarin and acetaminophen.

Opioids

Opioids, such as codeine, oxycodone, and hydrocodone

Table 3 A summary of the key adverse drug interactions with acetaminophen in a dental setting

Drug	Interaction	Considerations and recommendations
Ethanol	Ethanol and acetaminophen are both metabolized by CYP2E1. During acute ingestion of both, competitive inhibition results in reduced acetaminophen metabolism, thus reducing rate of NAPQI production	Safe to ingest together if dose does not exceed 4 g per day. Other alcohol-specific hepatotoxic effects should be separately considered. *In alcoholics, acetaminophen should be consumed with typical alcohol intake*
Phenytoin, phenobarbital, cannabinoids	All inhibit the enzyme UGT. Decreases acetaminophen glucuronidation, thus reducing metabolism	Consider reducing dose of acetaminophen
Warfarin	Acetaminophen potentiates warfarin in a dose-dependent manner; INR increases in 0.17 per gram of acetaminophen ingested daily	*Best practice to avoid combination*. Short duration and low dose can be considered

CYP2E1, cytochrome P450 2E1; NAPQI, N-acetyl-p-benzoquinone imine; UGT, uridine 5'-diphospho-glucuronosyltransferase; INR, international normalized ratio.

(e.g., Vicodin, Norco, Lortab), are used in dentistry as a second-line medication for the management of moderate to severe pain. Opioids contribute to analgesia through their ability to raise the pain threshold and alter the sensation of pain (56). Opioids cause a number of adverse effects, including respiratory depression, nausea, vomiting, constipation, sedation, and blood pressure modulation (56). Unfortunately, despite their utility, patients taking opioids are susceptible to developing a tolerance, physical dependence and addiction to the drug. With the opioid epidemic continuing to grow, special consideration and caution must be demonstrated by dental clinicians to protect our patients and the community. Beyond the alarming risk for misuse and abuse, there are a number of drug interactions to be aware of involving opioids.

Opioids and CYP450 influencers

The metabolism of various opioids is accomplished primarily in the liver by phase I oxidation by the CYP450 enzymes, CYP3A4 and CYP2D6 (62). Hydrocodone, codeine and dihydrocodeine are converted into their active metabolites, hydromorphone, morphine, and dihydromorphine by CYP2D6, which are then subsequently metabolized by phase II glucuronidation conjugation (63). CYP3A4 is the primary metabolizer of fentanyl, oxycodone, methadone, and tramadol (63). While inhibitors (amiodarone, SSRIs, bupropion, celecoxib) and inducers (rifampin) can affect codeine and morphine metabolism, the potential for interaction is significantly lower than that of CYP3A4 influencers (63). Therefore, patients taking oxycodone, compared to codeine, are of more concern with regards to CYP450 inhibition and induction. Statins and anticonvulsants are often CYP3A4 inducers; calcium channel blockers, psychiatric drugs, and macrolide and fluoroquinolone antibiotics inhibit CYP3A4 (63).

Opioids and monoamine oxidase inhibitors

Serotonin toxicity, also referred to as serotonin syndrome, occurs when there are elevated intrasynaptic concentrations of serotonin in the central nervous system (64). Serotonin toxicity can vary in degree but is generally characterized by changes in neuromuscular hyperactivity (clonus, flexion and rigidity), autonomic system hyperactivity (tachycardia and hyperthermia), and altered mental state (agitation, confusion, restlessness) (64,65). While mild toxicity is generally harmless, severe cases can be life-threatening. Some opioids, namely methadone, meperidine, and tramadol, have all been associated with cases of serotonin toxicity. The associated mechanism of action involves the opioid-mediated inhibition of serotonin transporter (SERT)—an important transporter found in platelets and neurons that allows for the rapid reuptake of serotonin into the presynaptic nerve terminals (64). Troublingly, the concomitant use of meperidine and a monoamine oxidase inhibitor—which prevents the degradation of monoamines such as serotonin—has resulted in severe cases of serotonin toxicity, with multiple cases of fatalities (65). Consequently, under no condition should a clinician prescribe meperidine to an individual taking an SSRI or a monoamine oxidase inhibitor, such as phenelzine or tranylcypromine, as the risk for fatal serotonin toxicity is too significant. However, despite the significant interaction seen with meperidine,

evidence suggests that other phenanthrene opioids, including codeine, hydromorphone, oxycodone, and morphine, do not inhibit SERT (65). Therefore, serotonin toxicity with those opioids is of no concern, whether taken individually or concurrently with a monoamine oxidase inhibitor or SSRI.

Tramadol and serotonergic medications

Tramadol is a weak μ-opioid receptor agonist and serotonin and norepinephrine reuptake inhibitor (SNRI) (66). Despite being a significantly weaker agonist than morphine—about ¼ the potency—tramadol does not have a more favourable safety profile (66). Due to its inherent SNRI activity, tramadol has the potential to induce serotonin-related toxicity. From 1997 to 2017 in the United States, there were over 2,000 cases and over 900 cases of tramadol-induced seizures and serotonin syndrome, respectively (66). Since tramadol alone is capable of causing serotonin toxicity, it is reasonable to presume that the risk of serotonin syndrome would be increased when combined with other serotonergic medications, including SSRIs, tryptophan and herbal medications like St. Johns Wort. While data surrounding the severity of this interaction is not available, clinicians should be mindful of the potential synergistic adverse effects before prescribing tramadol to patients taking other serotonergic medications.

