Short-term use of nonsteroidal anti-inflammatory drugs and adverse effects

An updated systematic review

Anita Aminoshariae, DDS, MS, Dipl (American Board of Endodontics); James C. Kulild, DDS, MS, Dipl (American Board of Endodontics); Mark Donaldson, BSP, PharmD, ACPR, FACHE

In July 2015, the US Food and Drug Administration (FDA) strengthened warnings about the risk of heart attack and stroke associated with nonsteroidal anti-inflammatory drugs (NSAIDs).[1] In patients with NSAID-exacerbated respiratory disease (NERD), NSAIDs are considered the greatest infractor, with reactions typically occurring within 3 hours of ingestion.[2] Thus, the FDA lists the use of NSAIDs as a contraindication in patients suspected of having NERD.[3]

Although long-term use of NSAIDs may be associated with adverse cardiovascular (CV),[4-7] renal,[8-11] gastrointestinal (GI),[12-14] and respiratory[15] events, preoperative and postprocedural dental pain are usually short-term episodes with the dental procedure itself, or the normal healing process, being the final disease-modifying entities, and therefore requiring limited (fewer than 10 days) NSAID exposure. A systematic review of the peer-reviewed literature focusing on the evidence regarding the CV, renal, GI, and respiratory adverse effects and safety of these medications in patients taking routine NSAIDs for 10 days or fewer, which is within the usual time for dental patients exposed to an NSAID, compared with patients who were not exposed to these medications, has yet to be published.

Because the potential benefits of pain reduction always must be balanced against the potential adverse effects of medications, the goal of this investigation is to report the available scientific evidence regarding potential adverse effects of short-term use of NSAIDs and CV,

ABSTRACT

Background. In this article, the authors examine the available scientific evidence regarding adverse effects of short-term use of nonsteroidal anti-inflammatory drugs (NSAIDs). Short-term use was defined as 10 days or fewer.

Methods. The authors reviewed randomized controlled clinical trials and cohort and case-controlled clinical studies published between 2001 and June 2015 in which the investigators reported on the safety of nonselective cyclooxygenase inhibitors and of cyclooxygenase-2 selective inhibitor NSAIDs.

Results. The systematic review process according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines allowed the authors to identify 40 studies that met the inclusion criteria.

Conclusions. On the basis of the available scientific evidence, NSAIDs may be considered relatively safe drugs when prescribed at the most effective dose and for the shortest duration of time, which was defined to be 10 days or fewer.

Practical Implications. Although the US Food and Drug Administration recommends the use of NSAIDs beyond 10 days to be accompanied by a consultation with a health care provider, the use of NSAIDs may be considered relatively safe when prescribed at the most effective dose and for the shortest duration of time, which was defined as 10 days or fewer. Exceptions would be for patients at risk of developing NSAID-exacerbated respiratory disease, patients with prior myocardial infarction who are receiving antithrombotic therapy, patients with asthma, and patients with a history of renal disease.

Key Words. NSAIDs; cardiovascular risk; myocardial infarction; gastrointestinal; renal; respiratory; randomized controlled clinical trials; cohort studies; case-controlled studies; vascular events.

JADA 2016:147(2):98-110

http://dx.doi.org/10.1016/j.adaj.2015.07.020

renal, GI, and respiratory complications. Short-term use is defined as 10 days or fewer.

METHODS

Formulating the review question. We developed the following problem, intervention, comparison, and outcomes (PICO) framework for this systematic review: What is the evidence regarding adverse effects and safety of NSAIDs in patients taking them routinely for 10 days or fewer compared with that in patients who are not exposed to these medications?[16] Table 1[17,18] identifies the recommended doses of NSAIDs available in the United States.[19,20]

Inclusion and exclusion criteria. Inclusion criteria were as follows:

- randomized controlled clinical trials (RCTs) and case-controlled studies of patients ingesting NSAIDs for 10 days or fewer;
- publications from 2001 to June 2015;
- human adult patients 18 years or older;
- head-to-head comparisons between different NSAIDs;
- the end point of adverse effect or safety as a primary objective;
- quantitative results reported.

We excluded published study results if they were not vetted in the peer-reviewed literature or if they did not meet any of the inclusion criteria.

Search methodology. We registered the protocol for this systematic review in the PROSPERO database (registration number CRD42015023343). We included the following databases in this review: the Cochrane Oral Health Group Trials Register to June 2015, the Cochrane Central Register of Controlled Trials to June 2015 (Cochrane Library 2015), MEDLINE via Ovid to June 2015, EMBASE via Ovid to June 2015, and the meta-Register of Controlled Trials to June 2015. We searched the bibliographies of relevant clinical trials, the gray literature, and review articles individually.[21] *Gray literature* generally is defined as material that is not published formally. We applied no language restriction to the searches of the electronic databases as long as a translation was provided in English. We used the Assessing the Methodological Quality of Systematic Reviews checklist; the Oxford Systematic Review Appraisal Sheet, Critical Appraisal Skills Programme; and the Grading of Recommendations Assessment, Development and Evaluation system for grading evidence to ensure the accuracy of this data analysis in this systematic review.[16,22-24]

Search and key words. Using the PICO-formatted question, the authors generated methodological medical subject heading terms to make the search strategy more sensitive in identifying studies. We reviewed RCTs and cohort and case-controlled clinical studies reporting the safety of nonselective cyclooxygenase (COX) inhibitors and COX-2 selective inhibitor NSAIDs. Two of the authors (A.A., J.C.K.) systematically reviewed research evidence published between 2001 and 2015 pertaining to the topic. In the case of any disagreement over inclusion or exclusion of a particular article, these authors would come together to discuss the divergence and then agree on the final outcome. There were no disagreements between the 2 authors. Key search terms included "NSAIDs," "cardiovascular risk," "myocardial infarction," "randomized controlled clinical trials," "cohort and case-controlled studies," "hypertensive effects," "cardiovascular effects," "respiratory effects," "renal effects," "GI effects," and "gastrointestinal effects."

RESULTS

On the basis of all of the different study methodologies, it was not possible to perform a meta-analysis. The figure[16] presents a flowchart of the systematic review process according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines. We identified 11 studies that met the inclusion criteria for CV safety.[19,25-34] We identified 6 studies that met the inclusion criteria for renal safety.[33,35-39] We identified 14 studies that met the inclusion criteria for GI safety.[17,18,30,40-50] We identified 9 studies that met the inclusion criteria for respiratory safety.[51-59]

Tables 2-5[17-19,25-60] detail the risk of bias assessment as performed according to guidelines outlined by the Cochrane Collaboration for CV, GI, and renal safety, respectively.[61] We graded evidence according to the Grading of Recommendations Assessment, Development and Evaluation system.[24]

DISCUSSION

We found 40 publications published within the past decade in the peer-reviewed literature that met the PICO framework for this investigation to address the deficit of such articles and that demonstrated remarkable consonance in their conclusions (Tables 2-5).[17-19,25-60]

CV risk with the short-term use of NSAIDs. A comprehensive search of the literature failed to indicate that short-term use of NSAIDs for 10 days or fewer was associated with myocardial infarction or any other major

ABBREVIATION KEY. **ASA:** Acetylsalicylic acid (aspirin). **COI:** Conflict of interest. **COX:** Cyclooxygenase. **CV:** Cardiovascular. **DM:** Double masked. **FDA:** Food and Drug Administration. **GI:** Gastrointestinal. **LSS:** Low sample size. **MPP:** Masking of participants and personnel. **MS:** Manufacturer sponsored. **NERD:** NSAID-exacerbated respiratory disease. **NSAID:** Nonsteroidal anti-inflammatory drug. **OTC:** Over the counter. **PICO:** Problem, intervention, comparison, and outcomes. **RCT:** Randomized controlled clinical trial. **RSG:** Random sequence generation. **Rx:** Prescription required for certain strengths. **SM:** Single masked. **SR:** Selective reporting. **SS:** Sample size.

