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Rational use of analgesic combinations

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Current techniques for analgesic management of pain have benefited from recent pharmacologic advances and a better understanding of the mechanisms of action of the older analgesic agents. Practitioners commonly use commercially available analgesics that take advantage of incorporating opioid agents with nonopioids such as acetaminophen (APAP) or non-steroidal anti-inflammatory agents (NSAID). Opioid and APAP combinations account for 5 of the top 200 prescription medications sold in the United States based on total number of prescriptions written. Hydrocodone combined with APAP was the single most commonly written United States prescription in 2000 [1]. This field is growing with the newest commercially available compounded analgesic not containing an opioid, but incorporating two nonopioid analgesics with distinctly different analgesic actions, tramadol and APAP. Though the practitioner and patient typically find commercially available analgesic combinations convenient, certain pain management situations are optimized by compounding analgesics from separate prescriptions for each analgesic agent. This article will focus primarily on the use of oral analgesics for acute pain management.

Analgesic drugs interrupt nociceptive pathways that transmit impulses destined to be interpreted as pain in the central nervous system (CNS). Analgesics are classified as opioids and nonopioids, but the older terms "narcotic" and "non-narcotic" are used interchangeably. Conventional thought has credited opioids as acting within the brain and spinal cord, whereas the action of nonopioids is confined to the periphery, ie, the site of injury. Both have been shown, however, to act centrally and peripherally

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to varying degrees [2]. Therefore, the principal feature that distinguishes these two classes of analgesics is their mechanism of action.

Opioids act on specific receptors. The three major opioid receptors include the μ, κ, and δ receptors. Current knowledge indicates that opioid analgesia is mediated primarily by binding to the μ receptor. This results in postsynaptic membrane hyperpolarization following activation of inwardly rectifying potassium channels and presynaptic depolarization secondary to the inhibition of voltage-dependent calcium channels. But some opioids, ie, methadone and levorphanol, have N-methyl-d-aspartate (NMDA) receptor antagonist properties and inhibit the reuptake of serotonin and noradrenaline, which may make them useful in the treatment of complex regional pain syndromes (CRPS). Opioids have no dose limit or ceiling dose, ie, the patient can increase the dose until analgesia is obtained or limiting side effects occur. The agonist-antagonist, pentazocine, and weak mμ receptor binding agent, propoxyphene, are also listed in the opioid category. Pentazocine and propoxyphene are labeled as Drug Enforcement Administration (DEA) schedule IV agents. Tramadol, though binding weakly to mμ opioid receptors, is not scheduled by the DEA and is covered in the nonopioid section of this article.

The largest class of nonopioids is the NSAIDs, which interrupt prostaglandin synthesis and have a maximal dose or ceiling; greater NSAID doses provide no additional analgesia. Other commonly used nonopioid analgesics are acetaminophen and tramadol, which do not have anti-inflammatory properties.

It is rational for the practitioner to combine these classes when managing pain. To select combination regimens wisely, it is important first to understand the significant pharmacologic features of each category alone.

Nonopioids

The nonopioids include NSAIDs, APAP, and tramadol. NSAIDs demonstrate good analgesic efficacy for mild to moderate orofacial pain. NSAIDs are recommended for the initial management of orofacial pain with an inflammatory component and musculoskeletal pain. Acetaminophen and tramadol are options to be considered in place of, or in addition to NSAID therapy.

NSAIDs

Actions, side effects, and contraindications

NSAIDs include a large group of synthetic compounds having analgesic, anti-inflammatory, and antipyretic efficacy. These therapeutic effects, as well as their most notable side effects, are presumably the result of inhibiting

cyclooxygenases that catalyze the synthesis of prostaglandins and thromboxanes.

The most frequent side effects attributed to NSAIDs are gastrointestinal in nature and include dyspepsia, erosions, and ulcerations. Interestingly, patient complaint of dyspepsia (upset stomach) is usually unrelated to mucosal injury. The incidence of dyspepsia with the newly released COX-2 inhibitors is similar to that of other NSAIDs (see article in this issue on COX-2 agents). The anti-platelet effect of conventional NSAIDs is a consideration, but aspirin is the only NSAID that prolongs bleeding time to a significant extent. This is because aspirin's anti-platelet action is irreversible, lasting the lifespan of the platelet (10–14 days). Other NSAIDs bind weakly and reversibly to platelet cyclooxygenases with their influence completely lost after drug elimination.

