Peer Review File

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Response to Reviewer A:

Thank you so much for your comments and suggestions. We are extremely excited to see that you believe this paper may be of interest to clinicians who proscribe drugs on a daily basis.

Reviewer A commented: "Title: Please consider including anti-inflammatories in the title."

Authors' response:

We agree that the given the proportion of the paper dedicated to NSAIDs, that the suggestion to consider including anti-inflammatory drugs in the tile is warranted.

The title previously was:

"An Update on Analgesic Drug Interactions in Oral and Maxillofacial Medicine"

The title has been changed to:

"An Update on Drug Interactions Involving Anti-Inflammatory and Analgesic Medications in Oral and Maxillofacial Medicine"

This change is reflected in lines 1-3 of page 1.

The choice of the words "Drug interactions **involving** anti-inflammatory and analgesic medications" was chosen over "Analgesic and anti-inflammatory drug interactions" to avoid potential confusion about whether the paper was outlining interactions between anti-inflammatory drugs and other analgesics, or between anti-inflammatory/analgesic drugs with other commonly prescribed medications.

Reviewer A commented: Introduction: I strongly suggest adding a brief introduction to the main text. The introduction should report the rationale of the study:

- ***The definition of drug interaction and why dental practitioners need to be aware of them.***
- ***What is known about drug interactions in Dentistry? (e.g.: Data on prevalence, trends, and hospitalizations to treat adverse events induced by interactions).***

• To define the scope of the study (There are different kinds of drug interactions, such as food-drug interactions, tobacco-drug interactions, and drug-drug interactions; It should be clear to the reader that this study only focused on drug-drug and drug-alcohol interactions).

The following paragraphs were subsequently added to page 2 lines 46-62:

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 (34). 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 numerous studies have identified interactions that may arise from drugs commonly used in a dental setting. 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.

This paragraph introduces the necessity for pain management in dentistry, thus [providing context for why these medications are commonly prescribed. It also provides a definition for both drug interactions and reasons for the resultant adverse effects. To address the second point, it has been quite difficult to identify the prevalence or trends in observed adverse effects seen in analgesics prescribed by dental clinicians. That said, I can potentially include data on the amount of analgesics prescriptions annually given by dentists—thereby serving as the basis for the relatively reasonable probability of an adverse interaction happening in a given dental practice.

Reviewer A commented: Some reference to lines 47-53 (p.1) is needed.

Authors Response:

This is definitely necessary. The appropriate citations have been added.

Reviewer A commented: "Angiotensin converting enzyme inhibitors (ACEIs), angiotensin receptor blockers (ARBs), and diuretics…" (lines 71-2, p.2). Perhaps, it would be easier for the reader if the authors mention the name of some drugs belonging to each therapeutic group.

Authors Response:

This is an excellent point. Examples of commonly used drugs belonging to the mentioned drug classes have been added.

Lines 71-76 in original manuscript:

Angiotensin converting enzyme inhibitors (ACEIs), angiotensin receptor blockers (ARBs), and diuretics all significantly increase the expression of COX-2 in this region (Figure 1A), thus serving as the basis for the interaction (9). Beta blockers also stimulate prostacyclin production, though this is believed to occur in extrarenal blood vessels (11). Notably, antihypertensives with no mechanism related to prostaglandin function—such as calcium channel blockers like nifedipine—do not exhibit any worrisome interaction with NSAIDs.

Lines 103-108 in edited manuscript:

Angiotensin converting enzyme inhibitors (ACEIs; e.g. Captopril (gen.)/Capoten (tr.), Enalapril (gen.)/Innovace (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 1A), thus serving as the basis for the interaction (9). Beta blockers (Atenolol (gen.)/Tenormin (tr.), Metropolol (gen.)/Betaloc (tr.)) also stimulate prostacyclin production, though this is believed to occur in extrarenal blood vessels (11). Notably, antihypertensives with no mechanism related to prostaglandin function—such as calcium channel blockers like nifedipine (Adalat (tr.))—do not exhibit any worrisome interaction with NSAIDs.

Reviewer A commented: It is necessary to present the full-written form of all acronyms (or abbreviations) the first time they are mentioned in the text. Notice that only the abbreviated forms are presented to ATII, ADH, ARB, ACE, ASA, pts, among others. Please double-check all acronyms used in the manuscript.

Authors response:

Thank you for the suggestion.

The following edits were made:

Page 5/Line 147: "…potent vasoconstrictor and stimulator of antidiuretic hormone (ADH) and aldosterone."