TABLE 1

Currently available nonsteroidal anti-inflammatory drugs in the United States for mild to moderate orofacial pain.*

CHEMICAL CLASS OR GENERIC NAME	BRAND NAME	PRESCRIPTION STATUS	ORAL DOSAGE† FORMULATIONS AND USUAL ADULT DOSAGES	MAXIMUM RECOMMENDED DAILY DOSE (MILLIGRAMS)	NOTES
Acetic Acid					
Diclofenac immediate release	Cataflam, Cambia	Rx‡	50 mg every 8-12 h	225	Zipsor (diclofenac potassium) 25-mg capsules are given every 6 h
Diclofenac delayed release	Voltaren	Rx	50 mg every 12 h	200	Do not crush or chew
Etodolac	Lodine	Rx	200-400 mg every 6-8 h	1,000	200 mg comparable to ibuprofen 400 mg
Indomethacin immediate release	Indocin	Rx	25-50 mg every 6-8 h	200	Liquid: 5 mg per milliliter
Indomethacin sustained release	Indocin SR	Rx	75 mg every 12-24 h	150	Do not crush or chew
Ketorolac§	Toradol	Rx	Tablets: 10 mg every 4-6 h	Intramuscular: 120 By mouth: 40	Intramuscular: 30 mg every 6 h (limit 5 days maximum)
Ketorolac	Sprix	Rx	1 spray in each nostril every 6-8 h	126	Intranasal: 15.75 mg per spray
Sulindac	Clinoril	Rx	200 mg every 12 h	400	Should be taken with food
Tolmetin	Tolectin	Rx	400-600 mg every 8 h	2,000	None
Propionic Acid					
Fenoprofen	Nalfon	Rx	50-100 mg every 8-12 h	3,200	None
Flurbiprofen	Ansaid	Rx	100 mg every 12 h	300	FDA¶ approved for treatment of rheumatoid arthritis and osteoarthritis; however, often used off label for postoperative pain management
Ibuprofen	Advil, Motrin	OTC# and Rx	Tablets: 200-400 mg every 4-6 h	3,200	Liquid: 20-40 mg/mL
Ibuprofen	Caldolor	Rx	Intravenous: 400-800 mg every 6 h	1,200	100 mg/mL intravenous solution
Ketoprofen	Orudis	Rx	50 mg every 6 h or 75 mg every 8 h	300	25 mg comparable to ibuprofen 400 mg
Naproxen	Naprosyn	Rx	250 mg every 6-8 h or 500 mg every 12 h	1,250 the first day, then 1,000	Liquid: 25 mg/5 mL
Naproxen sodium	Anaprox, Aleve	OTC and Rx	275 mg every 6-8 h or 550 mg every 12 h	1,375 the first day, then 1,100	Aleve 220-mg capsules are OTC
Oxaprozin	Daypro	Rx	1,200 mg every day	1,800	Patients less than 50 kilograms should receive 600 mg per day
Cyclooxygenase-2 Inhibitor					
Celecoxib	Celebrex	Rx	200 mg every 12 h	600 the first day, then 400	Less effective than full doses of naproxen or ibuprofen
Nonacidic Agent					
Nabumetone	Relafen	Rx	500-750 mg every 8-12 h	2,000	FDA approved only for osteoarthritis and rheumatoid arthritis
Salicylic Acid Derivative					
Diflunisal	Dolobid	Rx	500 mg every 12 h	1,500	None
Salsalate	Disalcid	Rx	1,000 mg every 8 h	3,000	None

* Sources: Diener and colleagues[17] and Lanas and colleagues.[18]
† Dosage is for a 70-kilogram adult with normal hepatic and renal function. Food decreases the rate of absorption and may delay the time to peak levels. Caution is required for patients with allergy or renal or liver impairment or for use in combination with anticoagulant or antiplatelet medications. Common adverse effects are dyspepsia, nausea, abdominal pain, headache, dizziness, somnolence, rash, elevated liver enzyme levels, constipation, fluid retention, peripheral edema, tinnitus, and ecchymosis.
‡ Rx: Prescription required for certain strengths.
§ Ketorolac (Toradol) is approved for moderate to severe pain.
¶ FDA: Food and Drug Administration.
# OTC: Over the counter (nonprescription).
** Acetaminophen is included in multiple prescription and OTC products for treatment of pain, cough, cold, flu, migraine, insomnia, and so on, increasing the risk of accidental overdosage; the FDA is asking drug manufacturers to limit the amount of acetaminophen in prescription products to 325 mg and perhaps reduce the maximum recommended dose to less than 3,250 mg.

TABLE 1 (CONTINUED)

CHEMICAL CLASS OR GENERIC NAME	BRAND NAME	PRESCRIPTION STATUS	ORAL DOSAGE† FORMULATIONS AND USUAL ADULT DOSAGES	MAXIMUM RECOMMENDED DAILY DOSE (MILLIGRAMS)	NOTES
Oxicam					
Meloxicam	Mobic	Rx	7.5-15 mg every day	15	FDA approved only for osteoarthritis and rheumatoid arthritis
Piroxicam	Feldene	Rx	10-20 mg every 12-24 h	20	None
Fenamate					
Meclofenamate	Meclomen	Rx	50-100 mg every 4-6 h	400	None
Mefenamic acid	Ponstel	Rx	250 mg every 6 h	1,250 the first day, then 1,000	Maximum therapy of 1 wk
N-acetyl-*p*-aminophenol					
Acetaminophen**	Tylenol	OTC	650 mg every 6 h or 1,000 mg every 8 h	4,000	None

CV event. The exception would be for patients with cardiac disease such as a prior myocardial infarction or atrial fibrillation who were receiving antithrombotic therapy for 14 days or fewer.[30,62] Investigators have reported CV complications due to routine and long-term use of NSAIDs widely in the literature, and these can range from simple hypertensive episodes to the exacerbation of heart failure and even sudden cardiac death.[63-69] Investigators in 1 systematic review reported the high risk of acute myocardial infarction associated with diclofenac and first-time users of rofecoxib in the first 30 days of treatment.[63] However, in the same systematic review, these investigators did not report an increased risk with celecoxib. As a result, COX-2 inhibitors, except for celecoxib, have been removed from the US market.[64,66,70]

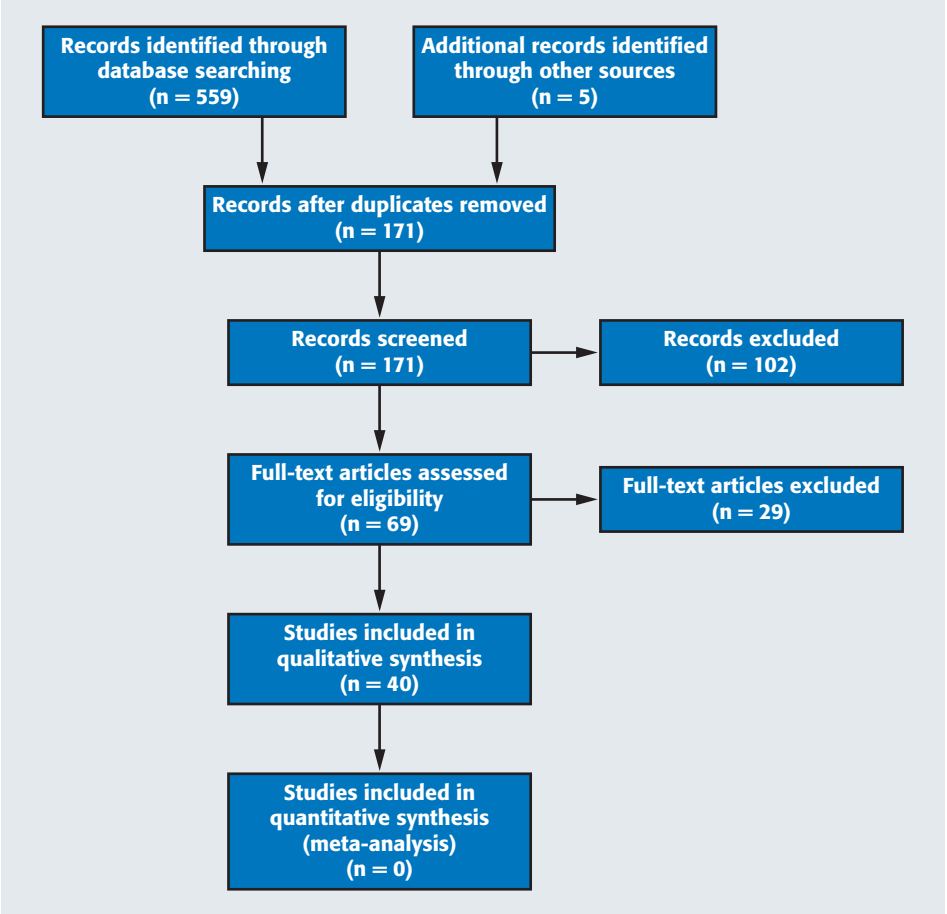

Figure. Preferred Reporting Items for Systematic Reviews and Meta-Analyses flowchart. *Source: Moher and colleagues.*[16]

TABLE 2

Profile of outcomes data from included cardiovascular studies and level of evidence.