All NSAIDs shunt the arachidonic pathway toward leukotriene synthesis. These substances mediate a variety of tissue responses, including those associated with bronchospasm and anaphylaxis [3]. It has been suggested that certain individuals may be extremely sensitive to even subtle elevations in leukotriene synthesis, which may induce signs and symptoms of an allergic response. It has been suggested that the term "aspirin intolerance" should be used to distinguish this reaction from true hypersensitivity responses. Acetaminophen and/or tramadol can be recommended for patients reporting allergic reactions to any NSAID, unless the patient can identify a particular NSAID they have tolerated in the past.

Several medical conditions present relative and/or absolute contraindications for routine use of NSAIDs. These include: a current history of nephropathy, erosive or ulcerative conditions of the gastrointestinal (GI) mucosa, anticoagulant therapy, hemorrhagic disorders, pregnancy, and a prior history of intolerance or allergy to any NSAID. Several drug interactions involving NSAIDs are noteworthy and require a thorough drug history [4] (Table 1). Acetaminophen and/or tramadol are the primary alternatives when NSAIDs are contraindicated.

Efficacy, selection, and dosages

All NSAIDs have greater potency as analgesics and antipyretics than as anti-inflammatory agents. For example, a single 325–1000 mg dose of aspirin may reduce pain and fever, but daily doses of 4–6 gm are required to suppress inflammation effectively. This is not to say that NSAIDs have poor anti-inflammatory efficacy; it merely illustrates the fact that the clinician must consider the desired outcome when determining an appropriate dose.

The analgesic dose-response curves for NSAIDs, as well as acetaminophen, demonstrate a ceiling effect. A point is reached where increasing the dose further provides no improvement in pain relief. For aspirin, this ceiling response occurs at approximately 1000 mg, and for ibuprofen, 400 mg. A

Table 1
Drug interactions of clinical concern related to patient pain management

Prescribed drug	Interaction agent	Interaction explanation
NSAID	Antihypertensives	Effectiveness of most classes of antihypertensive drugs is reduced following prolonged use of most NSAIDs. If NSAIDs are required for longer than 4 days, patient's blood pressure control should be assessed. Calcium channel blockers have not been implicated.
NSAID	Hypoglycemics (eg, glyburide/ Micronase, glipizide/ Glucotrol)	Avoid aspirin and phenylbutazone as combined therapy with insulin and oral hypoglycemics may result in hypoglycemia. Other NSAIDs have not been implicated.
NSAID	Lithium (Lithobid®)	Lithium excretion is reduced and toxic blood levels of lithium may develop over 5–10 days of NSAID therapy. Limit NSAID use to 2 or 3 days.
NSAID	Methotrexate (Rheumatrex®)	Increasing methotrexate serum levels leading to systemic toxicity an increased incidence of stomatitis.
NSAID	Warfarin (Coumadin®)	Antiplatelet effects of NSAIDs may add to anticoagulant effect of warfarin. Gl erosive effects may be more prone to hemorrhage.
Other NSAIDs	Combining NSAIDs, especially ASA	Diminishes serum levels of each.
Acetaminophen	Ethanol/Hydantoins (eg, phenytoin/ Dilantin®)	Chronic use of alcohol or phenytoin increases risk of hepatotoxicity. Reduce daily dose limit from 4 grams to 2 grams.
Acetaminophen	Warfarin (Coumadin®)	Acetaminophen may inhibit metabolism of warfarin leading to elevated INR. Use caution if prescribing APAP for more than 3 days.
Acetaminophen	Carbamazepine (Tegretol®)	Increases metabolite of acetaminophen, decreasing its analgesic effect but increasing accumulation of hepatotoxic metabolite
Propoxyphene	Carbamazepine (Tegretol®)	Increased serum levels of carbamazepine leading to toxicity.
Tramadol	Opioid dependency	May reinitiate physical dependence. Agents that lower seizure threshold (eg, SSRI, TCA, Neuroleptics) increase risk of seizures.
Pentazocine	Opioid dependency	May precipitate withdrawal.
Opioids (all)	Sedatives	Profound sedation and respiratory depression may occur with any drug class having a sedative effect.
Opioids (all)	H2 Blockers (eg, ranitidine/ Zantac and climetidine/ Tagamet®)	May delay opioid metabolism. Use caution in determining opioid dose and duration of use.

