PHARMACOLOGY

Utilizing synergism to maximize therapeutic effects of postoperative analgesics

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High rates of opioid analgesic prescriptions continue to be a dominant public health concern, fueling the ongoing opioid abuse epidemic in the United States.[1-4] Areas of the United States with a higher number of dentists per capita are linked to increased opioid prescription rates, and oral healthcare providers were found to be the third highest prescribers, behind primary care physicians and pain medicine specialists.[5,6] In 2011, Denisco et al noted that "the appropriate use of opioids requires dentists to follow responsible and tailored prescribing practices to provide adequate pain control while limiting opportunities for abuse and diversion."[7] More than 10 years later, oral healthcare providers continue to be responsible for a significant portion of all outpatient immediate-release opioid prescriptions in the United States.[6,7] Many statistics have been published to highlight this issue, but specific guidance to help practicing dentists choose alternative nonopioid analgesic strategies is still needed.[8-15]

According to the Centers for Disease Control and Prevention (CDC), fatal opioid-related overdoses spiked in 2021, increasing from 56,064 the previous year to 75,673.[16] For the first time ever in the United States, the total number of opioid-related deaths exceeded 100,000 over the course of a continuous 12-month period (April 2020 to April 2021).[16] In February 2022, the Stanford-Lancet Commission on the North American Opioid Crisis concluded that, without urgent intervention, the United States will see more than 1.2 million fatal opioid-related overdoses during the next 10 years.[17]

On November 4, 2022, the CDC published an updated "Clinical Practice Guideline for Prescribing Opioids for Pain—United States, 2022."[18] These guidelines are designed to serve as a clinical tool for primary care physicians as well as for other clinicians, including dentists, who provide pain management for patients 18 years or older who have acute (duration less than 1 month), subacute (duration 1 to 3 months), and/or chronic pain (duration more than 3 months). The CDC states that this guideline is not intended to be a replacement for clinical judgment or individualized patient-centered care, nor should it be considered to represent inflexible standards of care for healthcare professionals or a substitute for labeling approved by the Food and Drug Administration (FDA). The updated CDC guideline contains 12 recommendations for prescribing opioids for outpatients with pain, the first 2 of which focus on whether to initiate these drugs at all (Box). The first recommendation addresses acute pain specifically and states that nonopioid therapies are at least as effective as opioids for many types of acute pain and that clinicians should maximize nonopioid therapies unless the benefits of opioid therapy outweigh the risks. Nonopioid analgesics discussed in the guideline include nonsteroidal anti-inflammatory drugs (NSAIDs) and acetaminophen, but the guidelines do not discuss the potential benefit of administering these 2 medications together.[18]

While clinicians should reserve the prescription of opioid-containing medications for cases in which they are truly indicated, it is important not to overlook the legitimate necessity of opioids for certain patients with anticipated moderate to severe acute dental pain. The aim of this column is to discuss pharmacologic synergism and to provide examples of nonopioid therapies that can help limit prescriptions of opioid-containing medications while still offering analgesic effectiveness to dental patients.

Synergism

In pharmacology, *synergy* or *synergism* is defined as the effect of 2 or more agents working in combination that is greater than the expected additive effect of either drug alone.[19] Synergism can help maximize the therapeutic effects of 2 or more medicines while minimizing the potential adverse effects.[20,21] Traditionally, if a patient required a greater effect of a medication, the clinician would simply prescribe a higher dose. This is referred to as an *additive effect*, sometimes called *inertism* or *noninteraction*, whereby the drug effect can be expressed numerically as 1 + 1 = 2.[20] The risk in simply administering more and more of the same

Box. Centers for Disease Control and Prevention (CDC) recommendations for prescribing opioids for outpatients with pain.[a]