STUDY	SAMPLE SIZE	INTERVENTION	OUTCOME	RISK OF BIAS*	LEVEL OF EVIDENCE†
Catella-Lawson and Colleagues,[28] 2001	18	Randomized, crossover study of combinations of single daily doses of 2 treatments for 6 days, with a washout period of at least 14 days. The inhibition of platelet cyclooxygenase-1 was assessed by using measurements of serum thromboxane B2.	Treatment with ibuprofen in patients with increased cardiovascular risk may limit the cardioprotective effects of ASA.‡	−; MPP§; COI¶; LSS#; SM**; RSG††	2
Whelton and Colleagues,[31] 2001	348	Edema, changes in systolic blood pressure, and changes in diastolic blood pressure as measured in patients with antihypertensive therapy. Measurements occurred at baseline and after 1, 2, and 6 wks of treatment.	In patients treated with celecoxib, blood pressure decreased; but in patients treated with rofecoxib blood pressure increased: week 1, 2.4 millimeters of mercury ($P = .014$); week 2, 2.8 mm Hg ($P = .006$); week 6, 3.1 mm Hg ($P = .007$).	−; RSG; DM‡‡	2
Dilger and Colleagues,[33] 2002	24 (12 young, 12 elderly)	Effects of celecoxib (200 milligrams twice a day) and diclofenac (75 mg twice a day) on blood pressure and renal function in 2 groups (young and elderly) were measured (changes in 24 h, 3 days, and 15 days).	Blood pressure and renal function were not affected significantly by short-term treatment with standard doses of celecoxib and diclofenac.	−; RSG; DM; LSS	2
Cryer and Colleagues,[29] 2005	51	Patients receiving ASA 81 mg every day for 8 days were assigned randomly to receive either ibuprofen 400 mg 3 times a day or placebo 3 times a day, in addition to ASA, for 10 days.	No clinically apparent loss of cardioprotection was found as reflected by thromboxane 2 inhibition.	+/−; COI; MS§§; RSG	2
Sowers and Colleagues,[25] 2005	136 (celecoxib), 138 (rofecoxib), 130 (naproxen)	24-h ambulatory blood pressure monitoring and validated arthritis efficacy assessments were conducted at random assignment and at wks 6 and 12 of treatment.	Rofecoxib but not celecoxib or naproxen induced a significant increase in 24-h systolic blood pressure.	+/−; COI; MS; RSG	2
Chan and Colleagues,[34] 2006	70,971	Prospective cohort study with 12-y follow-up of women who had no previous cardiovascular conditions and used NSAIDs¶¶ occasionally (1-4, 5-14, and 14-21 days) compared with >22 days (more frequent).	Women who reported occasional (1 to 21 days per mo) use of NSAIDs or acetaminophen did not experience a significant increase in the risk of cardiovascular events. Compared with nonusers, the risk for a cardiovascular event among women who used >15 tablets per wk were 1.86 (95% confidence interval, 1.27 to 2.73) for NSAIDs.	−; not RSS; not DB; large SS##	2
Gladding and Colleagues,[27] 2008	24	Platelet function was measured 12 h after the administration of each NSAID. The NSAID was administered 2 h before ASA 300 mg, and platelet function was reassessed 24 h later.	Ibuprofen, indomethacin, naproxen, and tiaprofenic acid all blocked the antiplatelet effect of ASA. Sulindac and celecoxib did not demonstrate any significant antiplatelet effect or reduce the antiplatelet effect of ASA.	−; RSG	2

* Risk of bias: −, low; +/−, moderate.
† The Oxford Centre for Evidence-Based Medicine is updating its levels of evidence scale.[60]
‡ ASA: Acetylsalicylic acid (aspirin).
§ MPP: Masking of participants and personnel.
¶ COI: Conflict of interest.
# LSS: Low sample size.
** SM: Single masked.
†† RSG: Random sequence generation.
‡‡ DM: Double masked.
§§ MS: Manufacturer sponsored.
¶¶ NSAID: Nonsteroidal anti-inflammatory drug.
SS: Sample size.
*** SR: Selective reporting.

TABLE 2 (CONTINUED)

STUDY	SAMPLE SIZE	INTERVENTION	OUTCOME	RISK OF BIAS*	LEVEL OF EVIDENCE†
van den Hondel and Colleagues,[32] 2011	5,307	NSAID current use was divided into short-term (≤14 days) and long-term (>14 days). Associations between drug exposure and echocardiographic measurements were assessed using linear and logistic regression analyses.	Current NSAID use for less than 14 days was associated with a significantly higher left ventricular end-systolic dimension and left ventricular end-diastolic dimension and a significantly lower fractional shortening compared with findings in nonusers.	−; not RSG; large SS; not DM	2
Meek and Colleagues,[26] 2013	30	ASA's antithrombocyte effect after administration of naproxen, ibuprofen, meloxicam, or etoricoxib taken 2 h before ASA was measured using the platelet function analyzer 100. ASA nonresponse was defined as circulation time prolongation less than 40% in the placebo cycle.	Ibuprofen and naproxen inhibited ASA's antithrombocyte effect if taken 2 h before ASA. Etoricoxib and meloxicam did not cause relevant changes in ASA thrombocyte inhibition.	−; not RSG; SM	2
Saxena and Colleagues,[19] 2013	7 donors; a population size of 50 and a maximum iteration of 1,500 were used for parameter settings	Human platelet-rich plasma was used for arachidonic acid–induced aggregation and determination of thromboxane synthesis. Further docking studies were used to explain the molecular basis of the NSAID-ASA interaction.	Celecoxib, dipyrone (active metabolite), ibuprofen, flufenamic acid, naproxen, nimesulide, oxaprozin, and piroxicam significantly interfered with the antiplatelet activity of ASA, but diclofenac, ketorolac, and acetaminophen did not.	+/−; LSS	4
Olsen and Colleagues,[30] 2015	88,662	Use of NSAIDs with ongoing antithrombotic treatment after first-time myocardial infarction. NSAID use was determined: time of 0-7, 8-30, 31-90, and more than 90 days.	An increased risk of bleeding and cardiovascular events was evident with concomitant use of NSAIDs, regardless of antithrombotic treatment, types of NSAIDs, or duration of use.	+/−; not RSG; large sample size; SR*** (patients with myocardial infarction only, without comparison or other medical history)	2

Although short-term use of NSAIDs was not reported to cause any major CV event, it was reported to negate the cardioprotective effect of acetylsalicylic acid (aspirin) (ASA), even as short as 24 hours after administration in 1 study.[28] Although this can be a clinically significant concern, it is the result of a drug interaction and not necessarily an intrinsic CV adverse effect of NSAID medications. Often this risk can be mitigated with more appropriate timing of the ingested interacting medications.[28] However, investigators in epidemiologic studies are inconsistent in reporting NSAID interactions with ASA's cardioprotective mechanism.[71-73] Investigators also discussed this inconsistency in a double-masked, RCT study in which they reported no meaningful loss of cardioprotection when ibuprofen and ASA were administered concomitantly.[29]

GI risk with the short-term use of NSAIDs. Short-term use of NSAIDs has been associated with GI complications, with abdominal pain being the most frequent symptom. Concomitant use of NSAIDs with antithrombotic therapy in particular was associated with ulcers and bleeding.[18,44,62] The concurrent use of misoprostol, or a proton pump inhibitor or substitution of a COX-2 specific NSAID, significantly reduced the risk of developing GI complications.[74-76]

Renal risk with the short-term use of NSAIDs. NSAIDs and coxibs have been associated with adverse renal events because they are nephrotoxic. Significant changes in renal function were reported as early as 2 weeks of using ASA 100 milligrams per day in elderly patients.[77,78]

Although acute renal function changes due to NSAIDs are usually reversible with cessation of the medication, the changes may trigger other adverse effects, specifically in elderly patients, that can result in acute renal failure.[79] A higher prevalence of kidney disease also may be due to other medically debilitating diseases such as diabetes, hypertension, higher body mass index, and concurrent nephrotoxic medications.[80] NSAIDs can affect renal function adversely in as short a time as the first 72 hours.[36] However, renal complications with the use of NSAIDs were controversial in the literature. To date, epidemiologic data from a large case-controlled study did not support the assumption of irreversible damage by NSAIDs and renal failure, unless 3 or more kilograms of NSAIDs had been consumed over a patient's lifetime.[81] Although NSAIDs

TABLE 3

Profile of outcomes data from included gastrointestinal studies and level of evidence.