Table 1 (*continued*)

Prescribed drug	Interaction agent	Interaction explanation
Codeine derivatives	SSRI antidepressants (eg, fluoxetine/ Prozac® and paroxetine/ Paxil®)	Some SSRI antidepressants inhibit demethylation of prodrug to active metabolite, rendering analgesic ineffective. Drugs that inhibit hepatic CYP2D6 enzymes are implicated. See H2 blockers above.
Meperidine	MAO inhibitors (eg, phenelzine/Nardil®)	Mechanism of interaction unclear, but seizures and coma have been reported.

GI, gastrointestinal; INR, international normalization ratio; MAO, monoamine oxidase; SSRI, selective serotonin reuptake inhibitor; TCA, tricyclic anti-depressant; NSAID, non-steroidal anti-inflammatory drugs.

ceiling for their anti-inflammatory response cannot be ascertained because at higher dosages, side effects become prohibitive. As typically higher NSAID doses are required to suppress inflammation than to provide analgesia, many NSAIDs are marketed in several dosages (ie, ibuprofen is available in dosages ranging from 200–800 mg). When prescribing a NSAID, select low dose ranges for noninflammatory pain and reserve higher dosages for those situations in which inflammation and swelling are a consideration.

Compared with other NSAIDs, aspirin not only produces a greater incidence of side effects but also has been shown to have slightly less analgesic efficacy. Thus, aspirin is a questionable choice for managing postoperative pain. All NSAIDs have the potential to produce side effects similar to aspirin, but most exhibit a lower frequency. In particular, ibuprofen is one of the safest. It produces GI symptoms in less than 3% of patients treated, and its antiplatelet activity is considerably less than aspirin and most other NSAIDs.

Clinical trials comparing NSAIDs, including the COX-2 inhibitors (ie, rofecoxib [Vioxx®] and celecoxib [Celebrex®]) have not identified substantive differences in their anti-inflammatory or analgesic efficacy. Conclusions from clinical trials, however, are based on summaries of data from large groups of patients. The clinician must appreciate that there can be considerable variation among individual patients in terms of clinical response and GI tolerance. In a given patient, an unsatisfactory response with one NSAID does not preclude therapeutic success with another. Considering its low cost and side-effect profile, ibuprofen is a logical first-line agent. The COX-2 agent rofecoxib does offer the advantage of once-a-day dosing, no increase in bleeding times, and minimal GI issues (see COX-2 article in this issue). But the practitioner must weigh the patient benefits against the increase in COX-2 drug cost over generic NSAIDs when prescribing. Regardless of the drug selected initially, one should optimize agent dosage before assuming the response is inadequate and switching to another agent.

The preoperative use of NSAIDs has been demonstrated repeatedly to decrease the intensity of postoperative pain and swelling [5]. This is not surprising because NSAIDs inhibit the ''formation'' of prostaglandins; they do

not destroy or inhibit those already formed. More recent understanding of pain mechanisms has found that benefits of this practice are evident as long as prostaglandin synthesis is inhibited before local anesthesia wanes. Otherwise, prostaglandins trigger nociceptive impulses that travel to the brain and "wind up" the brain's interpretation of pain intensity. When an extensive surgical procedure is planned, optimal serum levels of an NSAID should be established either preoperatively or prior to patient discharge and while tissues remain anesthetized. This use of "pre-emptive analgesia" may also be useful for endodontic and extensive restorative procedures as well.