1. Nonopioid therapies are at least as effective as opioids for many common types of acute pain. Clinicians should maximize use of nonpharmacologic and nonopioid pharmacologic therapies as appropriate for the specific condition and patient and only consider opioid therapy for acute pain if benefits are anticipated to outweigh risks to the patient.
2. Nonopioid therapies are preferred for subacute and chronic pain. Clinicians should maximize use of nonpharmacologic and nonopioid pharmacologic therapies as appropriate for the specific condition and patient and only consider initiating opioid therapy if expected benefits for pain and function are anticipated to outweigh risks to the patient.
3. When starting opioid therapy for acute, subacute, or chronic pain, clinicians should prescribe immediate-release opioids instead of extended-release and long-acting (ER/LA) opioids.
4. When opioids are initiated for opioid-naïve patients with acute, subacute, or chronic pain, clinicians should prescribe the lowest effective dosage. If opioids are continued for subacute or chronic pain, clinicians should use caution when prescribing opioids at any dosage, should carefully evaluate individual benefits and risks when considering increasing dosage, and should avoid increasing dosage above levels likely to yield diminishing returns in benefits relative to risks to patients.
5. For patients already receiving opioid therapy, clinicians should carefully weigh benefits and risks and exercise care when changing opioid dosage. If benefits outweigh risks of continued opioid therapy, clinicians should work closely with patients to optimize nonopioid therapies while continuing opioid therapy. If benefits do not outweigh risks of continued opioid therapy, clinicians should optimize other therapies and work closely with patients to gradually taper to lower dosages or, if warranted based on the individual circumstances of the patient, appropriately taper and discontinue opioids. Unless there are indications of a life-threatening issue such as warning signs of impending overdose (eg, confusion, sedation, or slurred speech), opioid therapy should not be discontinued abruptly, and clinicians should not rapidly reduce opioid dosages from higher dosages.
6. When opioids are needed for acute pain, clinicians should prescribe no greater quantity than needed for the expected duration of pain severe enough to require opioids.
7. Clinicians should evaluate benefits and risks with patients within 1-4 weeks of starting opioid therapy for subacute or chronic pain or of dosage escalation. Clinicians should regularly reevaluate benefits and risks of continued opioid therapy with patients.
8. Before starting and periodically during continuation of opioid therapy, clinicians should evaluate risk for opioid-related harms and discuss risk with patients. Clinicians should work with patients to incorporate into the management plan strategies to mitigate risk, including offering naloxone.
9. When prescribing initial opioid therapy for acute, subacute, or chronic pain, and periodically during opioid therapy for chronic pain, clinicians should review the patient's history of controlled substance prescriptions using state prescription drug monitoring program (PDMP) data to determine whether the patient is receiving opioid dosages or combinations that put the patient at high risk for overdose.
10. When prescribing opioids for subacute or chronic pain, clinicians should consider the benefits and risks of toxicology testing to assess for prescribed medications as well as other prescribed and nonprescribed controlled substances.
11. Clinicians should use particular caution when prescribing opioid pain medication and benzodiazepines concurrently and consider whether benefits outweigh risks of concurrent prescribing of opioids and other central nervous system depressants.
12. Clinicians should offer or arrange treatment with evidence-based medications to treat patients with opioid use disorder. Detoxification on its own, without medications for opioid use disorder, is not recommended for opioid use disorder because of increased risks for resuming drug use, overdose, and overdose death.

[a]Recommendations for prescribing opioids for outpatients with pain, excluding pain management related to sickle cell disease, cancer-related pain treatment, palliative care, and end-of-life care. Adapted from Dowell D, Ragan KR, Jones CM, Baldwin GT, Chou R. CDC Clinical Practice Guideline for Prescribing Opioids for Pain—United States, 2022. *MMWR Recomm Rep*. 2022;71(3):1-95. doi:10.15585/mmwr.rr7103a1

medication, however, is that higher doses of medications increase the likelihood of adverse effects.