Page 6/Line 176-177: "…demonstrated that flurbiprofen attenuates the antihypertensive effect of propranolol, but another ~~RCT~~ randomized controlled trial found no significant effect with prescription-strength ibuprofen (1, 14)."

Reviewer A commented: NSAIDs and Anticoagulants (p.5): Is the information provided under this subheading related to all anticoagulants (vitamin K antagonist oral anticoagulants, new oral anticoagulants)?"

Authors response:

Vitamin K antagonist oral anticoagulants have the more significant adverse effects, which is Warfarin was heavily emphasized. I agree that new oral anticoagulants need to be addressed. Per the study by

Mendell, J., Lee, F., Chen, S., Worland, V., Shi, M., & Samama, M. M. (2013). The Effects of the Antiplatelet Agents, Aspirin and Naproxen, on Pharmacokinetics and Pharmacodynamics of the Anticoagulant Edoxaban, a Direct Factor Xa Inhibitor. Journal of Cardiovascular Pharmacology. 62(2), 212-221. https://doi.org/10.1097/FJC.0b013e3182970991

new oral anticoagulant drugs 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. That pharmacokinetic interactions were unaffected, and concomitant administration of edoxaban and ASA or Naproxen was well tolerated. Overall, some degree of caution should be taken before prescribing NSAIDs to patients taking new oral anticoagulants.

The following sentences were added to Page 7 Lines 231-236:

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 (60). That pharmacokinetic interactions were unaffected, and concomitant administration of edoxaban and ASA or Naproxen was well tolerated (60). 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.

Reviewer A commented: "Additionally, two systematic reviews determined that there is reduced risk of gastric ulcers between 74% and 91% in patients taking COX-2 inhibitors…" (lines 213-5, p.6). Please, cite the mentioned systematic reviews.

Authors response:

They have been added.

Reviewer A commented: "Therefore, a prudent clinician would consider modifying NSAID therapy…" (lines 234-5, p.6-7). The authors reported that patients concomitantly taking NSAIDs, and SSRIs might require NSAID replacement. In this sense, it would be interesting to mention which other drugs could be prescribed to manage orofacial pain.

Authors response:

The recommendation was to either shorten the duration of use or use an adjunct gastroprotective medication in healthy patients. This was outlined later in the paragraph of the quoted line, as well as the summary table on page 8. I am happy to add a line providing an alternative to NSAID use. For moderate to severe pain in these patients, Tylenol in combination with an opioid is appropriate management.

The following modifications have been made to page 8 lines 276-280:

"…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 gastrointestinal bleeding (29). Alternatively, for moderate to severe pain, acetaminophen in combination with an opioid can be used for pain management."

Reviewer A commented: "The FDA recommends that ibuprofen should be taken either more than eight hours prior to or at least thirty minutes…" (lines 326-7, p.9). In this sentence, instead of citing Moore et al., (2015), I suggest citing the original FDA report (https://www.fda.gov/media/76636/download).

Authors response:

This is a good point. The modification has been made.

"Non-selective NSAIDs […] have the potential to interact with herbal medications that are known to affect platelet aggregation…" (lines 332-3, p.9). Please, describe some herbal medications that are known to affect platelet aggregation.

Authors response:

This is a good suggestion and will be helpful to the reader. I have added a list of herbal medications that are known to affect platelet aggregation and vitamin K synthesis, respectively.

The following modifications were made to page 11 lines 377-379:

"…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)(44)."

Reviewer A commented: The authors very well reported an array of drug interactions involving analgesics and NSAIDs. However, little emphasis has been given to the clinical repercussions of the interactions and how they may affect the delivery of dental care. For example, patients taking an antidepressant (SSRI), who are prescribed pre-emptive NSAIDs for tooth extraction may present increased bleeding during the surgery. For this reviewer reporting such repercussions could be useful for dental practitioners who will read the paper.

Authors response:

This point is well taken. While many of the adverse interactions mentioned in this paper are discussed to help avoid medical emergencies and poorer health outcomes, some interactions could also impact dental care. As you mentioned, increased bleeding risk may affect surgical dental procedures like extractions.

The following paragraph was added to page 12/13 lines 424-432:

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.

Reviewer A commented: Illustrations: Please, consider adding the source of each figure as a footnote.

Authors response:

The illustrations were created by the authors. The information sources used to create the illustrations are referenced in the text of the manuscript.

Reviewer A commented: Conclusion / Final considerations: If possible, include a brief final section to the manuscript. An overview and future insights about drug interactions in Dentistry may be presented.

This is well received. We have added a paragraph on page 17 from lines 578-592 for this purpose:

Final Considerations

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 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.