Acetaminophen

The action of acetaminophen is poorly defined but is believed to interrupt the influence of prostaglandins within CNS pathways. Acetaminophen is approximately as active as aspirin in inhibiting prostaglandin synthetase (cyclooxygenase) within the CNS but has little influence on peripheral prostaglandin synthesis. This is one of several explanations for it lacking anti-inflammatory efficacy and sharing none of the peripheral side effects common to NSAIDs. As an analgesic and antipyretic, however, acetaminophen is equal in potency and efficacy to aspirin, achieving its analgesic ceiling at 1000 mg. This would suggest that it is somewhat inferior to ibuprofen and other NSAIDs.

The major adverse effect of acetaminophen is hepatotoxicity. This is attributed to a metabolite that is not adequately conjugated following acute doses of 10–15 g (150–250 mg/kg). A lower dose may be toxic for patients having depleted storage of glycogen such as that associated with dieting, anorexia, and those suffering primary liver dysfunction or receiving hepatotoxic medications. For example, patients suspected of chronic alcoholism should limit their daily acetaminophen intake to 2 gm rather than the normal daily maximum of 4 gm [6].

Tramadol

Tramadol, though not classified as a controlled substance by the DEA, is a central analgesic with binary action (CABA). Tramadol binds weakly to mμ opioid receptors and inhibits the reuptake of norepinephrine and serotonin. Tramadol's principal metabolite (M1) demonstrates, however, a more significant agonist action on mμ receptors than the parent agent. Tramadol-induced analgesia is only partially antagonized by the opiate antagonist naloxone. Because of the dual mechanism of action, the adverse-event profile of tramadol differs from that of NSAIDs (eg, gastrointestinal or renal/cardiovascular considerations) or traditional opioids. Tramadol is marketed as an effective and safe analgesic for moderate to moderately severe pain. It was available in Europe and Asia for over a decade before being approved for use in the United States. Nausea, vomiting, and dizziness may occur with

the use of tramadol. Tramadol should be used with caution in patients with a history of seizure disorder. Tramadol is considered to have a low incidence for abuse (0.5–1.0 case per 100,000 patients) and is not a scheduled drug. But tramadol is not recommended for patients with a tendency for opioid abuse or dependence [7,8]. A single dose of tramadol as the sole analgesic has been shown to provide pain relief within 1 hour that continues for at least 6 hours [9]. Tramadol offers the clinician the potential to reduce the incidence of somnolence and constipation commonly seen with opioid use, but tramadol monotherapy may not be safer or more effective than mild opioid/acetaminophen combinations [10]. Consequently, the practitioner may find tramadol useful when added for breakthrough pain to NSAID, COX-2, and/or acetaminophen used for baseline acute pain management.

In situations where the practitioner wishes to avoid opioid therapy, the rationale for prescribing an NSAID for baseline inflammation and pain management with consideration of tramadol, acetaminophen, or the tramadol/acetaminophen combination for breakthrough pain in acute, postoperative orofacial pain management has been suggested [11]. The use of the tramadol/APAP combination tablet in patients with dental pain has been shown to have more rapid onset and greater efficacy than tramadol alone, without an apparent increase in adverse events [12]. In a comparison of tramadol/acetaminophen tablets with codeine/acetaminophen capsules for chronic pain, the pain rating scores for onset, duration, and relief were similar. The incidence of somnolence, however, was 17% with tramadol/acetaminophen, and 24% with codeine/acetaminophen. The incidence of constipation was 11% with tramadol/acetaminophen and 21% with codeine/acetaminophen. Headache was more common in the tramadol/acetaminophen group (11%) than the codeine/acetaminophen group (7%). Both groups had an 8% incidence of discontinuance from allergic reactions, primarily rash or pruritus [13].

Summary of nonopioids

In most cases, postoperative dental pain includes an inflammatory component. For this reason, NSAIDs are rational first-line agents, often superior to conventional dosages of opioids. Should a patient present a contraindication to NSAIDs, acetaminophen and/or tramadol are the only alternatives in this category of agents. Nonopioids exhibit a ceiling to their analgesic response, and optimal doses should be established before assuming the NSAID has failed.

