Cover Story

Benefits and harms associated with analgesic medications used in the management of acute dental pain

An overview of systematic reviews

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Supplemental material is available online.

ABSTRACT

Background. Effective pain management is a priority in dental practice. Government and private agencies highlight the need to provide optimal pain relief, balancing potential benefits and harms of both opioid and nonopioid analgesic agents. The purpose of this study is to summarize the available evidence on the benefits and harms of analgesic agents, focusing on preexisting systematic reviews.

Types of Studies Reviewed. An overview of systematic reviews was conducted to evaluate the efficacy or reported adverse events associated with orally administered medication or medication combinations for relief of acute pain. Reviews were inclusive of all age populations but were limited to those that evaluated medication and medication combinations marketed in the United States and had moderate or high methodological quality according to the A MeaSurement Tool to Assess systematic Reviews (AMSTAR) 2 tool.

Results. Five reviews were found eligible for inclusion. The data identified combinations of ibuprofen and acetaminophen as having the highest association with treatment benefit in adult patients and the highest proportion of adult patients who experienced maximum pain relief. Diflunisal, acetaminophen, and oxycodone were found to have the longest duration of action in adult patients. Medication and medication combinations that included opioids were among those associated most frequently with acute adverse events in both child and adult-aged patient populations.

Practical Implications. The best available data suggested that the use of nonsteroidal medications, with or without acetaminophen, offered the most favorable balance between benefits and harms, optimizing efficacy while minimizing acute adverse events.

Key Words. Analgesia; pain relief; adverse events; systematic review; decision-making opioids; nonsteroidal anti-inflammatory drugs; opioids; acetaminophen.

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Safe and effective pain management is an essential goal for all dental practitioners. Oral formulations, including both opioid and nonopioid analgesic agents, are among the medications commonly provided to manage pain for dental patients. Although the 2016 recommendations from the Centers for Disease Control and Prevention (CDC) about management of long-term pain were less well codified with respect to analgesic use for acute pain, it did include recommendations about limiting dose and duration of opioid-containing medications.[1] This likely reflects growing concern about the increasing occurrence of opioid misuse leading to deaths from both prescription and illegal opioids.[2] Although effective redress of this problem will be multifaceted, it will likely result in increased scrutiny about the choice of medications to be used when managing acute pain. The dual goals for pain management are safety and efficacy.

A variety of oral formulations of prescription and over-the-counter analgesic agents are often included alone or in combination as a component in strategies to manage acute dental pain.[3]

Clinical considerations when determining the analgesic agent to be used include, but are not limited to, severity of the pain, patient pain sensitivity, medical history, specific dental pathologic process, and, in postoperative situations, the degree of surgical trauma.

The objective of our study is to summarize the data on oral analgesic medications with the aim of creating a compendium that details both the benefits and harms of these medications as a resource for dentists to use in their clinical decision making. This work was conducted in response to a request from the American Dental Association (ADA) Council on Dental Practice, using a protocol established a priori (available from the authors) and registered with the International Prospective Register of Systematic Reviews (PROSPERO) database (no. CRD42017080270) to summarize the best available evidence with respect to questions of safety and efficacy for relief of acute pain relevant to dental practice in the United States.

METHODS

This overview of reviews used the rapid review methodology[4] to identify and summarize the available evidence from existing systematic reviews that examined the relative safety and efficacy of oral opioid and nonopioid analgesic agents available for use in the United States for the management of acute postoperative dental pain.

Selection criteria of included reviews

Type of Studies

We included systematic reviews and overviews of reviews with or without meta-analysis. We considered a report to be a systematic review by using a combination of selection criteria

- identified by the authors as a systematic review;
- included an explicit description of the search strategy;
- conducted the search in at least 2 electronic databases.

In addition, we selected reviews that ranked as moderate to high methodological quality according to the A MeaSurement Tool to Assess systematic Reviews (AMSTAR) 2 tool.[5] Narrative reviews, editorials, and letters to the editor were excluded.

Type of Participants and Interventions

Systematic reviews or overviews of reviews that summarized data on the use of orally administered medications for the management of acute pain from studies that involved either adults or children were eligible for inclusion. The source of pain was mostly acute postoperative dental pain (for example, following third-molar extraction).