STUDY	SAMPLE SIZE	INTERVENTION	OUTCOME	RISK OF BIAS*	LEVEL OF EVIDENCE†
Le Parc and Colleagues,[42] 2002	4,101	Randomized, multicenter study comparing the tolerability (GI‡, nervous system) of ASA§, acetaminophen, and ibuprofen in common pain resulting from musculoskeletal conditions in general practice with patients with other nonmusculoskeletal pain conditions. Patients took ASA or acetaminophen (both up to 3 grams daily) or ibuprofen (up to 1.2 g daily) for up to 7 days.	No serious digestive events were observed with any of the 3 treatments in either group up to 6 days. For digestive system events, ibuprofen was not only superior to ASA but also associated with a significantly lower event rate than acetaminophen was.	–; RSG¶; DM#	2
Moore and Colleagues,[41] 2002	2,815	Randomized study comparison of the tolerability of ibuprofen (up to 1.2 g daily) and ASA and acetaminophen (both up to 3 g daily) for up to 7 days.	Adverse effects for ibuprofen, ASA, and acetaminophen were, respectively, 12.0%, 15.7%, and 12.3%. Ibuprofen was tolerated significantly better than ASA ($P = .02$) and had comparable tolerability with that of acetaminophen.	–; RSG; DM	2
Rampal and Colleagues,[40] 2002	8,633	Either ibuprofen up to 1,200 milligrams daily, or acetaminophen or ASA, each up to 3,000 mg daily, for 1 to 7 days. The main outcome was the proportion of patients with GI adverse events.	More GI adverse events, principally abdominal pain, dyspepsia, nausea and diarrhea, with ASA (18.5%) than with ibuprofen (11.5%), but the difference between ibuprofen and acetaminophen (13.1%) was not significant.	–; RSG; SM**	2
Fiorucci and Colleagues,[49] 2003	40	7 days of treatment with nitric oxide derivative of ASA (400 and 800 mg twice daily), equimolar doses of ASA (200 and 420 mg twice daily), or placebo. Upper endoscopy was performed before and at the end of the treatment period.	Gastric or duodenal injury was found in all participants treated with ASA 200 and 420 mg twice daily for 7 consecutive days.	–; RSG; LSS††; DM	2
Seymour and Colleagues,[48] 2003	167	Comparison of the efficacy of soluble ASA 900 mg and acetaminophen 1,000 mg in patients with postoperative pain after third-molar surgery; 4-h investigation.	ASA reduced pain and had minor GI risk; the incidence of nausea was comparable in the soluble ASA and solid acetaminophen groups (15% and 16%, respectively) and was greater than that in the placebo group (6%).	–; RSG	2
Diener and Colleagues,[17] 2005	1,743	Efficacy, safety, and tolerability of 250 mg ASA + 200 mg acetaminophen + 50 mg caffeine (Thomapyrin) in comparison with 2 tablets of 250 mg ASA + 200 mg acetaminophen; 2 tablets of 500 mg ASA; 2 tablets of 500 mg acetaminophen; 2 tablets of 50 mg caffeine; and placebo for 4 h.	141 of 1,743 patients experienced adverse effects, with the most frequently reported being GI disorders, especially abdominal pain, in all treatment groups. The severity of all adverse effects was mild to moderate except in 5 cases that were classified as severe.	–; RSG; DM	2
Van Ganse and Colleagues,[43] 2005	8,677	The tolerability of acetaminophen, ASA, and ibuprofen at OTC doses, with patient-reported adverse event data as the primary outcome—7 days: acetaminophen up to 3 g/day, ASA up to 3 g/day, or ibuprofen up to 1,200 mg/day.	Adverse effects: ASA had the highest incidence, and ibuprofen and acetaminophen demonstrated lower but comparable adverse effects, but they were not significant during short-term therapy.	–; RSG; SM	2

* Risk of bias: –, low; +/–, moderate.
† The Oxford Centre for Evidence-Based Medicine is updating its levels of evidence scale.[60]
‡ GI: Gastrointestinal.
§ ASA: Acetylsalicylic acid (aspirin).
¶ RSG: Random sequence generation.
# DM: Double masked.
** SM: Single masked.
†† LSS: Low sample size.
‡‡ RCT: Randomized controlled clinical trial.
§§ NSAID: Nonsteroidal anti-inflammatory drug.
¶¶ SR: Selective reporting.

TABLE 3 (CONTINUED)

STUDY	SAMPLE SIZE	INTERVENTION	OUTCOME	RISK OF BIAS*	LEVEL OF EVIDENCE†
Goldstein and Colleagues,[44] 2006	1,045	RCT‡‡: 1-wk study, participants (age, 50-75 y) received ASA 325 mg once a day combined with either celecoxib 200 mg once a day, naproxen 500 mg twice a day, or placebo. Endoscopy was performed for incidence of 1 or more gastric and duodenal ulcers.	Fewer endoscopic ulcers were observed in patients treated with celecoxib and ASA than in those treated with naproxen and ASA. However, celecoxib and ASA was associated with a significantly higher incidence of gastric and duodenal ulcers than was ASA alone.	–; RSG; DM; SM	2
Lanas and Colleagues,[18] 2006	2,777	Case-controlled study use of NSAID§§ within a week.	Coxib use presents a lower relative risk of upper GI bleeding than does use of nonselective NSAIDs. However, when combined with low-dose ASA, the differences between nonselective NSAIDs and coxibs tend to disappear.	–; RSG; LSS	3
Fujimori and Colleagues,[45] 2009	34	Two groups: an NSAID-control group underwent NSAID (diclofenac sodium, 25 mg 3 times daily) and omeprazole (20 mg once daily) treatment, and an NSAID-prostaglandin group, who received prostaglandin (misoprostol, 200 μg 3 times daily) in addition to the same NSAID-omeprazole treatment. There were 15 participants per group, and they underwent capsule endoscopy before and 14 days after treatment.	NSAID treatment significantly increased the mean (standard deviation) number of mucosal breaks per participant.	–; RSG; SM	2
Steiner and Voelker,[46] 2009	2,852	The frequencies of all GI adverse events and adverse drug reactions were calculated from the pooled individual patient data of 9 similar randomized, double-masked, placebo-controlled clinical trials of single doses of ASA 1,000 mg in the treatment of acute migraine attacks, episodic tension-type headache, and dental pain (5 days).	The GI adverse effect differences between ASA and placebo were not great enough for short-lasting acute pain.	–; RSG; DM	1
Lanas and Colleagues,[47] 2011	67 RCTs, 6,181 patients	A meta-analysis of 67 studies was performed with the primary end point of patient-reported GI adverse events: 6,181 patients were treated with ASA, 3,515 with placebo, 1,145 with acetaminophen, and 754 with ibuprofen.	GI adverse effects were more frequent with ASA (9.9%) than with placebo (9.0%; odds ratio, 1.3; 95% confidence interval, 1.1-1.5). Dyspeptic symptoms were infrequent (4.6% in participants receiving placebo). The odds ratios for ASA were 1.3 versus placebo, 1.55 versus ibuprofen, and 1.04 versus acetaminophen. There were few serious GI adverse effects. Single dose and of 1-day duration for the treatment of pain, fever, or colds at common over-the-counter doses showed a low incidence of adverse events.	–; RSG	2
Baron and Colleagues,[50] 2013	76 RCTs, 48,774 patients	RCTs with at least 1 ASA arm at a dose between 325 and 4,000 mg/day and a treatment duration of at most 10 days compared with placebo.	ASA was associated with a higher risk of minor GI events than placebo or active comparators. Ulcers, perforation, and serious bleeding were not seen after use of ASA or any of the other interventions.	–; RSG	1
Olsen and Colleagues,[30] 2015	88,682	Patients 30 y or older admitted with first-time myocardial infarction and alive 30 days after discharge. Subsequent treatment with ASA, clopidogrel, or oral anticoagulants and their combinations, as well as ongoing concomitant NSAID use, was determined: time of 0-7, 8-30, 31-90, and more than 90 days.	NSAID use was associated with a marked risk of bleeding from the beginning of treatment (days 0-3 crude incidence rate, 7.3), and the risk persisted (days 31-90 crude incidence rate, 3.3). The same pattern of an association of increased early (days 0-3) bleeding risk was present for the individual antithrombotic groups.	+/–; not RSG; LSS; SR¶¶ (patients with myocardial infarction only, without comparison or other medical history)	2

TABLE 4

Profile of outcomes data from included respiratory safety studies and level of evidence.