In pain management situations involving acute pain and inflammation, where the practitioner wishes to avoid or limit opioid therapy, there is the consideration of using a NSAID for baseline inflammation and pain management with the option of adding APAP, tramadol, or the combination of tramadol/APAP for baseline and/or breakthrough pain control.

Data relevant for prescribing the more commonly used nonopioids is summarized below (Table 2).

Table 2
Selected nonopioid analgesics useful for reducing postoperative pain and inflammation

Nonsteroidal anti-inflammatory drugs (NSAIDs)	Dosage (70 kg adult)	Clinical characteristics (hours)		
		Onset	Peak	Duration
Ibuprofen (Motrin®)	400–800mg tid/qid	0.5	1–2	4–6
Naproxen (Anaprox®)	275–550mg bid/tid	1	2–4	5–7
Celecoxib (Celebrex®) COX-2	200 mg bid	0.5	1–2	11–15
Rofecoxib (Vioxx®)	25–50mg qd	1	1–2	17–24
Valdecoxib (Bextra®)	20–40mg qd	0.5	1–2	24
Non-NSAID analgesics				
Acetaminophen (Tylenol®)	500–1000mg qid[a]	0.5	0.5–2	4–6
Tramadol (Ultram®)[b]	25–100mg qid	1	1–2	4.66

[a] Daily total dose not to exceed 4 gm on healthy 70 kg adult.
[b] Considered nonopioid because mechanism of action is by serotonin/norepinephrine reuptake inhibition in addition to weak opioid μ binding.
(*Adapted from* American Pain Society: Principles of analgesic use in the treatment of acute pain and cancer pain, 4th edition. Glenview (IL): American Pain society; 1999. p 5–10; with permission.)

Opioid analgesics

Actions and effects

Opioids produce the majority of their therapeutic and adverse effects by acting as agonists at μ and/or κ opioid receptors. Unlike the nonopioids, which exhibit a ceiling effect, the analgesic response to opioids acting at mμ receptors continues to improve as their dose is increased. Although their analgesic efficacy is unlimited, side effects often preclude the use of doses adequate to completely relieve severe pain. These include sedation, respiratory depression, dependence, nausea, miosis, and constipation. Following prolonged use, patients develop tolerance to most opioid effects. Constipation and miosis are notable exceptions, however. For this reason, patients suffering chronic and/or terminal illnesses may require astonishing doses to achieve analgesia, but constipation and visual impairment are troublesome. Similar doses, if administered to patients who have not developed tolerance, so-called ''opioid-naive'' patients, would be lethal because of respiratory depression. Use caution when considering newer high-dose, sustained-release opioids designed for tolerant patients.

Therapeutic use of opioids

Patients and practitioners are often concerned with the potential for addiction, which may limit prescribing and use, leading to inadequate management of pain [13,14]. This can be attributed to confusion regarding drug dependence and drug addiction. Patients consuming opioids regularly for more than 1 week may develop a degree of drug dependence. This may require gradual tapering of the dosage to avoid withdrawal symptoms.

Drugs do not produce addiction, however. This is a compulsive pattern of behavior in which an individual continues to seek the drug for effects they perceive as pleasurable. Addictive behavior is a psychiatric condition that can be reinforced by a particular drug, but it is not a pharmacodynamic property. Obviously, opioids must be prescribed cautiously for patients who demonstrate addictive personality.

The practitioner should carefully consider the use of opioid therapy for the short-term management of breakthrough pain in acute, orofacial pain that is moderate to severe. Despite popular belief, all of the traditional opioids have unlimited efficacy. This is to say that, at equipotent doses, opioids provide the same degree of pain relief. It is a misconception that pain unresponsive to codeine will respond to oxycodone, meperidine, or morphine. It may be desirable to change to one of these medications, but the decision should not be based on delusions regarding efficacy. A more likely explanation would be that an equianalgesic dose of one agent could not be achieved without significant side effects. Issues in opioid dosage are predicated on the pharmacokinetic profiles of the various agents, not their efficacy at opioid receptors.

Equianalgesic doses have been confirmed for opioids administered by parenteral routes. Those following oral administration are problematic because of altered bioavailability attributed to first-pass metabolism into inactive metabolites. Opioids used for treating moderate to moderately severe pain are compared below by equipotent dose, DEA schedule, and clinical duration (Table 3).