Response to Reviewer B:

Thank you for the kind comments and numerous suggestions. I appreciate the provision of credible and pertinent sources to add value to this narrative review.

Reviewer B commented: Instead of just repeating my edits and comments let me just send you your paper back with by annotated edits/comments. Let me just give you a couple of the highlights that I think should be addressed.

Response from authors:

This is very appreciated.

Spelling mistakes have been corrected.

Amended Line 43 on page 2 to this:

"…placed on NSAIDs, as these drugs are commonly prescribed, are available over the counter, are non-addicting, and…"

Reviewer B commented: You might want to mention that there is a lot of heterogeneity associated with this interaction. Some patients show it while others dont even in normal volunteers.

The following lines were added to page 4 lines 112-116:

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 (65). Despite this, only 129 of the 200 participants with normotensive baselines that were continuously taking NSAIDs developed hypertension at the 7-year follow-up (65).

Reviewer B commented: Acetaminophen IS NOT THE DRUG OF CHOICE FOR MOST DENTAL SURGICAL PROCEDURES. Postsurgical dental pain in mainly driven by inflammation and that's why 400 mg of ibuprofen or 440 mg of naproxen sodium are consistently superior to accetaminophen 1000 mg in the degree of pain relief. See Nonsteroidal Anti-Inflammatory Drugs and Opioids in Postsurgical Dental Pain. Hersh EV, Moore PA, Grosser T, Polomano RC, Farrar JT, Saraghi M, Juska SA, Mitchell CH, Theken KN. J Dent Res. 2020 Jul;99(7):777-786. doi: 10.1177/0022034520914254. Epub 2020 Apr 14.

Authors response:

This point is well received. The claim has been removed.

The following modifications have been made to page 13 lines 236-437:

In dentistry, acetaminophen is a commonly utilized drug for the management of mild to moderate post-operative pain ~~is the drug of choice for post-operative pain~~ in all age groups due to its favourable risk-benefit ratio (49).

Reviewer B commented: Under NSAIDs and Lithium I supplied you with a paper published in 2015 in the dental literature that highlighted the seriousness of this interaction.

Authors response:

Unfortunately, I cannot access the full text of this paper. Even with my school's login, I can only access the abstract. Since the abstract of the paper does not comment on the seriousness of the interaction between lithium and NSAIDs, I have chosen not to use this resource.

Reviewer B commented: Using a highly selective COX-2 inhibitor on patients on anticoagulants (you mainly discussed warfarin). These COX-2s carry their own set of baggage and maybe a better choice who be what I call a semi-selective COX-2 inhibitor like etodolac or diclofenac or you prescribe to these patients acetaminophen or acetaminophen plus an opioid (obviously only 2 or 3 days worth max).

Authors response: This point is well received. I have added this suggestion to page 7 paragraph 2.

The following modifications were added to page 7 paragraph 2 lines 243-246:

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 (66).

Reviewer B commented: SSRIs and NSAIDs: SSRIs have their own anti-platelet effects. So that might also contribute to interaction. Gave you a reference in dental literature.

Authors response: This is very useful. The following sentence was added to page 8 lines 269-271:

SSRIs also exhibit inherent antiplatelet properties, which is a product of the inhibition of serotonin-regulated expression of surface receptors required for platelet aggregation (67).

Reviewer B commented: Probably should bring up that methotrexate as far as causing any pain relief takes one to two months (inhibition of joint destruction comes on quicker). NSAIDs while not helping with the join destruction has analgesic effects that may come on in the first dose or two. So rheumatologists using this combo may be stuck between a rock and a hard place.

Authors response:

This makes a lot of sense. I understand that rheumatologists have no risk-free pain management strategy. I am choosing not to make any additions to the paper because the choice of the rheumatologist to recommend NSAIDs for pain relief is not influenced by dentists. A dentist should not be recommending NSAIDs to patient for relief of their rheumatoid arthritis pain, and since there are alternatives for pain management in dental care, those options should be explored in this patient population. Further, if the patient is already taking NSAIDs for rheumatoid arthritis management, then that already negates them from additional use of NSAIDs for dental pain management.

Reviewer B commented: Is there any literature out there with acute alcohol consumption, a hangover headache and a single dose of 400 mg ibuprofen or 440 mg of naproxen sodium? I would think that the risk would be a lot less.

Authors response:

This is a great question because the prevalence of acute NSAID and acute alcohol consumption is a lot higher than chronic consumption. That said, there is very limited information on this interaction in non-chronic users. I can add a line that says that while there is no conclusive evidence of a significant interaction when consumed acutely, the potential for adverse effects should still warrant the recommendation to avoid the combination all together.