STUDY	SAMPLE SIZE	INTERVENTION	OUTCOME	RISK OF BIAS*	LEVEL OF EVIDENCE†
Martin-Garcia and Colleagues,[57] 2002	40	Rofecoxib on 3 different days, until either the therapeutic dose of 25 milligrams or intolerance was reached. Each patient was rechallenged with 25 mg of rofecoxib 7 days later if no evidence of intolerance had been observed previously.	Rofecoxib 25 mg was well tolerated.	−; SM‡; LSS§; not RSG¶	2
Woessner and Colleagues,[59] 2002	60 participants with asthma	Celecoxib (100 mg, 200 mg, and 2 placebos) over 48 h. The next day, sensitivity to ASA# was proven in all patients with the use of SM ASA challenges.	Cross-reactivity between ASA and celecoxib does not occur in patients with NERD.**	−; DM††; LSS	2
Gyllfors and Colleagues,[55] 2003	33	Placebo or celecoxib (10, 30, or 100 mg in suspension) on 2 occasions 7 days apart. Participants were exposed to 400 mg of celecoxib administered during an open challenge session as 2 200-mg doses 2 h apart.	Cyclooxygenase-2 inhibitor was tolerated well in patients with asthma.	−; RSG; DM	2
Martin-Garcia and Colleagues,[56] 2003	33	Celecoxib on 3 different days, until either the therapeutic dose of 200 mg or intolerance was reached. Each patient was rechallenged with 200 mg celecoxib 7 days later if no evidence of intolerance was observed previously.	Celecoxib is a suitable NSAID.‡‡	−; LSS; not RSG; SM	2
Bavbek and Colleagues,[52] 2004	127	First day: placebos were given to all. Second day: one-fourth and three-fourths of the therapeutic doses of the active drugs (nimesulide 100 mg, meloxicam 7.5 mg, or rofecoxib 25 mg) were given at 60-min intervals. There was at least a 3-day interval between challenge tests.	Among 37 patients challenged with all 3 drugs, 11 reacted to nimesulide, and 1 patient reacted only to meloxicam. Three patients reacted to more than 1 of the drugs tested, and 1 of them reacted to all drugs.	+/−; SM; not RSG	2
El Miedany and Colleagues,[54] 2006	77	First day: patients were given placebo. Second day: once-daily etoricoxib in 3 different doses: 60 mg on day 2, 90 mg on day 3, and 120 mg on day 4. If no evidence of intolerance was seen, each patient was rechallenged with 60 or 90 mg of etoricoxib once daily (according to the rheumatic condition) 7 days later.	Lack of cross-reactivity between specific cyclooxygenase-2 inhibitors and ASA in NERD. Etoricoxib was safe for treating inflammation in patients with NERD.	+/−; not RSG	2
Bavbek and Colleagues,[53] 2007	21 patients with asthma	2-day NSAID, 7.5 mg of meloxicam on 2 separate days. One and three-fourths of the divided doses of placebo and the active drug were given at 1-h intervals.	7.5 mg of meloxicam is a safe alternative treatment for ASA-hypersensitive asthma.	+/−; SM, SR§§ (all patients had asthma); LSS; not RSG	4
Prieto and Colleagues,[58] 2007	70 patients intolerant to NSAID	First day: placebo. Second day: 2 doses of 250 and 500 mg nabumetone with a 2-h interval. Third day: 1 gram nabumetone. All patients who tolerated 1 g, except for the 11 patients evaluated first, were given an additional dose of 2 g nabumetone on day 4. Meloxicam placebo-controlled test in 51 patients 15 days after nabumetone administration, as follows: 2 doses of placebo on day 1; 2 doses of 3.75 and 7.5 mg with a 2-h interval on day 2; 15 mg on day 3.	The results of this study confirm a high percentage of tolerability to the maximum therapeutic dosage of nabumetone and meloxicam in patients with NSAID intolerance.	−; not RSG; SM	2
Gaber and Colleagues,[51] 2008	21 participants with asthma	Induced sputum, saliva, urine, and blood were obtained; baseline visit (visit 1) followed by an ASA provocation visit after 3 to 10 days (visit 2), except 1 participant who returned after 3 mo; Cysteinyl leukotrienes and leukotriene B4 were measured.	Increase in cysteinyl leukotriene production in ASA-intolerant asthma.	+/−; Not RSG; not DM or SM; LSS	4

* Risk of bias: −, low; +/−, moderate.
† The Oxford Centre for Evidence-Based Medicine is updating its levels of evidence scale.[60]
‡ SM: Single masked.
§ LSS: Low sample size.
¶ RSG: Random sequence generation.
# ASA: Acetylsalicylic acid (aspirin).
** NERD: NSAID-exacerbated respiratory disease.
†† DM: Double masked.
‡‡ NSAID: Nonsteroidal anti-inflammatory drug.
§§ SR: Selective reporting.

TABLE 5

Profile of outcomes data from included renal safety studies and level of evidence.

STUDY	SAMPLE SIZE	INTERVENTION	OUTCOME	RISK OF BIAS*	LEVEL OF EVIDENCE†
Ahmad and Colleagues,[35] 2002	630 reports (256 reports with celecoxib and 374 with rofecoxib)	The authors performed a search in the FDA‡ Adverse Event Reporting System to identify cases of renal failure submitted to the FDA.	The time of onset in 4 cases with celecoxib was about 3 days, and in 33 (41%) cases, this was less than or equal to 14 days.	+/−; SR§	4
Dilger and Colleagues,[33] 2002	24 (12 young, 12 elderly)	Effects of celecoxib (200 milligrams twice a day) and diclofenac (75 mg twice a day) on blood pressure and renal function in 2 groups of young (mean age = 32 y) and elderly (mean age = 68 y) patients over 2 wks.	Blood pressure and renal function were not affected significantly by short-term nonsteroidal anti-inflammatory drug treatment in either the young or elderly patients.	−; RSG¶; DM#; LSS**	2
Farker and Colleagues,[39] 2002	32 patients with type 2 diabetes: with and without impaired renal function	16 patients with impaired renal function received 140 mg diclofenac-cholestyramine (corresponding to 75 mg diclofenac sodium) or placebo twice a day on days 1 and 2 and once on day 3 with a washout period of 6 days between the 2 periods.	Nonspecific cyclooxygenase inhibition by short-term administration of diclofenac-cholestyramine did not affect renal function in patients with type 2 diabetes.	−; RSG; SM††; LSS	2
Schwartz and Colleagues,[36] 2002	67 elderly patients	Patients received rofecoxib, 25 mg daily (n = 17); celecoxib, 200 mg twice daily (n = 17); naproxen, 500 mg twice daily (n = 17); or matching placebo (n = 16) for 28 days. Patients were sequestered in the clinic for the first 14 treatment days receiving a controlled diet.	Urinary sodium excretion during the first 72 h of treatment (primary end point) significantly decreased in the rofecoxib, celecoxib, and naproxen groups compared with baseline ($P \leq .05$). No serious adverse effect was reported even after 28 days.	−; RSG; DM	2
Clària and Colleagues,[38] 2005	28 patients with cirrhosis and ascites	Comparing the effects of the selective cyclooxygenase-2 inhibitor celecoxib (200 mg every 12 h for a total of 5 doses) on platelet and renal function and the renal response to furosemide (40 mg intravenously) with those of naproxen (500 mg every 12 h for a total of 5 doses) and placebo in 28 patients with cirrhosis and ascites.	Celecoxib did not impair platelet and renal function and the response to diuretics in decompensated cirrhosis but naproxen did.	−; RSG; LSS; DM	2
Mizuno and Colleagues,[37] 2012	164 patients with renal carcinoma undergoing laparoscopic radical nephrectomy	Short-term administration of nonsteroidal anti-inflammatory drugs during the first week after laparoscopic radical nephrectomy.	Diclofenac sodium was a risk factor for renal impairment after laparoscopic radical nephrectomy in elderly patients, but loxoprofen sodium had a negligible effect.	+/−; not RSG	3