If 2 drugs act synergistically, particularly if each drug has a different mechanism of action, the combined effect of each drug at lower doses can provide the desired outcome while minimizing the potential for adverse effects. This is referred to as a *potentiated* or *synergistic effect* and can be expressed numerically as $1 + 1 > 2$ to imply that the combined effects of 2 or more drugs can be amplified when they are administered together. This effect is also described as *augmentation* or *super-additivity*.[19,20] The term *coalism* is used to refer to a form of synergism in which neither drug, or no drugs in a mixture of more than 2 chemicals, is effective on its own, but the combination of drugs produces an effect.[20]

There are a number of examples of synergism in prescription therapeutics as well as over-the-counter (OTC) medications. Common OTC synergistic combination medications include Advil PM (ibuprofen and diphenhydramine), Excedrin (aspirin, acetaminophen, and caffeine), Tylenol PM (acetaminophen

Table. Combination products that contain acetaminophen[a] or a nonsteroidal anti-inflammatory drug in addition to an opioid.[33-35]

	Codeine + acetaminophen	Hydrocodone + acetaminophen	Hydrocodone + ibuprofen	Oxycodone + acetaminophen
Brand names	Tylenol 2, Tylenol 3, and Tylenol 4	Lorcet, Lortab, Margesic, Maxidone, Norco, Stagesic, Vicodin, Xodol, and Zydone	Ibudone, Reprexain, and Vicoprofen	Endocet, Magnacet, Percocet, Primlev, Roxicet, and Tylox
Available strengths, mg	15/300, 30/300, and 60/300	5/300, 5/325, 7.5/300 7.5/325, 10/300, and 10/325	5/200, 7.5/200, and 10/200	2.5/325, 5/325, 7.5/325, and 10/325
Drug schedule[b]	III	II	II	II
Usual adult dosages[c]	15-60 mg of codeine every 4 h	5-10 mg of hydrocodone every 4-6 h	5-10 mg of hydrocodone every 4-6 h	5-15 mg of oxycodone every 4 h
Elixir formulations	12/120 mg per 5 mL	2.5/167, 10/325, 10/300, and 7.5/500 mg per 5 mL	7.5/325 and 10/300 mg per 15 mL	Not available in the United States

[a]Although combination products that include aspirin and an opioid such as codeine (Empirin) or oxycodone (Endodan, Oxycodan, and Percodan) are available, combination products with acetaminophen are preferred because they have comparable efficacy to aspirin but a superior adverse effect profile (less postoperative bleeding and lower ulcerogenic risk).

[b]US Drug Enforcement Administration controlled substance schedules.

[c]Be sure not to exceed the maximum recommended daily dose of acetaminophen from all sources.

and diphenhydramine), and Advil Cold & Sinus (ibuprofen and pseudoephedrine). An early example of synergism in dentistry is the topical local anesthetic EMLA (eutectic mixture of local anesthetics), approved by the FDA in 1992.[22] EMLA is a combination product containing 2.5% prilocaine and 2.5% lidocaine. When compared to 20% benzocaine gel applied topically, EMLA was found to be more efficacious and safer.[23] Other examples of pharmacologic synergism used in dentistry include postoperative analgesic combination products containing an opioid plus either acetaminophen or an NSAID such as ibuprofen (Table).[24-26]

Another example of synergy in dentistry is the combination of the vasoconstrictor epinephrine with the local anesthetic lidocaine. Since the duration of anesthesia is influenced by the time a local anesthetic remains in close proximity to the neural fibers, lidocaine is only clinically effective as a dental local anesthetic when it is administered with epinephrine. Without epinephrine, the duration of the profound local anesthesia achieved with lidocaine is less than 10 minutes, which explains why the plain solution was removed from the market in 2011 and is no longer available in dental cartridges.[27]

Ibuprofen and acetaminophen

In 1995, the American Association of Endodontists developed a flexible analgesic strategy for the management of acute odontogenic pain, offering guidelines that have been updated by other investigators in recent years.[28-31] NSAIDs such as ibuprofen have shown to be more effective at reducing acute dental pain than opioid analgesics and are recommended as the preferred therapy for pain management.[18,32-35] This makes intrinsic sense because orofacial pain is typically the result of inflammation, and opioid analgesics are not anti-inflammatory agents. In fact, the American Dental Association House of Delegates adopted a statement that reads: "Dentists should consider nonsteroidal anti-inflammatory analgesics as the first-line therapy for acute pain management."[27] When NSAIDs alone are not effective, the combination of an NSAID with acetaminophen is recommended.[36]