Type of Outcome Measures

Systematic reviews or overviews of reviews with data on the pharmacologic management of acute pain that reported on efficacy of pain relief (defined as at least 50% relief from maximum pain that lasted 46 hours), duration of pain relief (time before rescue remedication was requested), or any acute adverse events were included in this review.

Search methods for systematic review retrieval

The literature search strategy used the key words "(acute pain) AND (dental OR dentist* OR postop* OR postsurg*)" and was performed with the PubMed Clinical Queries for Systematic Reviews tool on April 13, 2017. In addition, manual searches of the reference lists of key articles were conducted to complement the electronic search. We also searched PROSPERO to identify systematic reviews under development that may have been relevant for our study.

Study selection, data collection, and analysis

The preliminary screening of titles and abstracts for all potentially eligible citations identified in the literature search was conducted in duplicate with the use of EndNote (Clarivate Analytics). In a second stage, the full text of any citation considered as potentially eligible was retrieved, and the eligibility was assessed. In case of disagreements among screeners, a third researcher acted as arbiter.

Assessment of the Methodological Quality of Reviews

We used the AMSTAR 2 tool to evaluate the methodological quality of the potentially eligible systematic reviews,[5] and we used the AMSTAR rating of the individual reviews included in the

ABBREVIATION KEY

ADA:	American Dental Association.
AMSTAR:	A MeaSurement Tool to Assess systematic Reviews.
CDC:	Centers for Disease Control and Prevention.
NNTB:	Number needed to treat for benefit.
NNTH:	Number needed to treat to harm.
PROSPERO:	International Prospective Register of Systematic Reviews.

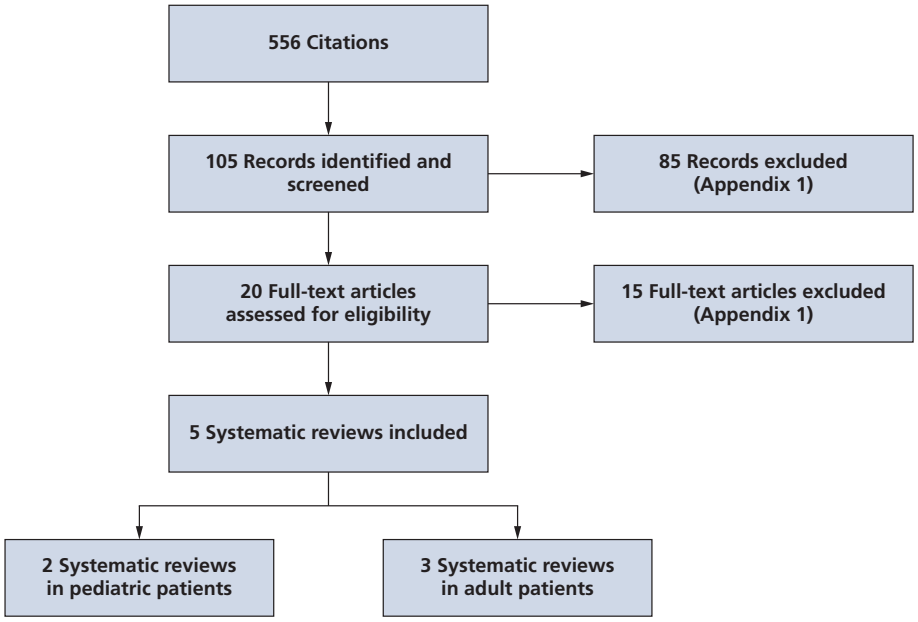

Figure. Scheme of citations identified in the PubMed Clinical Queries search.

overviews of reviews provided by the overview authors. The AMSTAR 2 tool includes 16 items; only reviews that did not contain critical flaws were considered to provide a sufficiently accurate summary of the results from available studies to be included in our overview.

Data Extraction

After identification of eligible reviews, we collected numerical and narrative data reporting on desirable and undesirable outcomes when using any type of analgesic medication. The data were extracted by 1 researcher and entered directly into tables that were checked for accuracy by a second researcher in an independent fashion. We used the DynaMed Plus database (EBSCO Information Services) to determine which medications or medication combinations were marketed in the United States so as to only report data on medications or medication combinations marketed as of May 2017 in the United States.