* Risk of bias: −, low; +/−, moderate.
† The Oxford Centre for Evidence-Based Medicine is updating its levels of evidence scale.[60]
‡ FDA: Food and Drug Administration.
§ SR: Selective reporting.
¶ RSG: Random sequence generation.
# DM: Double masked.
** LSS: Low sample size.
†† SM: Single masked.

are nephrotoxic, the ultimate complication of dialysis is not recorded systematically.[82]

Respiratory risk with the short-term use of NSAIDs. Investigators in a 2015 systematic review and meta-analysis reported that the prevalence of NERD triggered by ASA is high.[83] Our findings agree with this review, and we also concur that acetaminophen and COX-2 specific inhibitors such as celecoxib pose only a minimum risk to patients with stable mild to moderate asthma.[84] However, although traditional NSAIDs such as ASA should be avoided in patients with NERD in favor of acetaminophen or COX-2 specific inhibitors, despite the high level of evidence provided, clinicians should be aware that cross-reaction of COX-2 inhibitors, and even acetaminophen, has been reported in some patients.[85-87]

The severity of these complications often varies depending on a patient's overall health, concurrent medical conditions and medications, and length of exposure at varying doses to the many different NSAIDs available. When prescribed by oral health care professionals to treat orofacial pain, typical NSAID prescription durations are for generally less than 10 days, which minimizes a patient's exposure and, therefore, the

potential for any possible clinically significant adverse effects.

The limitations of the studies reviewed were that most of the investigations provided little or no information on dosage, frequency, and baseline disease risk (CV, GI, renal, and respiratory). RCTs with large study populations are needed to assess any specific negative CV, GI, renal, and respiratory outcomes associated with the short-term use of NSAIDs, as is typical in the treatment in orofacial discomfort.

There are several multidose oral surgery pain studies of NSAIDs taken for up to 1 week in which the investigators did not report any CV, GI, renal, and respiratory complications in young healthy adults but did report other adverse effects such as drowsiness, headache, and dizziness.[88,89] On the basis of the available scientific evidence, NSAIDs may be considered relatively safe drugs when prescribed at the most effective dose and for the shortest duration of time, which was defined to be fewer than 10 days.

CONCLUSIONS

The available scientific evidence regarding adverse effects and safety of NSAIDs suggests that, in patients taking routine NSAIDs for 10 days or fewer to alleviate pain, most patients are not at any increased risk of developing adverse CV, GI, renal, or respiratory adverse effects when compared with patients who were not exposed to these medications. The exceptions would be patients with NERD, patients with prior myocardial infarction who are receiving antithrombotic therapy, patients with asthma, and patients with a history of renal disease. ■

Dr. Aminoshariae is the director, Predoctoral Endodontics, Case Western Reserve University School of Dental Medicine, 2124 Cornell Rd., Cleveland, OH 44106, e-mail axa53@case.edu. Address correspondence to Dr. Aminoshariae.

Dr. Kulild is a professor emeritus, Department of Endodontics, University of Missouri-Kansas City School of Dentistry, Kansas City, MO.

Dr. Donaldson is the director, Performance Services, VHA Clinical Pharmacy, Irving, TX; a clinical professor, School of Pharmacy, University of Montana, Missoula, MT; and a clinical assistant professor, School of Dentistry, Oregon Health & Science University, Portland, OR.

Disclosure. None of the authors reported any disclosures.

1. US Food and Drug Administration. FDA strengthens warning of heart attack and stroke risk for non-steroidal anti-inflammatory drugs. Available at: http://www.fda.gov/ForConsumers/ConsumerUpdates/ucm453610.htm. Accessed July 20, 2015.

2. Stevenson DD. Diagnosis, prevention, and treatment of adverse reactions to aspirin and nonsteroidal anti-inflammatory drugs. *J Allergy Clin Immunol*. 1984;74(4):617-622.

3. US Food and Drug Administration. Medication guide for nonsteroidal anti-inflammatory drugs (NSAIDs). Available at: http://www.fda.gov/downloads/Drugs/DrugSafety/UCM191085.pdf. Accessed June 11, 2015.

4. García Rodríguez LA, Tacconelli S, Patrignani P. Role of dose potency in the prediction of risk of myocardial infarction associated with nonsteroidal anti-inflammatory drugs in the general population. *J Am Coll Cardiol*. 2008;52(20):1628-1636.

5. Kohli P, Steg PG, Cannon CP, et al. NSAID use and association with cardiovascular outcomes in outpatients with stable atherothrombotic disease. *Am J Med*. 2014;127(1):53-60.e1.

6. Farkouh ME, Greenberg BP. An evidence-based review of the cardiovascular risks of nonsteroidal anti-inflammatory drugs. *Am J Cardiol*. 2009;103(9):1227-1237.

7. Garcia Rodríguez LA, González-Pérez A. Long-term use of nonsteroidal anti-inflammatory drugs and the risk of myocardial infarction in the general population. *BMC Med*. 2005;3(1):17.

8. Griffin MR, Yared A, Ray WA. Nonsteroidal antiinflammatory drugs and acute renal failure in elderly persons. *Am J Epidemiol*. 2000;151(5):488-496.

9. Sandler DP, Burr FR, Weinberg CR. Nonsteroidal anti-inflammatory drugs and the risk for chronic renal disease. *Ann Intern Med*. 1991;115(3):165-172.

10. Perneger TV, Whelton PK, Klag MJ. Risk of kidney failure associated with the use of acetaminophen, aspirin, and nonsteroidal antiinflammatory drugs. *N Engl J Med*. 1994;331(25):1675-1679.

11. Kristensen SL, Fosbøl EL, Kamper AL, et al. Use of nonsteroidal anti-inflammatory drugs prior to chronic renal replacement therapy initiation: a nationwide study. *Pharmacoepidemiol Drug Saf*. 2012;21(4):428-434.

12. Henry D, McGettigan P. Epidemiology overview of gastrointestinal and renal toxicity of NSAIDs. *Int J Clin Prac Suppl*. 2003;135:43-49.

13. Straube S, Tramèr MR, Moore RA, Derry S, McQuay HJ. Mortality with upper gastrointestinal bleeding and perforation: effects of time and NSAID use. *BMC Gastroenterol*. 2009;9(1):41.

14. Sakamoto C, Kawai T, Nakamura S, Sugioka T, Tabira J. Comparison of gastroduodenal ulcer incidence in healthy Japanese subjects taking celecoxib or loxoprofen evaluated by endoscopy: a placebo-controlled, double-blind 2-week study. *Aliment Pharmacol Ther*. 2013;37(3):346-354.

15. Stevenson DD, Hankammer MA, Mathison DA, Christiansen SC, Simon RA. Aspirin desensitization treatment of aspirin-sensitive patients with rhinosinusitis-asthma: long-term outcomes. *J Allergy Clin Immunol*. 1996;98(4):751-758.

16. Moher D, Liberati A, Tetzlaff J, Altman DG. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. *Ann Intern Med*. 2009;151(4):264-269.

17. Diener H, Pfaffenrath V, Pageler L, Peil H, Aicher B. The fixed combination of acetylsalicylic acid, paracetamol and caffeine is more effective than single substances and dual combination for the treatment of headache: a multicentre, randomized, double-blind, single-dose, placebo-controlled parallel group study. *Cephalalgia*. 2005;25(10):776-787.

18. Lanas A, García-Rodríguez LA, Arroyo MT, et al. Risk of upper gastrointestinal ulcer bleeding associated with selective cyclo-oxygenase-2 inhibitors, traditional non-aspirin non-steroidal anti-inflammatory drugs, aspirin and combinations. *Gut*. 2006;55(12):1731-1738.

19. Saxena A, Balaramnavar VM, Hohlfeld T, Saxena AK. Drug/drug interaction of common NSAIDs with antiplatelet effect of aspirin in human platelets. *Eur J Clin Pharmacol*. 2013;721(1):215-224.

20. Lexicomp. Lexicomp online for dentistry. Available at: http://webstore.lexi.com/ONLINE-Software-for-Dentists. Accessed June 6, 2015.