Opioids and ethanol

Since both opioids and ethanol are respiratory depressants, the additive effect of their concurrent use significantly increases the risk for morbidity and mortality (67). As such, healthy patients should be strongly advised to avoid the consumption of alcohol when taking opioid medication. Additionally, alcoholic patients are not good candidates for opioids and therefore should never be prescribed opioids for pain management. This is primarily because in dentistry, opioids are taken in combination with acetaminophen. Since alcoholics must consume alcohol with acetaminophen to avoid the build-up of NAPQI, they would not be able to avoid concomitant consumption of alcohol and opioids. Please see *Table 4* for summary of the key adverse drug interactions with opioids.

Strengths and limitations

This narrative review offers a comprehensive summary of the current literature on drug interactions involving analgesics in a dental environment. One notable strength of this study is its extensive utilization of various types of studies. By incorporating multiple meta-analyses, systematic reviews, case-control studies, and case reports, a broad range of analgesic interactions is examined with sufficient depth and accuracy. Moreover, the quality of available information has significantly improved since the last review of this nature. For instance, a previous identification of the interaction between lithium and renal influencing medications was solely based on case reports, whereas a recent 500-person case-control study has now provided more reliable evidence (21).

However, a limitation of this review is the absence of information regarding the prevalence and severity of these interactions specifically in dental settings. Many of the studies included in this review evaluated analgesic interactions in other medical contexts, which may involve different dosages and durations of use. Given that analgesics are typically prescribed in lower doses and for shorter durations in dental practice, it is plausible that interactions observed in other medical areas may not manifest in the same way in dentistry.

Overall, this review presents an honest and comprehensive overview of potential interactions that clinicians may encounter in their daily dental practice.

Conclusions

This narrative review serves as an update on the numerous potential adverse interactions involving frequently prescribed analgesic and anti-inflammatory medications used in dentistry with other common medications. A prudent clinician should be mindful of the patient's degree of pain, comorbidities, current medication, and health status when determining appropriate pain management strategies. Some adverse reactions—including NSAIDs with methotrexate, lithium, digoxin (long-term), and in patients taking both a diuretic and either an ACEI or ARB—should be completely avoided. Other interactions—including COX-1 inhibitors and SSRIs—have only relative adverse outcomes, which can be managed with appropriate considerations. Importantly, limited clinical evidence exists to demonstrate the severity of interaction with herbal medications and commonly prescribed analgesics and anti-inflammatory drugs. Future research should help uncover the uncertainty surrounding these interactions. Moreover, as novel medications become more widely adopted, such

Table 4 A summary of the key adverse drug interactions with opioids in a dental setting

Drug	Interaction	Considerations and recommendations
CYP2D6 influencers	CYP2D6 converts hydrocodone, codeine, and dihydrocodeine into active metabolites	Consider adjusting dose or switching type of analgesic based on expected and reported effectiveness
	Inhibitors: SSRIs, amiodarone, bupropion, celecoxib	*For inhibitors, consider alternate medication or increased dose*
	Reduce analgesic effect	*For inducers, consider reduced dose*
	Inducers: rifampin	
	Exaggerate analgesic effect	
	Severity of interaction less concerning than CYP3A4 inhibitors (63)	
	Genetics also affects CYP2D6 activity	
CYP3A4 influencers	CYP3A4 is the primary metabolizer of fentanyl, oxycodone, methadone, and tramadol	*Avoid combining oxycodone and CYP3A4 inhibitor*
	Inhibitors: calcium channel blockers, macrolides, and fluoroquinolones	Consider alternate medication when patient is taking a CYP3A4 inducer
	Exaggerate analgesic effect, increased risk for toxicity	
	Inducers: statins and anticonvulsants	
	Reduced analgesic effect	
	Severity of interaction less concerning than CYP3A4 inhibitors (63)	
Ethanol	Ethanol and opioids both cause respiratory depression	*Avoid combination*
	Risk for abuse	
Monoamine oxidase inhibitors and other serotonergic medications	Serotonin syndrome noted when combined with *methadone, meperidine, and tramadol*	*Never combine methadone, tramadol, or meperidine with monoamine oxidase inhibitors, SSRIs, or other serotonergic medications*
	Mortality associated with opioid-mediated inhibition of SERT resulting in serotonin syndrome	*Codeine, hydromorphone, oxycodone and morphine are not a risk for serotonin syndrome*
	Codeine, hydromorphone, oxycodone, and morphine, do not inhibit SERT	
	Tramadol is an SNRI	
	Serotonin syndrome risk when tramadol is taken with serotonergic medications, including SSRIs, tryptophan, herbal medications (St. John's Wort)	

CYP2D6, cytochrome P450 2D6; CYP3A4, cytochrome P450 3A4; SERT, serotonin transporter; SNRI, selective noradrenaline reuptake inhibitor; SSRI, selective serotonin reuptake inhibitor.

as new oral anticoagulants, the risk for adverse bleeding episodes should decrease when compared to interactions involving vitamin K anticoagulants. Despite the landscape of prescriptions evolving in the future, anti-inflammatory and analgesic administration will continue to be a staple in dental pain management. Therefore, an understanding of characteristic interactions will be beneficial to all current and aspiring dental care providers.

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Footnote

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