Absolute Estimates to Summarize Study Results

We present analgesic efficacy data as the number of patients needed to treat for benefit (NNTB) along with the 95% confidence interval (CI) and the proportion of people attaining at least 50% maximum pain relief over 4 to 6 hours. In terms of pain medications, the NNTB is the number of people who must be treated by a specific dose of pain medication to receive 50% pain relief, which is considered clinically meaningful pain relief.[6] The lower the NNTB, the more effective the analgesic agent. For example, an analgesic agent with an NNTB of 1 means that the medicine is 100% effective at reducing pain by 50%; that is, everyone who takes the medicine has effective pain relief. A drug with an NNTB of 2 means that 2 people must be treated for 1 to receive effective relief. According to a National Safety Council report,[7] for oral pain medications, an NNTB of 1.5 would be considered very good and an NNTB of 2.5 would be considered good, whereas a drug with an NNTB of 10 would not be considered an effective analgesic (that is, 10 patients would have to be treated for 1 patient to experience pain relief). Analogous to NNTB, to compare risk of harm, the number needed to treat to harm (NNTH) can be calculated. NNTH is the number of patients needed to be treated for an additional adverse event to occur compared with the placebo group.

RESULTS

No ongoing or completed systematic reviews were identified through the search of the PROSPERO database that were relevant to this work. The PubMed Clinical Queries search identified 556 citations (Figure). Title and abstract screening of the retrieved citations, as well as any identified in manual searches of the reference lists of key articles, narrowed the results set of potential citations to 105.

Of these, a total of 74 (Appendix 1, available online at the end of this article) were excluded from the evidence review for having been superseded by subsequent systematic reviews or meta-analysis; 1 was excluded for not answering a relevant question; 4 were excluded for reviewing oral agents; and 6 were excluded for not being systematic reviews. After a review of the remaining 20 citations at the full-text level,[8-27] 15 were excluded (Appendix 2, available online at the end of this article) because they were included in subsequent reviews, were not systematic reviews, included studies that involved preoperative medication, examined an intervention unlikely to have a pharmacologic basis for efficacy, or reviewed medications that were not marketed in the United States. The remaining 5 systematic reviews or overviews of reviews were included.[17,18,21,22,24] Two of these specifically targeted pediatric populations; 1 compared as-required versus fixed-schedule dosing of analgesic agents for postoperative pain in children,[17] and the other focused on the safety of common analgesic agents for acute pain (albeit, nonsurgical) in the pediatric population.[18]

Among the systematic reviews that met the inclusion criteria, the 3 that explored pain management questions in adult populations[21,22,24] explicitly indicated that they used AMSTAR to assess methodological quality.[28] Of the 2 systematic reviews that explored pain management in pediatric populations, 1[17] simply documented adherence to these same principles for assessing the methodological quality of the systematic reviews they included, and the other[18] reported using the McMaster Quality Assessment Scale of Harms.[29] Along with appraising the literature on which they were based, 4 of the systematic reviews[17,21,22,24] also satisfied the AMSTAR 2 criteria for high methodological quality.[5] Appraisal of the work by Hartling and colleagues[18] found it to be of moderate methodological quality using AMSTAR 2.[5]

Relief of postoperative pain with the use of pharmacologic agents in adults

The data from randomized controlled trials that studied single-dose oral analgesic agents in acute postoperative pain come almost exclusively from studies that involved people after extraction of third molars. It derives from an overview of reviews of 39 Cochrane reviews by Moore and colleagues,[22] which included only randomized clinical trials. The results are from more than 58,000 adult participants (15 years or older) in approximately 460 individual studies.

Evidence was considered high quality if data were available from at least 2 studies, each of which included at least 200 participants, and the results were of low risk of publication bias.[23] High-quality evidence was available for 53 medication and medication combinations. Several studied more than 1 dose in "painful postsurgical conditions"; these included various fixed-dose combinations and fast-acting formulations of some analgesic agents. Table 1 provides data for drugs available in the United States with the use of NNTB in order from most to least effective. NNTB ranged from 1.5 to 12 for at least 50% maximum pain relief over 4 to 6 hours compared with placebo with the proportion of participants achieving this level of benefit ranging from approximately 77% to 26% compared with 40% to 0% for placebo.