21. Hopewell S, McDonald S, Clarke M, Egger M. Grey literature in meta-analyses of randomized trials of health care interventions. *Cochrane Database Syst Rev*. 2007;(2):MR000010.

22. Shea BJ, Grimshaw JM, Wells GA, et al. Development of AMSTAR: a measurement tool to assess the methodological quality of systematic reviews. *BMC Med Res Methodol*. 2007;7(1):10.

23. Masood M, Thaliath ET, Bower EJ, Newton JT. An appraisal of the quality of published qualitative dental research. *Community Dent Oral Epidemiol*. 2011;39(3):193-203.

24. Guyatt GH, Oxman AD, Vist GE, et al. GRADE: an emerging consensus on rating quality of evidence and strength of recommendations. *BMJ*. 2008;336(7650):924-926.

25. Sowers JR, White WB, Pitt B, et al; Celecoxib Rofecoxib Efficacy and Safety in Comorbidities Evaluation Trial (CRESCENT) Investigators. The effects of cyclooxygenase-2 inhibitors and nonsteroidal anti-inflammatory therapy on 24-hour blood pressure in patients with hypertension, osteoarthritis, and type 2 diabetes mellitus [published correction appears in *Arch Intern Med*. 2005;165(5):551]. *Arch Intern Med*. 2005;165(2):161-168.

26. Meek I, Vonkeman H, Kasemier J, Movig K, van de Laar M. Interference of NSAIDs with the thrombocyte inhibitory effect of aspirin: a placebo-controlled, ex vivo, serial placebo-controlled serial crossover study. *Eur J Clin Pharmacol*. 2013;69(3):365-371.

27. Gladding PA, Webster MW, Farrell HB, et al. The antiplatelet effect of six non-steroidal anti-inflammatory drugs and their pharmacodynamic

interaction with aspirin in healthy volunteers. *Am J Cardiol*. 2008;101(7):1060-1063.

28. Catella-Lawson F, Reilly MP, Kapoor SC, et al. Cyclooxygenase inhibitors and the antiplatelet effects of aspirin. *N Engl J Med*. 2001;345(25):1809-1817.

29. Cryer B, Berlin RG, Cooper SA, Hsu C, Wason S. Double-blind, randomized, parallel, placebo-controlled study of ibuprofen effects on thromboxane B2 concentrations in aspirin-treated healthy adult volunteers. *Clin Ther*. 2005;27(2):185-191.

30. Olsen AMS, Gislason GH, McGettigan P, et al. Association of NSAID use with risk of bleeding and cardiovascular events in patients receiving antithrombotic therapy after myocardial infarction. *JAMA*. 2015;313(8):805-814.

31. Whelton A, Fort JG, Puma JA, et al. Cyclooxygenase-2–specific inhibitors and cardiorenal function: a randomized, controlled trial of celecoxib and rofecoxib in older hypertensive osteoarthritis patients. *Am J Ther*. 2001;8(2):85-95.

32. van den Hondel KE, Eijgelsheim M, Ruiter R, et al. Effect of short-term NSAID use on echocardiographic parameters in elderly people: a population-based cohort study. *Heart*. 2011;97(7):540-543.

33. Dilger K, Herrlinger C, Peters J, et al. Effects of celecoxib and diclofenac on blood pressure, renal function, and vasoactive prostanoids in young and elderly subjects. *J Clin Pharmacol*. 2002;42(9):985-994.

34. Chan AT, Manson JE, Albert CM, et al. Nonsteroidal antiinflammatory drugs, acetaminophen, and the risk of cardiovascular events. *Circulation*. 2006;113(12):1578-1587.

35. Ahmad SR, Kortepeter C, Brinker A, Chen M, Beitz J. Renal failure associated with the use of celecoxib and rofecoxib. *Drug Saf*. 2002;25(7):537-544.

36. Schwartz J, Vandormael K, Malice M, et al. Comparison of rofecoxib, celecoxib, and naproxen on renal function in elderly subjects receiving a normal-salt diet. *Clin Pharmacol Ther*. 2002;72(1):50-61.

37. Mizuno T, Ito K, Miyagawa Y, et al. Short-term administration of diclofenac sodium affects renal function after laparoscopic radical nephrectomy in elderly patients. *Jpn J Clin Oncol*. 2012;42(11):1073-1078.

38. Clària J, Kent JD, López-Parra M, et al. Effects of celecoxib and naproxen on renal function in nonazotemic patients with cirrhosis and ascites. *Hepatology*. 2005;41(3):579-587.

39. Farker K, Merkel U, Schweer H, et al. Effects of short-term treatment with diclofenac-colestyramine on renal function and urinary prostanoid excretion in patients with type-2 diabetes. *Eur J Clin Pharmacol*. 2002;58(2):85-91.

40. Rampal P, Moore N, Van Ganse E, et al. Gastrointestinal tolerability of ibuprofen compared with paracetamol and aspirin at over-the-counter doses. *J Int Med Res*. 2002;30(3):301-308.

41. Moore N, Le Parc J, Van Ganse E, et al. Tolerability of ibuprofen, aspirin and paracetamol for the treatment of cold and flu symptoms and sore throat pain. *Int J Clin Pract*. 2002;56(10):732-734.

42. Le Parc J, Van Ganse E, Moore N, et al. Comparative tolerability of paracetamol, aspirin and ibuprofen for short-term analgesia in patients with musculoskeletal conditions: results in 4291 patients. *Clin Rheumatol*. 2002;21(1):28-31.

43. Van Ganse E, Jones JK, Moore N, Parc JM, Wall R, Schneid H. A large simple clinical trial prototype for assessment of OTC drug effects using patient-reported data. *Pharmacoepidemiol Drug Saf*. 2005;14(4):249-255.

44. Goldstein J, Lowry S, Lanza F, Schwartz H, Dodge W. The impact of low-dose aspirin on endoscopic gastric and duodenal ulcer rates in users of a non-selective non-steroidal anti-inflammatory drug or a cyclo-oxygenase-2-selective inhibitor. *Aliment Pharmacol Ther*. 2006;23(10):1489-1498.

45. Fujimori S, Seo T, Gudis K, et al. Prevention of nonsteroidal anti-inflammatory drug–induced small-intestinal injury by prostaglandin: a pilot randomized controlled trial evaluated by capsule endoscopy. *Gastrointest Endosc*. 2009;69(7):1339-1346.

46. Steiner T, Voelker M. Gastrointestinal tolerability of aspirin and the choice of over-the-counter analgesia for short-lasting acute pain. *J Clin Pharm Ther*. 2009;34(2):177-186.

47. Lanas A, McCarthy D, Voelker M, et al. Short-term acetylsalicylic acid (aspirin) use for pain, fever, or colds: gastrointestinal adverse effects. *Drugs R D*. 2011;11(3):277-288.

48. Seymour R, Hawkesford J, Sykes J, Stillings M, Hill CM. An investigation into the comparative efficacy of soluble aspirin and solid paracetamol in postoperative pain after third molar surgery. *Br Dent J*. 2003;194(3):153-157.

49. Fiorucci S, Santucci L, Gresele P, et al. Gastrointestinal safety of NO-aspirin (NCX-4016) in healthy human volunteers: a proof of concept endoscopic study. *Gastroenterology*. 2003;124(3):600-607.

50. Baron JA, Senn S, Voelker M, et al. Gastrointestinal adverse effects of short-term aspirin use: a meta-analysis of published randomized controlled trials. *Drugs R D*. 2013;13(1):9-16.

51. Gaber F, Daham K, Higashi A, et al. Increased levels of cysteinyl-leukotrienes in saliva, induced sputum, urine and blood from patients with aspirin-intolerant asthma. *Thorax*. 2008;63(12):1076-1082.

52. Bavbek S, Çelik G, Özer F, Mungan D, Mısırlıgil Z. Safety of selective COX-2 inhibitors in aspirin/nonsteroidal anti-inflammatory drug-intolerant patients: comparison of nimesulide, meloxicam, and rofecoxib. *J Asthma*. 2004;41(1):67-75.

53. Bavbek S, Dursun AB, Dursun E, Eryılmaz A, Mısırlıgil Z. Safety of meloxicam in aspirin-hypersensitive patients with asthma and/or nasal polyps. *Int Arch Allergy Immunol*. 2007;142(1):64-69.