Genetic predisposition for patient conversion of opioids can lead to poor analgesia in certain patients. Codeine has very little affinity for the mμ receptor and may be considered a prodrug because 10% of the drug is metabolically converted to morphine by cytochrome P450 CYP2D6. Morphine is analgesic and codeine is antitussive. Approximately 7% of the Caucasian population metabolizes codeine and hydrocodone poorly because they have inherited two nonfunctional alleles for cytochrome P450 CYP2D6. In these individuals, analgesia resulting from codeine, oxycodone, or hydrocodone will be less than expected with the general population.

Specific opioid considerations

Codeine

Morphine 10 mg and codeine 120 mg are equipotent following intramuscular (IM) administration. The lower potency and greater incidence of nausea attributed to codeine can be explained by the following information. The only difference in their molecular structure is a methyl group that prevents their binding to mμ receptors. Codeine and its derivatives are prodrugs, meaning that they are inactive in the form administered. Approximately 10% of a parenterally administered dose of codeine is demethylated to morphine, and this is responsible for its analgesic influence. This accounts for low analgesic

Table 3
Commonly prescribed opioids in the United States shown with oral doses that are equipotent to morphine 10 mg IM

Drug	DEA Schedule	PO dose equivalent to 10 mg morphine IM (mg)	Clinical duration (hours)	Comments
Morphine	II	60[a]	4–6	M-6-G and M-3-G can accumulate in renal failure
Meperidine	II	300	2–3	Poor choice for oral use because of 25% bioavailability. Normeperidine, a neurotoxin, can accumulate.
Oxycodone	II	20	4–6	Available commercially combined or separately
Hydrocodone	III	30	3–4	Only available commercially combined
Codeine	II as separate agent; III when commercially combined	200	3–4	Concerns with itching and nausea
Propoxyphene	IV	200	6	Available commercially combined or separately. Norpropoxyphene, a neurotoxin, can accumulate.
Pentazocine	IV	50	4	Agonist-antagonist—not to be used in presence of other opioids or narcotic dependent patient. PO only available combined commercially with APAP.

APAP, acetaminophen; DEA, Drug Enforcement Agency; PO, oral.

These doses should be viewed as maximum for outpatient use and seldom required for acute orofacial pain management, especially when combined with a non-opioid for baseline pain control. Initial dose should be a fourth to half these maximums.

[a] 60 mg PO is appropriate only for the initial dose. Subsequently, equipotent doses are 30–40 mg.

(*From* Baumann TJ. Pain management. In: DiPiro JT, Talbert RL, Yee GC, et al, editors. Pharmacotherapy: a pathophysiologic approach. Stamford (CT): Appleton and Lange; 1997. p. 1259–78; and Kastrup EK. Opioids. In: Olin BR, Hebel SK, editors. Drug facts and comparisons 2000, 54th edition. St. Louis: Facts and Comparisons; 2000. p. 784–806.)

potency because 90% remains as the methylated parent drug having little or no analgesic efficacy but retaining useful antitussive properties. Unfortunately, this parent molecule also produces nausea and constipation, and for this reason, codeine is used only in lower doses (eg, 30–90 mg) for managing milder pain intensity.

It is not uncommon for patients to report prior episodes of nausea as an "allergic reaction." IgE antibodies, however, have been detected that react with several opioids, including codeine, and nearly all opioids are capable of triggering degranulation of mast cells leading to the direct release of histamine. Until issues regarding cross reactivity among opioids are resolved, a prudent approach would be to select alternatives that are molecularly dissimilar. For example, when a patient reports clinical signs that are allergic in nature, eg, rash or pruritis, one should select an agent that is not derived from codeine, eg, propoxyphene or meperidine. Drug interactions involving opioids are summarized below (see Table 1). The influence of certain antidepressants on the effectiveness of codeine and its derivatives has significant efficacy implications.