Medication and medication combinations with the lowest NNTBs, meaning that patients were most likely to experience treatment benefit, were 400 milligrams of ibuprofen plus 1,000 mg of acetaminophen with an NNTB of 1.5 (95% CI, 1.4 to 1.7), 200 mg of ibuprofen plus 500 mg of acetaminophen with an NNTB of 1.6 (95% CI, 1.5 to 1.8), 1,000 mg of acetaminophen plus 10 mg of oxycodone with an NNTB of 1.8 (95% CI, 1.6 to 2.2), and 100 mg of diclofenac potassium with an NNTB of 1.9 (95% CI, 1.7 to 2.3).

Medication and medication combinations with the highest proportion of patients who experienced at least 50% maximum pain relief for 4 to 6 hours were 600 mg of ibuprofen (77%), 400 mg of ibuprofen mg plus 1,000 mg of acetaminophen (72%), 200 mg of ibuprofen plus 500 mg of acetaminophen (69%), and 50 mg of flurbiprofen (69%) (Table 1).

Duration of postoperative pain relief with the use of pharmacologic agents in adults

Duration of postoperative pain relief, assessed as the time to remedication ranged from 1.5 hours (placebo) to more than 20 hours (Table 1).[22] Medication and medication combinations with the longest duration of action, meaning that they had the longest time before rescue remedication was requested, was 10.9 hours for 1,000 mg of diflunisal, 9.9 hours for 650 mg of acetaminophen and 10 mg of oxycodone, 9.8 hours for 500 mg of diflunisal, and 8.9 hours for 500 to 550 mg of naproxen. The medications and medication combinations that provided the shortest duration of pain

Table 1. Efficacy data from high-quality studies for analgesic agents available in the United States in order of effectiveness (most to least) according to NNTB*.[22,24]

DRUG OR DRUG COMBINATION, DOSE	NNTB	95% CONFIDENCE INTERVAL	AT LEAST 50% MAXIMUM PAIN RELIEF OVER 4-6 HOURS, %		MEAN OR MEDIAN TIME TO REMEDICATION, HOURS	
			Active	Placebo	Active	Placebo
Ibuprofen Plus Acetaminophen, 400 Milligrams/1,000 mg	1.5	1.4 to 1.7	72	6	8.3	1.7
Ibuprofen Plus Acetaminophen, 200 mg/500 mg	1.6	1.5 to 1.8	69	6	7.6	1.7
Acetaminophen Plus Oxycodone, 1,000 mg/10 mg	1.8	1.6 to 2.2	68	13	9.8	1.5
Diclofenac (Potassium), 100 mg	1.9	1.7 to 2.3	65	13	6.3	2.0
Ketoprofen, 25 mg	2.0	1.8 to 2.3	62	12	46†	79†
Diclofenac (Potassium), 50 mg	2.1	1.9 to 2.5	64	17	4.5	1.7
Diflunisal, 1,000 mg	2.1	1.8 to 2.6	62	15	10.9	3.2
Ibuprofen (Fast-Acting), 200 mg	2.1	1.9 to 2.4	57	10	43†	78†
Ibuprofen (Fast-Acting), 400 mg	2.1	1.9 to 2.3	65	18	32†	82†
Ibuprofen Plus Caffeine, 100 mg/200 mg	2.1	1.9 to 3.1	59	10	26‡	60‡
Ketoprofen, 100 mg	2.1	1.7 to 2.6	66	18	43†	85†
Acetaminophen Plus Codeine, 800-1,000 mg/60 mg	2.2	1.8 to 2.9	53	7	5.0	2.3
Ibuprofen Plus Codeine, 400 mg/26-60 mg	2.2	1.8 to 2.6	64	18	NA§	
Fenoprofen, 200 mg	2.3	1.9 to 3.0	57	13	NA	
Ibuprofen Plus Oxycodone, 400 mg/10 mg	2.3	2.0 to 2.8	60	17	NA	
Aspirin, 1,200 mg	2.4	1.9 to 3.2	62	19	NA	
Diclofenac (Fast-Acting), 50 mg	2.4	2.0 to 3.0	61	20	7.6	3.8
Diclofenac (Potassium), 25 mg	2.4	2.0 to 2.9	56	15	3.1	1.2
Ibuprofen Plus Caffeine, 100 mg/100 mg	2.4	1.9 to 3.1	43	0	34‡	79‡
Ketoprofen, 12.5 mg	2.4	1.9 to 3.1	56	13	80†	98†
Flurbiprofen, 100 mg	2.5	2.0 to 3.1	65	24	16†	68†
Ibuprofen (Acid), 400 mg	2.5	2.4 to 2.6	52	12	5.6	1.9
Celecoxib, 400 mg	2.6	2.3 to 3.0	43	5	8.4	1.6
Diflunisal, 500 mg	2.6	2.1 to 3.3	53	14	9.8	3.2
Acetaminophen Plus Oxycodone, 650 mg/10 mg	2.7	2.4 to 3.1	51	14	9.8	1.5
Flurbiprofen, 50 mg	2.7	2.3 to 3.3	69	32	25†	66†
Ibuprofen (Acid), 600 mg	2.7	2.0 to 4.2	77	40	NA	
Naproxen, 400-440 mg	2.7	2.2 to 3.5	49	11	NA	
Naproxen, 500-550 mg	2.7	2.3 to 3.3	52	15	8.9	2.0
Piroxicam, 20 mg	2.7	2.1 to 3.8	63	26	NA	
Etodolac, 400 mg	2.9	2.3 to 4.0	39	5	NA	
Ibuprofen (Acid), 200 mg	2.9	2.7 to 3.2	41	7	4.7	2.1
Etodolac, 200 mg	3.3	2.7 to 4.2	44	13	NA	
Flurbiprofen, 25 mg	3.3	2.5 to 4.9	35	5	35†	70†
Ketoprofen, 50 mg	3.3	2.7 to 4.3	48	18	48†	81†
Acetaminophen, 500 mg	3.5	2.7 to 4.8	61	32	35†	63†
Acetaminophen, 975-1,000 mg	3.6	3.2 to 4.1	46	18	3.9	2.7
Acetaminophen Plus Codeine, 600-650 mg/60 mg	3.9	3.3 to 4.7	43	17	4.1	2.4
Aspirin, 600-650 mg	4.2	3.8 to 4.6	39	15	55‡	75‡
Aspirin, 1,000 mg	4.2	3.8 to 4.6	41	14	67‡	83‡