54. El Miedany Y, Youssef S, Ahmed I, El Gaafary M. Safety of etoricoxib, a specific cyclooxygenase-2 inhibitor, in asthmatic patients with aspirin-exacerbated respiratory disease. *Ann Allergy Asthma Immunol*. 2006;97(1):105-109.

55. Gyllfors P, Bochenek G, Overholt J, et al. Biochemical and clinical evidence that aspirin-intolerant asthmatic subjects tolerate the cyclooxygenase 2-selective analgetic drug celecoxib. *J Allergy Clin Immunol*. 2003;111(5):1116-1121.

56. Martin-Garcia C, Hinojosa M, Berges P, Camacho E, García-Rodriguez R, Alfaya T. Celecoxib, a highly selective COX-2 inhibitor, is safe in aspirin-induced asthma patients. *J Investig Allergol Clin Immunol*. 2003;13(1):20-25.

57. Martin-Garcia C, Hinojosa M, Berges P, et al. Safety of a cyclooxygenase-2 inhibitor in patients with aspirin-sensitive asthma. *Chest*. 2002;121(6):1812-1817.

58. Prieto A, De Barrio M, Martín E, et al. Tolerability to nabumetone and meloxicam in patients with nonsteroidal anti-inflammatory drug intolerance. *J Allergy Clin Immunol*. 2007;119(4):960-964.

59. Woessner KM, Simon RA, Stevenson DD. The safety of celecoxib in patients with aspirin-sensitive asthma. *Arthritis Rheum*. 2002;46(8):2201-2206.

60. Center for Evidence-Based Medicine. OCEBM levels of evidence. Available at: http://www.cebm.net/index.aspx?o=5653. Accessed September 4, 2015.

61. Higgins JP, Altman DG, Gøtzsche PC, et al. The Cochrane Collaboration's tool for assessing risk of bias in randomised trials. *BMJ*. 2011;343:d5928.

62. Lamberts M, Lip GY, Hansen ML, et al. Relation of nonsteroidal anti-inflammatory drugs to serious bleeding and thromboembolism risk in patients with atrial fibrillation receiving antithrombotic therapy: a nationwide cohort study. *Ann Intern Med*. 2014;161(10):690-698.

63. McGettigan P, Henry D. Cardiovascular risk and inhibition of cyclooxygenase: a systematic review of the observational studies of selective and nonselective inhibitors of cyclooxygenase 2. *JAMA*. 2006;296(13):1633-1644.

64. McGettigan P, Henry D. Use of non-steroidal anti-inflammatory drugs that elevate cardiovascular risk: an examination of sales and essential medicines lists in low-, middle-, and high-income countries. *PLoS Med*. 2013;10(2):e1001388.

65. Hernández-Díaz S, Varas-Lorenzo C, García Rodríguez LA. Non-steroidal antiinflammatory drugs and the risk of acute myocardial infarction. *Basic Clin Pharmacol Toxicol*. 2006;98(3):266-274.

66. McGettigan P, Henry D. Cardiovascular risk with non-steroidal anti-inflammatory drugs: systematic review of population-based controlled observational studies. *PLoS Med*. 2011;8(9):e1001098.

67. García Rodríguez LA, Hernández-Díaz S. Nonsteroidal antiinflammatory drugs as a trigger of clinical heart failure. *Epidemiology*. 2003;14(2):240-246.

68. Huerta C, Varas-Lorenzo C, Castellsague J, Rodriguez LG. Non-steroidal anti-inflammatory drugs and risk of first hospital admission for heart failure in the general population. *Heart*. 2006;92(11):1610-1615.

69. Chan CC, Reid CM, Aw TJ, et al. Do COX-2 inhibitors raise blood pressure more than nonselective NSAIDs and placebo? An updated meta-analysis. *J Hypertens*. 2009;27(12):2332-2341.

70. Antman EM, Bennett JS, Daugherty A, et al. Use of nonsteroidal antiinflammatory drugs: an update for clinicians—a scientific statement from the American Heart Association. *Circulation*. 2007;115(12):1634-1642.

71. MacDonald T, Wei L. Effect of ibuprofen on cardioprotective effect of aspirin. *Lancet*. 2003;361(9357):573-574.

72. Curtis JP, Wang Y, Portnay EL, et al. Aspirin, ibuprofen, and mortality after myocardial infarction: retrospective cohort study. *BMJ*. 2003; 327(7427):1322-1323.

73. Patel TN, Goldberg KC. Use of aspirin and ibuprofen compared with aspirin alone and the risk of myocardial infarction. *Arch Intern Med*. 2004; 164(8):852-856.

74. Hooper L, Brown TJ, Elliott R, Payne K, Roberts C, Symmons D. The effectiveness of five strategies for the prevention of gastrointestinal toxicity induced by non-steroidal anti-inflammatory drugs: systematic review. *BMJ*. 2004;329(7472):948.

75. Zhang W, Doherty M, Arden N, et al. EULAR evidence based recommendations for the management of hip osteoarthritis: report of a task force of the EULAR Standing Committee for International Clinical Studies Including Therapeutics (ESCISIT). *Ann Rheum Dis*. 2005;64(5):669-681.

76. Zhang W, Moskowitz RW, Nuki G, et al. OARSI recommendations for the management of hip and knee osteoarthritis, Part II: OARSI evidence-based, expert consensus guidelines. *Osteoarthritis Cartilage*. 2008; 16(2):137-162.

77. Segal R, Lubart E, Leibovitz A, Iaina A, Caspi D. Renal effects of low dose aspirin in elderly patients. *Isr Med Assoc J*. 2006;8(10):679-682.

78. Segal R, Lubart E, Leibovitz A, et al. Early and late effects of low-dose aspirin on renal function in elderly patients. *Am J Med*. 2003;115(6): 462-466.

79. Chronopoulos A, Cruz DN, Ronco C. Hospital-acquired acute kidney injury in the elderly. *Nat Rev Nephrol*. 2010;6(3):141-149.

80. Coresh J, Selvin E, Stevens LA, et al. Prevalence of chronic kidney disease in the United States. *JAMA*. 2007;298(17):2038-2047.

81. van der Woude FJ, Heinemann LA, Graf H, et al. Analgesics use and ESRD in younger age: a case-control study. *BMC Nephrol*. 2007;8(1):15.

82. Wehling M. Non-steroidal anti-inflammatory drug use in chronic pain conditions with special emphasis on the elderly and patients with relevant comorbidities: management and mitigation of risks and adverse effects. *Eur J Clin Pharmacol*. 2014;70(10):1159-1172.

83. Morales DR, Guthrie B, Lipworth BJ, Jackson C, Donnan PT, Santiago VH. NSAID-exacerbated respiratory disease: a meta-analysis evaluating prevalence, mean provocative dose of aspirin and increased asthma morbidity. *Allergy*. 2015;70(7):828-835.

84. Morales DR, Lipworth BJ, Guthrie B, Jackson C, Donnan PT, Santiago VH. Safety risks for patients with aspirin-exacerbated respiratory disease after acute exposure to selective nonsteroidal anti-inflammatory drugs and COX-2 inhibitors: meta-analysis of controlled clinical trials. *J Allergy Clin Immunol*. 2014;134(1):40-45.

85. Kim YJ, Lim KH, Kim MY, et al. Cross-reactivity to acetaminophen and celecoxib according to the type of nonsteroidal anti-inflammatory drug hypersensitivity. *Allergy Asthma Immunol Res*. 2014; 6(2):156-162.

86. Settipane RA, Stevenson DD. Cross sensitivity with acetaminophen in aspirin-sensitive subjects with asthma. *J Allergy Clin Immunol*. 1989; 84(1):26-33.

87. Dona I, Blanca-López N, Jagemann L, et al. Response to a selective COX-2 inhibitor in patients with urticaria/angioedema induced by nonsteroidal anti-inflammatory drugs. *Allergy*. 2011;66(11):1428-1433.

88. Hersh EV, Cooper S, Betts N, et al. Single dose and multidose analgesic study of ibuprofen and meclofenamate sodium after third molar surgery. *Oral Surg Oral Med Oral Pathol*. 1993;76(6):680-687.

89. Cooper S, Hersh E, Betts N, et al. Multidose analgesic study of two meclofenamate acid formulations in a postsurgical dental pain model. *Analgesia*. 1994;1(6):65-71.