Hydrocodone and oxycodone

Hydrocodone and oxycodone are attractive analgesics because they have oral bioavailability comparable to codeine (ie, 60%, and their greater potency reduces the portion of an administered dose contributing to nausea and constipation). Unfortunately, equianalgesic doses were initially poorly understood and spawned the release of combination products that contain irrational formulations.

Like codeine, oxycodone, and hydrocodone are methylated molecules having little or no analgesic efficacy. Presumably, 10% of a dose administered parenterally is demethylated to its respective morphine counterpart, hydromorphone and oxymorphone. Evaluation of the information (see Table 3) reveals that the oral dose for codeine is approximately 20× the IM dose of morphine. (200 mg versus 10 mg). This table indicates that 200 mg codeine, 30 mg hydrocodone, and 20 mg oxycodone are equipotent oral doses and are equianalgesic to morphine 10 mg IM. Clinical studies that have attempted to address equianalgesic doses of codeine derivatives are sparse, but they support this opinion. Beaver et al found that oxycodone 10 mg was comparable to codeine 100 mg, and this would extrapolate to oxycodone 20 mg and codeine 200 mg. Studies by Hopkinson and by Beaver have shown that hydrocodone 10 mg was approximately equipotent to codeine 60 mg, and this would extrapolate to 33 mg hydrocodone and 200 mg codeine [15].

Meperidine

Meperidine 75 mg is equianalgesic to morphine 10 mg following IM administration. A significant portion of an IM dose of meperidine is converted to normeperidine, a metabolite that has no analgesic properties but

is a noted CNS stimulant. Furthermore, this metabolite has a 15–20-hour elimination half-life, compared with 3 hours for the parent drug. For hospitalized patients, meperidine is used only for a day or two; otherwise, normeperidine will accumulate. This issue becomes even more problematic following oral administration. The oral bioavailability for meperidine is approximately 25%, which requires a 300 mg dose to be equianalgesic to its IM dose of 75 mg. This introduces an even greater risk for accumulation of normeperidine. Poor oral absorption and accumulation of normeperidine make meperidine a very poor choice as an oral analgesic.

Propoxyphene

Propoxyphene is available only for oral administration. Its equianalgesic dose compared with morphine has not been established, but its potency is low. By convention, 100 mg is considered equipotent to oral codeine 60 mg. It is similar to meperidine in that it is converted to norpropoxyphene, a CNS stimulant having an elimination half-life of 30 hours. Propoxyphene is a DEA class IV agent. Its use should be limited to short-term management of mild to moderate pain.

Pentazocine (opioid agonist-antagonist)

Pentazocine is the only oral agonist-antagonist analgesic available in the United States. Pentazocine in the United States is available for oral use compounded with naloxone, a narcotic antagonist, presumably to prevent parenteral injection abuse issues. When taken by mouth as intended, naloxone does not inactivate the pentazocine, as naloxone has no bioavailability when taken orally. Additionally, pentazocine is available compounded with APAP. Though this agent can provide agonist analgesia when administered as the sole analgesic, pentazocine should not be used in the presence of other opioids. When other opioids are present, pentazocine will serve as an opioid antagonist, thus reducing the patient's analgesia. Additionally, it should not be prescribed for patients who are at risk for opioid withdrawal for the same reason. Pentazocine is a DEA schedule IV agent. It can be considered for the limited short-term management of mild to moderate pain.

Adjunctive therapy

A final consideration is the use of adjuvant agents that complement the opioid and nonopioid agents. Local anesthetics and GABAergic drugs are two examples of agents in this group that can be used to control pain. Longer-acting local anesthetics such as bupivacaine (Marcaine®) can be useful as part of a compound approach to patient pain control. Additionally, where muscle spasm, sleep disturbance, and/or anxiety are a consideration, the use of benzodiazepines such as lorazepam (Ativan®) can be added to the pain management combination.

Analgesic regimens

Mild and moderate pain can frequently be managed effectively using optimal doses of nonopioids (eg, 400–800 mg ibuprofen, 1000 mg acetaminophen, and 25–50 mg rofecoxib). Though it is unwise to combine NSAIDs, adding acetaminophen to an NSAID would be sensible considering their different sites of action [16]. Regardless of pain severity, one should optimize dosages of these agents and then, if necessary, add an opioid to the regimen. This practice will generally reduce the amount of opioid required, sometimes to only a fraction of the maximum doses listed in Table 3. Ideally, one should maintain the regular nonopioid dosing schedule and add an opioid product as needed for breakthrough pain.