The mnemonic "2-4-24" (2 drugs, in 4 doses, for 24 hours) is an effective way to help clinicians remember the nearly ideal postoperative prescription involving ibuprofen and acetaminophen.[32] This approach calls for 600 mg of ibuprofen and 650 mg of acetaminophen to be administered every 6 hours for 24 hours. This dosing is both safe and effective, and it should be recommended as first-line therapy in patients able to tolerate both medications.[30-36] For the treatment of acute nociceptive orofacial pain, the maximum recommended dose is 2400 mg of ibuprofen and 3000 mg of acetaminophen during a 24-hour period. The combination of acetaminophen and an NSAID such as ibuprofen administered every 6 hours for at least 24 hours has been validated by both meta-analyses and individual studies and is generally recognized as the postoperative prescription of choice for acute odontogenic pain.[30-36]

For some patients, taking the OTC forms of these 2 medications—12 tablets of 200-mg ibuprofen and 8 tablets of 325-mg acetaminophen every 24 hours—may seem to be an excessive burden. However, prescription of a new OTC combination product may offer a solution to this problem. Advil Dual Action is the first and only nonprescription FDA-approved pain relief medication to combine ibuprofen and acetaminophen.[37] Each tablet contains 125 mg of ibuprofen and 250 mg of acetaminophen. The recommended dose for individuals aged 12 years and older is 2 capsules every

8 hours while symptoms persist, not to exceed more than 6 tablets in a 24-hour period (ie, a total dose of 750 mg of ibuprofen and 1500 mg of acetaminophen).

While Advil Dual Action minimizes the potential pill burden to the patient and may seem like an attractive postoperative analgesic strategy, this combination product has shortcomings. Most important, because of the dose ratio of the active ingredients (125 mg of ibuprofen and 250 mg of acetaminophen per dose), it is not possible to achieve the target doses of the 2-4-24 strategy (600 mg of ibuprofen and 650 mg of acetaminophen per dose). The recommended maximum dose of acetaminophen will be greatly exceeded if patients attempt to match the optimal analgesic dose of 600 mg of ibuprofen using Advil Dual Action tablets. This could have serious health implications, including potential liver toxicity and mortality.[38,39]

Tramadol and celecoxib

While medications such as ibuprofen and acetaminophen can be given preoperatively to mitigate postoperative pain, celecoxib, a cyclooxygenase 2–selective NSAID, is ideally suited for this strategy and is often referred to as *preemptive analgesia*. Unlike the more common nonselective NSAIDs, celecoxib can preemptively ameliorate the inflammatory response without causing increased bleeding or delaying postoperative wound healing.[40-42] A 400-mg dose of celecoxib administered orally 30 minutes prior to dental procedures can maximize this benefit. For patients who are currently taking anticoagulants such as apixaban, betrixaban, dabigatran, edoxaban, rivaroxaban, or warfarin, celecoxib could also be used in place of postoperative ibuprofen. The recommended prescription in this case would be 200 mg of celecoxib every 12 hours, along with 650 mg of acetaminophen every 6 hours, for the initial 24-hour postoperative period.

Tramadol, a synthetic analog of codeine, is a centrally acting analgesic agent that has a relatively low affinity for opiate receptors.[43] It has been compared to many analgesics for treating odontogenic pain and has been shown to be more effective than codeine.[44,45] In a review of the literature, Moore found that tramadol may have limited utility for management of acute dental pain but may have some therapeutic advantage when combined with a peripherally acting analgesic such as an NSAID or acetaminophen (eg, Ultracet).[46] Possible indications for use in dentistry may include cases in which aspirin plus codeine combinations are contraindicated or poorly tolerated or NSAIDs are contraindicated due to gastrointestinal concerns.[46-48]