Reviewer B commented: Maybe add an additional qualifying statement that prescribing multiple NSAIDs only increases the risk for toxicity and does not increase efficacy of post-op dental pain.

Authors response: Good point. The following line was added to page 11 lines 361-362.

Due to their identical mechanism of action, combining NSAIDs does not increase efficacy, and only serves to increase risk for toxicity.

Reviewer B commented: line 465: Change hydromorphone to hydrocodone (in Vicodin, Norco, Lortab etc)

Authors response:

This is a good catch. Amendments have been made.

The following modifications have been made to page 15, paragraph 3, line 520-522:

"Opioids, such as codeine, oxycodone, and hydrocodone (e.g., Vicodin, Norco, Lortab) ~~hydromorphone~~, are used in dentistry as a second-line medication for the management of moderate to severe pain. Opioids contribute to ~~Opioids cause profound~~ analgesia ~~due~~ through ~~to~~ their ability to raise the pain threshold and alter the sensation…"

Reviewer B commented: Tell this to the Extra Strength Excedrin people which is now Glaxo Smith Kline. Their label says a maximum of 10 days use. However most people don't take anywhere as long for pain or headache.

This is in response to this statement from page 11:

"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 (34)."

Authors response: Good point. Mixed messaging is definitely confusing for patients. I do believe that the 10 day recommendation is short enough to not be considered chronic use. So, this doesn't detract from the point of the statement.

Reviewer B commented: As far as protein displacement, you would think that ibuprofen and naproxen sodium would do it also since they are at least 95% protein bound.

This is in response to this statement from page 12:

"Additionally, since SUs like glimepiride are more than 99% protein bound in plasma, and salicylates like aspirin displace highly protein bound drugs, aspirin likely increases SU concentration directly through displacement, and consequently increases SUs volume of distribution (47)."

Authors response:

Perhaps this statement should be excluded to avoid the inference that this interaction is applicable to other highly protein bound drugs. This statement is not certain, which is why the word likely was used. To avoid this confusion, I have amended it to 'possibly'. There are definitely other mechanisms at play, and the concrete underlying cause has not been identified. Since the literature only indicates an interaction between aspirin and SUs, I will not make assumptions about other NSAIDs.

Reviewer B commented: the opioids at doses we use DO NOT CAUSE PROFOUND ANALGESIA. For example, 5 mg of oxycodone is slightly inferior to 500 mg acetaminophen. Those results on in the JDR paper.

Authors response: This is a valid critique. A modification has been made.

The following modifications have been made to page 14, paragraph 3 lines 521-522:

"Opioids contribute to ~~Opioids cause profound analgesia~~ ~~due~~ through ~~to~~ their ability to raise…"

Reviewer B commented: What about ibuprofen, naproxen sodium and other NSAIDs besides Aspirin?

This was in response to the section **Aspirin and Carbonic Anhydrase Inhibitors**.

Authors response:

This does appear to be an interaction that is unique to ASA. I have not found literature to support other NSAIDs being involved in this interaction.

Reviewer B commented:

This is from all aspects a very controversial drug interaction. But an added issue is that chronic alcohol consumers already present with liver damage regardless of acetaminophen intake. You might want to add at least on the Tylenol label it states that if you plan to drink 3 or more alcoholic beverages per day consult your healthcare provider before consuming alcohol.

This is in response to the second paragraph on **Acetaminophen and Ethanol** interactions on page 14.

Authors response:

This is a good point. I have added the following statement on page 14 lines 485-487:

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.

Please indicate if a citation is required for this claim.

Reviewer B commented: Serotonin syndrome - While you properly make a big deal of meperidine and MAOIs (and it's the build up of normeperidine that causes it); the drug that scares me the most current is tramadol. You are not supposed to take it with other serotonergic drugs or supplements including all of the SSRIs, St Johns Wort, tryptophan and some illicit drugs with serotonergic properties.

Authors response:

Thank you for commenting on this. It is an essential topic to discuss. A new paragraph has been added, under the subheading 'Tramadol and serotonergic medications', to discuss this concept.

The following paragraph has been added to page 16, lines 557-567:

Tramadol and Serotonergic Medications

Tramadol is a weak μ-opioid receptor agonist and serotonin and norepinephrine reuptake inhibitor (SNRI) (64). Despite being a significantly weaker agonist than morphine—about ¼ the potency—tramadol does not have a more favourable safety profile (64). 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 (64). 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.

To keep in line with Narrative Review Guidelines, we added this method section to pages 2/3 lines 64-69

Method:

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.