Table 4
Management of mild, moderate and severe acute, orofacial pain in a healthy 70 kg adult

Indication	Regimen (70 KG adult examples)
Mild pain eg, root planning, routine endodontics	Ibuprofen: initial dose 400–800 mg, then 400–600 mg qid for 1–2 days, then PRN or Rofecoxib: Initial dose 50 mg, then 25–50 mg for 1–2 days then PRN and/or Acetaminophea: Initial dose 1000 mg, then 500–1000 mg q6h hours for 1–2 days, then PRN and/or Tramadol/acetaminophen[a]
Moderate pain eg, routine implant surgery, Soft tissue impactions	Baseline pain management with nonopioid: Establish regimen as per Mild Pain above plus Control breakthrough pain with Codeine 30–60 mg q4h PRN or Hydrocodone 5–10 mg q4h PRN or Oxycodone 5–10 mg q4h PRN or Pentazocine 25 mg q4h PRN and/or Tramadol 37.5–100 mg q4–6 hours PRN
Severe pain eg, bony impactions, complex implant surgery	Baseline pain management nonopioid: Establish regimen as per Mild Pain above, using maximum doses and continuing for 3–5 days before allowing PRN dosing plus Control breakthrough pain with: Hydrocodone 10–20 mg q4hours PRN or Oxycodone 5–15 mg q4h PRN or Pentazocine 50 mg q4h PRN and/or Tramadol 37.5–100 mg q4-6h prn

NSAID, nonsteroidal anti-inflammatory agent.

[a] NSAID use permits the use of tramadol/APAP combination with either q 4–6 h dosing or PRN.

When moderate to severe pain is anticipated with an inflammatory component, as NSAID should be used preoperatively. The practitioner should consider using a loading-dose for the initial NSAID, which is usually double the maintenance dose. Where concerns are present with exceeding the recommended daily ceiling dose of APAP- or NSAID-containing compounds, the practitioner can consider prescribing tramadol or an opioid that is not compounded, ie, oxycodone or codeine as a separate prescription. The practitioner must remember that titration to clinical response is necessary. Recommended doses do not apply to patients with renal or hepatic insufficiency or other medical conditions affecting drug metabolism. Elderly patients generally require lower doses, titrated slowly to the desired effect or side effects that are intolerable. Opioids for breakthrough pain may be prescribed commercially compounded. The nonopioid (generally APAP) compounded with the opioid must be considered when the baseline pain management analgesic is chosen to avoid nonopioid overdose and/or system toxicity. If tramadol is chosen as the initial breakthrough agent, another opioid may be added in addition if analgesia is inadequate at the maximum recommended dose of tramadol. Pentazocine should not be used if other opioids have been administered.

Based on this logic, it is not surprising that such a large number of commercially compounded analgesics have prepared containing both a nonopioid and an opioid ingredient. The opioid contained in most of these products is either codeine or one of its derivatives, eg, hydrocodone. It's unfortunate that some of these compounds were formulated with little consideration given to equianalgesic dosage strategies. Also, several products contain quantities of acetaminophen that preclude the use of multiple tablets to achieve an adequate amount of opioid for patients who experience severe pain. When prescribing combination products, the clinician must pay particular attention to the amount of acetaminophen in each compounded tablet so that the maximum daily dose is not exceeded. In some cases the clinician may choose to write separate prescriptions for the opioid and nonopioid analgesic needs of the patient to avoid acetaminophen overdose. Suggested regimens are presented in Table 4.

Summary

Careful selection of an effective analgesic regimen based on the amount and type of pain the patient is expected to have can prevent the stress and anxiety associated with breakthrough pain. When analgesics fail, it is not unusual for patients to go to desperate lengths to seek relief. The clinician can and should develop a variety of effective, safe analgesic regimens based on estimates of anticipated pain intensity that apply sound pharmacologic principles.

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