In 2021, the FDA approved a combination product of tramadol hydrochloride and celecoxib (Seglentis) for acute pain management in individuals with pain severe enough to require an opioid analgesic and for which alternative treatments are inadequate.[49] Each tablet contains 44 mg of tramadol hydrochloride (equivalent to 39 mg of tramadol) and 56 mg of celecoxib. The recommended dose is 2 tablets every 12 hours as needed for pain. Given the risks of addiction, abuse, and misuse with opioids, even at recommended doses, Seglentis should be reserved for use in patients for whom alternative treatment options (eg, nonopioid analgesics alone) have not provided or are not expected to provide adequate analgesia or for whom the alternative treatments have not been or are not expected to be tolerated.[49]

Orphenadrine, caffeine, and aspirin

Another recently approved nonopioid pain medication, Orphengesic Forte, is indicated for the treatment of patients suffering mild to moderate pain.[50] While orphenadrine alone is typically administered as 100-mg tablets every 12 hours in healthy adults, this new combination product has been shown to be effective with just 50 mg of orphenadrine, given the synergistic effect when combined with 60 mg of caffeine and 770 mg of aspirin.[51] Usual adult dosing is a half to 1 tablet 3 to 4 times per day, not to exceed 4 tablets daily.

The exact mechanism of action of orphenadrine is still unclear, but this drug reduces skeletal muscle spasms, possibly through actions on the medulla or cerebral motor centers. Orphenadrine does not directly relax skeletal muscles, but its analgesic activity certainly contributes to its skeletal muscle relaxant properties. Orphenadrine also has postganglionic anticholinergic effects, local anesthetic action, and some antihistaminic effects. The antihistaminic activity is less than that of diphenhydramine, and orphenadrine produces mild central nervous system stimulation, contrary to the sedative effects of diphenhydramine.

Caffeine is often combined with aspirin and acetaminophen to enhance their potential analgesic effects. Samieirad et al showed that, when a combination of acetaminophen and caffeine was compared with a combination of acetaminophen and codeine in a dental model, the caffeine-containing analgesic resulted in significantly less swelling during the first 3 days postoperatively. The authors concluded that the use of caffeine-containing analgesics is an effective treatment for postoperative pain without the use of a narcotic.[52]

The clinical effects of caffeine are well-known; however, its cellular mechanism of action is still uncertain.[53] Caffeine at high concentrations interferes with the uptake and storage of calcium by the sarcoplasmic reticulum of striated muscle, which would explain the effects of caffeine on skeletal muscles. However, this effect does not appear to occur at clinically achievable concentrations. Currently, it is postulated that xanthines such as caffeine act as adenosine receptor antagonists. Adenosine inhibits the release of neurotransmitters from presynaptic sites and works in concert with norepinephrine or angiotensin to augment the actions of these 2 chemicals. Adenosine acts as an autocoid, and virtually every cell contains adenosine receptors within the plasma membrane. Antagonism of adenosine receptors by caffeine promotes neurotransmitter release, resulting in its analgesic effects.[53]

Conclusion

The opioid epidemic continues to be one of our greatest challenges. Recent publications suggest that, without immediate intervention, the United States will recognize more than 1.2 million fatal opioid-related overdoses over the next 10 years.[17] According to the CDC's 2022 clinical practice guideline, dentists generate the third-most opioid prescriptions behind primary care physicians and pain medicine clinicians and have therefore been identified as having an important role in opioid abuse prevention efforts.[18] A reflex reaction to historical prescribing patterns is to simply discontinue opioid prescriptions for the management of

postoperative dental pain, but in some cases the benefits of opioid-containing analgesics may outweigh the risks, and clinicians should always attempt to match the right drug, at the right dose, for the right duration, to the clinical situation. Regardless, in most cases, nonnarcotic analgesic regimens, including those that leverage pharmacologic synergism (specifically ibuprofen and acetaminophen), should be considered as first-line therapy.

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Conflicts of interest

None reported.

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