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**Re: The letter from Dr Allan C. Jones, DDS, MS and Parish P. Sedghizadeh, DDS, MS**

**Entitled: “Nonsteroidal anti-inflammatory drug risks.”**

A response from:

**Martin H Thornhill MBBS, BDS, PhD<sup>a,b</sup>, Katie J Suda PharmD, MS<sup>c</sup>, Michael J. Durkin MD, MPH<sup>d</sup> and Peter B Lockhart DDS<sup>b</sup>**

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We thank Drs. Jones and Sedghizadeh for commenting on our article: “Is it time US dentistry ended its opioid dependence?”<sup>1</sup> They raise an important point regarding cardiovascular risks of nonsteroidal anti-inflammatory drugs (NSAIDs). As they point out, long-term NSAID prescriptions are associated with myocardial infarction, stroke, and gastrointestinal bleeding.

All drugs are associated with adverse events and the risks and benefits should be weighed when selecting any analgesic to manage dental pain. As large prospective comparative effectiveness and safety studies are unlikely to be performed, analyses using large administrative datasets, like those cited by the letter’s authors, must serve as surrogates. However, none of the cited studies compared NSAID and opioid safety. In a landmark trial published in Archives of Internal Medicine, Solomon et al. directly compared the safety of nonselective NSAIDs (e.g, ibuprofen), selective cyclooxygenase 2 inhibitors (e.g, celecoxib), or opioid treatment of over 36,000 elderly patients.<sup>2</sup> The authors used propensity score matching and hazard ratios (HR) to quantify the risk of cardiovascular events, gastrointestinal bleeding, fractures, safety events requiring hospitalization, and all-cause mortality with opioids compared with non-selective NSAIDs. The risk of a cardiovascular adverse event was 1.7 times higher with an opioid than a non-selective NSAID (HR=1.77 [95%CI, 1.39-2.24]). The risk of the other outcomes was also higher with opioids: fractures (HR=4.47 [95%CI, 3.12-6.41]); hospitalized adverse events (HR=1.68 [95%CI, 1.37-2.07]); and all-cause mortality (HR=1.87 [95%CI, 1.39-2.53]). To make it easier to understand what this means for prescribing, the authors also calculated the number needed to harm (NNH) comparing opioids with NSAIDs. For cardiovascular adverse events NNH=17. This means that for every 17 people who receive an opioid rather than an NSAID, there will be one extra adverse cardiovascular adverse event than would have been the case had they received an NSAID. The other NNH were; fractures (NNH=26), hospitalized adverse events (NNH=19) and all-cause mortality (NNH=27). The article has limitations and translating data from long-term use studies in the medical literature to short term use in dentistry is challenging. The pathophysiology of why an opioid would increase cardiovascular events remains unclear. However, opioids can cause hypotension, QT prolongation, and impaired cardiac contractility.<sup>3</sup> Short of a randomized controlled trial, these results provide the most conclusive evidence that for cardiovascular events opioids are more harmful than NSAIDs, even in elderly patients who would be at the highest risk for these events.

These data serve as a reminder that direct patient harms from opioids extend beyond addiction. Patients who receive opioids are at risk for cardiac events, falls, and accidental overdose.<sup>2</sup> Indeed, the National Safety Council estimates that the lifetime odds of dying from an accidental opioid overdose (1 in 96) is now higher than motor vehicle accidents (1 in 103).<sup>4</sup> Furthermore, dentists should also be aware that excessive or inappropriate opioid prescribing can have financial and professional consequences. Dentists misprescribing opioids have been included in lawsuits and received disciplinary actions by state dental boards. While not described by Drs. Jones and Sedghizadeh, it is important to note that most children, adolescents, and young adults are at low risk for heart attack and stroke. However, dentists are high prescribers of opioids in these groups.

Given this, it is unsurprising that the ADA has recommend that “NSAIDS alone or in combination with acetaminophen are generally more effective and are associated with fewer side effects compared to opioids.”<sup>5</sup>

#### References:

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- 4) National Safety Council Preventable Deaths. Lifetime odds of dying for selected causes, United States, 2018. Available at: <https://injuryfacts.nsc.org/all-injuries/preventable-death-overview/odds-of-dying/data-details/>. Accessed 10/29/2019.
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