* NNTB: Number needed to treat for benefit. † Percentage remedicating within 6 hours. ‡ Percentage remedicating within 8 hours. § NA: Not available.

Table 1. Continued

DRUG OR DRUG COMBINATION, DOSE	NNTB	95% CONFIDENCE INTERVAL	AT LEAST 50% MAXIMUM PAIN RELIEF OVER 4-6 HOURS, %		MEAN OR MEDIAN TIME TO REMEDICATION, HOURS	
			Active	Placebo	Active	Placebo
Celecoxib, 200 mg	4.2	3.4 to 5.6	35	11	6.6	2.6
Ibuprofen (Acid), 100 mg	4.3	3.2 to 6.4	31	8	NA	
Acetaminophen, 600-650 mg	4.6	3.9 to 5.5	38	16	3.5	2.4
Etodolac, 100 mg	4.8	3.5 to 7.8	41	20	NA	
Gabapentin, 250 Milliliters	11.0	6.4 to 35	15	5	2.4	2.1
Codeine, 60 mg	12.0	8.4 to 18	26	17	2.7	2.0

Table 2. Acute adverse events for medication or medication combination with statistically significant difference from placebo controls.[21]

DRUG OR DRUG COMBINATION, DOSE	NUMBER NEEDED TO TREAT TO HARM	95% CONFIDENCE INTERVAL	REPORTED ACUTE ADVERSE EVENT, %	
			Active	Placebo
Ibuprofen Plus Caffeine, 200 Milligrams/100 mg	2.2	1.0 to 4.9	11	6
Acetaminophen Plus Oxycodone, 650 mg/10 mg	1.8	1.4 to 2.3	58	28
Diflunisal, 1,000 mg	1.8	1.2 to 2.6	29	16
Acetaminophen Plus Codeine, 600-650 mg/60 mg	1.6	1.3 to 1.9	34	17
Acetaminophen Plus Oxycodone, 1,000 mg/10 mg	1.6	1.3 to 2.0	68	43
Aspirin, 1,000 mg	1.6	1.1 to 2.3	26	12
Acetaminophen Plus Codeine, 800-1,000 mg/60 mg	1.4	1.2 to 1.6	31	19
Ibuprofen Plus Acetaminophen, 200 mg/500 mg*	0.7	0.6 to 0.9	30	48
Ibuprofen Plus Acetaminophen, 400 mg/1,000 mg*	0.6	0.5 to 0.8	29	48

* Statistically fewer adverse events in medication combination than in placebo controls.

relief were 3.5 hours for 600 to 650 mg of acetaminophen, 3.1 hours for 25 mg of diclofenac potassium, 2.7 hours for 60 mg of codeine, and 2.4 hours for 250 mg of gabapentin.

Adverse events associated with provision of pharmacologic agents for relief of postoperative pain

Studies of medications for relief of acute pain are designed and powered for primary outcomes that have to do with analgesia rather than adverse events. Although reporting of adverse events in clinical trials is generally poor and variable depending on methodology, Moore and colleagues[21] have summarized the data on adverse events available from studies of sufficient quality to have been included in Cochrane reviews of pharmacologic agents used for single-dose oral analgesic agents for acute postoperative pain.[22,24] Although noting that accurate estimation of frequency or severity of adverse events is difficult at best, they calculated that serious, acute adverse events are rare and estimated that they occur in approximately 1 in 3,200 people.[21]

Methodologically, information about acute adverse events was most often gathered through the use of patient diaries. Adverse events included drowsiness, respiratory depression, nausea, vomiting, and constipation for the opioid medications and drowsiness, dizziness, nausea, and headache for the nonsteroidal anti-inflammatory drugs, although there was no effort made to parse the frequency of specific adverse events.[21] Table 2 presents the relatively short list of medication and medication combinations with a statistically significant difference in the proportion of patients who reported an adverse event compared with patients in the placebo group. Although the largest NNTH reported was for 200 mg of ibuprofen and 100 mg of caffeine (2.2; 95% CI, 1.0 to 4.9), 4 of the 6 other

Table 3. Alphabetical listing of medication and medication combination with no statistically significant difference in acute adverse events compared with placebo controls.[21]

DRUG OR DRUG COMBINATION, DOSE	NNTH	95% CONFIDENCE INTERVAL	REPORTED ACUTE ADVERSE EVENT, %	
			Active	Placebo
Acetaminophen, 500 milligrams	0.9	0.4 to 1.9	7	6
Acetaminophen, 600-650 mg	1.2	0.9 to 1.5	16	14
Acetaminophen, 975-1,000 mg	1.1	0.9 to 1.3	18	16
Aspirin, 600-650 mg	1.2	1.0 to 1.4	11.0	9.5
Codeine, 60 mg	1.3	0.9 to 1.7	20	16
Diclofenac (Fast-Acting), All Doses	1.0	0.6 to 1.8	8	46
Diclofenac (Potassium), All Doses	1.0	0.7 to 1.6	8	46
Diflunisal, 500 mg	1.3	0.8 to 1.9	18	15
Etodolac, 100 mg	1.6	0.9 to 2.8	11	7
Etodolac, 200 mg	1.2	0.9 to 1.7	22	17
Etodolac, 400 mg	0.8	0.5 to 1.2	28	34
Fenoprofen, 200 mg	0.9	0.4 to 2.1	6	6
Flurbiprofen, 100 mg	1.0	0.6 to 1.8	12	12
Flurbiprofen, 25 mg	0.9	0.5 to 1.7	14	16
Flurbiprofen, 50 mg	0.8	0.5 to 1.1	13	17
Gabapentin, 250 mg	0.9	0.7 to 1.3	28	32
Ibuprofen, 50 mg	1.3	0.6 to 3.0	10	7
Ibuprofen, 100 mg	1.2	0.7 to 2.1	14	13
Ibuprofen, 200 mg	0.9	0.7 to 1.02	19	19
Ibuprofen, 400 mg	0.9	0.8 to 1.04	17	16
Ibuprofen Plus Caffeine, 100 mg/100 mg	1.9	0.8 to 4.1	14	8
Ibuprofen Plus Codeine, 400 mg/26-60 mg	1.2	0.8 to 1.7	28	19
Ibuprofen Plus Oxycodone, 400 mg/10 mg	1.2	0.8 to 1.7	28	19
Ketoprofen, 100 mg	1.2	0.7 to 2.2	22	18
Ketoprofen, 12.5 mg	1.3	0.5 to 3.6	6	4
Ketoprofen, 25 mg	1.2	0.7 to 2.0	10	10
Ketoprofen, 50 mg	1.6	0.9 to 2.6	21	14
Naproxen, 400-440 mg	1.3	0.8 to 2.2	22	17
Naproxen, 500-550 mg	1.0	0.7 to 1.2	27	29
Oxycodone, 5 mg	1.1	0.8 to 1.6	31	29

medication and medication combinations in which the NNTH was statistically greater than placebo were for opioid-containing combinations (Tables 2 and 3). That the 2 combinations of ibuprofen and acetaminophen, at dosages of 200 mg/500 mg and 400 mg/1,000 mg, were observed to have statistically fewer adverse events in the active treatment group than in the placebo control group (Table 2) may reflect a sample size issue. The data on adverse events for the medication and medication combinations for which there was no statistically significant difference compared with the placebo control are presented in Table 3 in alphabetical order.

Relief of postoperative pain with the use of pharmacologic agents in children

A 2015 Cochrane review attempted to evaluate the management of postoperative pain in children younger than 16 years.[17] Three randomized clinical trials that met their inclusion criteria were found, enrolling a total of 246 children. (The only medication for which the researchers found data

Table 4. Acute adverse events observed in children for medications or medication combinations.[18]

MEDICATION OR MEDICATION COMBINATION, DOSE	STUDIES, NO.	ACUTE ADVERSE EVENTS REPORTED, NO.	STUDY PARTICIPANTS, NO.	ACUTE ADVERSE EVENTS, %
Codeine, 2 milligrams/kilograms	1	74	56	132
Oxycodone, 0.2 mg/kg	2	69	73	95
Morphine, 0.5 mg/kg	2	84	140	60
Ibuprofen, 10 mg/kg, and Oxycodone, 0.1 mg/kg	1	8	22	36
Acetaminophen Plus Codeine, 1 mg/kg	3	94	368	26
Ibuprofen, 10 mg/kg, and Codeine, 1 mg/kg	2	52	209	25
Ibuprofen, 10 mg/kg	9	74	510	15
Naproxen, 20 mg/kg	1	4	41	10
Ketoprofen, 40 mg	1	2	33	6
Tramadol, 2 mg/kg	1	3	67	4
Acetaminophen, 15 mg/kg	6	10	260	4

sufficient for calculating the risk ratio with 95% CI was dipyrone, which is only available for human use in Europe and Latin America. It is included here for completeness in reporting the results from this Cochrane review.) The researchers found moderate quality data to indicate that 500 mg of oral dipyrone provided 70% of patients with at least 50% relief of pain at 4 to 6 hours (95% CI, 1.8 to 3.1). They reported being unable to conduct analysis of adverse events because data were inconsistently reported.

Adverse events associated with provision of pharmacologic agents for management of acute, nonsurgical pain in children

A systematic review by Hartling and colleagues[18] on adverse events on children (defined as younger than 18 years) who received pharmacologic agents for managing acute pain included nausea; vomiting; headache; gastrointestinal symptoms other than nausea and vomiting; drowsiness, sleepiness, tiredness; dizziness; itchiness, rash, pruritus; central nervous system symptoms; and pulmonary symptoms. Although original data were insufficient to calculate NNTH, we qualitatively summarized the results in Table 4 which show that the medication and medication combinations that include opioids are associated with the largest proportion of acute adverse events, ranging from 132% (that is, more than 1 type of acute adverse event per patient) for 2 mg/kg of codeine, 95% for 0.2 mg/kg of oxycodone, and 60% for 0.5 mg/kg of morphine and, at the low end of the spectrum, 15% or fewer patients who reported an acute adverse event for 10 mg/kg of ibuprofen, 20 mg/kg of naproxen, 40 mg/kg of ketoprofen, 2 mg/kg of tramadol, or 15 mg/kg of acetaminophen. (The list of the medication and medication combinations are presented in descending order of study participants affected by adverse events in Table 4.)

DISCUSSION

To determine which oral analgesic medications to use for relief of acute dental pain appropriate for the patient, health care professionals should consider both the medication's potential to provide pain relief and its potential to cause harm. A variety of medication and medication combinations, including formulations that contain opioids, may be considered for the management of acute dental pain, and it is important to be cognizant that no medication or medication combination produces high levels of pain relief in all patients and that the analgesic agents prescribed are not intended to eliminate all pain that may present. When prescribing analgesic agents, practitioners should appreciate and counsel patients that the goal is for the patient to be as comfortable as possible, although patients should be aware that some discomfort is normal and may still occur. The range of results with single-dose analgesic agents in participants with moderate or severe acute pain was from 7 of 10 (70%) achieving good pain relief with the most effective medicine to approximately 3 of 10

(30%) with the least effective medicine. In terms of the decision-making process about what medication or medication combination to prescribe, the Joint Commission's statement on pain management indicates that pain management strategies should reflect a patient-centered approach and consider the patient's current presentation, the health care providers' clinical judgment, and the risks and benefits associated with the strategies, including potential risk of dependency, addiction, and abuse.[30] Although most data in adults presented here derive from the study of third-molar extraction, the results are more broadly applicable, because comparable findings, for example, have been reported for relief of pain of endodontic origin.[31]

When comparing the efficacy of nonsteroidal anti-inflammatory medications with opioids in relation to the magnitude of pain relief, the combination of 400 mg of ibuprofen plus 1,000 mg of acetaminophen was found to be superior to any opioid-containing medication or medication combination studied. In addition, the opioid-containing medications or medication combinations studied were all found to have higher risk of inducing acute adverse events than 400 mg of ibuprofen plus 1,000 mg of acetaminophen. Thus, in general, when considering either benefits or harms, management of acute pain with nonsteroidal medications, with or without acetaminophen, appears to have a therapeutic advantage to opioid-containing medications. Although there are situations in which clinical judgment indicates an opioid-containing medication may be warranted, the data make a compelling case favoring use of nonsteroidal medications, with or without acetaminophen.

Many factors contribute to prescribing decisions made by dentists, including education, training, and local legislation. There is reported geographic variation in opioid-prescribing patterns.[32] No single common course curriculum, objectives, or assessments are used by all dental schools.[33] Another approach may be dental school and continuing education programs about the CDC guidelines for prescribing opioids for long-term pain,[1] which have been effective in changing opioid-prescribing patterns for clinicians in the fields of surgery[34] and emergency medicine.[35] Although data presented in this study do not cover the breadth of the CDC recommendations, they are relevant to the concept of optimizing nonopioid therapy before moving to a trial of opioids. This is consistent with the recent ADA Statement on the Use of Opioids in the Treatment of Dental Pain revised in October 2016, which indicates that "Dentists should consider nonsteroidal anti-inflammatory analgesics as the first-line therapy for acute pain management."[36]

Strengths and limitations of current review

The AMSTAR 2 evaluations found that the information gleaned from the available systematic reviews on efficacy and acute adverse events is of moderate-high methodological quality. This should allow readers to have confidence that the use of appropriately selected nonsteroidal anti-inflammatory analgesic medication can deliver the desired pain management. Although studies are not designed with adverse events as a primary end point, with report of serious adverse events being minimal, clinicians can use this to extrapolate about the overall safety of these medications. In terms of limitations, the literature search strategy used was systematic, but broadening it to capture primary studies and eliminating the English-only language exclusion criterion may have yielded additional information. The data evaluated in randomized clinical trials to assess analgesic efficacy used a single-dose model of treatment and are unable to quantitatively evaluate adverse events that may require longer follow-up to be detected—that is, dependence or medication diversion that is increasingly seen to be problematic.

CONCLUSIONS

Opioid medication and medication combinations are not among the most effective or long lasting of the options available for relief of acute dental pain. In addition, opioid medication and medication combinations are associated with higher rates of acute adverse events. From the perspective of risk-benefit analysis, justifying general use of opioid medications as first-line therapy for management of acute pain remains unclear. The large set of published research reports summarized here suggests that relief of postoperative pain in dental practice with the use of nonsteroidal anti-inflammatory drugs, with or without acetaminophen, is equal or superior to that provided by opioid-containing medications. ■

SUPPLEMENTAL DATA

Supplemental data related to this article can be found at https://doi.org/10.1016/j.adaj.2018.02.012.

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APPENDIX 2

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REASON: INCLUDED IN A MORE RECENT OVERVIEW

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REASON: SUPERSEDED BY A MORE RECENT OVERVIEW

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