Pain Management in Infants, Children, Adolescents, and Individuals with Special Health Care Needs

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Abstract
This statement provides dentists and stakeholders with current best practices for pediatric pain management. Infants, children, adolescents, and individuals with special health care needs may experience pain resulting from dental/orofacial injury, infection, and dental procedures. Dental pain is an inflammatory condition that can be categorized as somatic (i.e., periodontal, alveolar, mucosal) or visceral (i.e., pulpal). Dental professionals should consider pain assessment for all patients. Inadequate pain management may lead to significant physical and psychological consequences for patients. Perioperative pain management approaches include pre-emptive pain management (e.g., anesthetics), use of local anesthesia during general anesthesia for post-operative pain control, non-pharmacological anxiolytic interventions (e.g., providing a calm environment, emotional support), distraction and imagery (e.g., counting, video games), and pharmacological pain control agents including non-opioid analgesics (e.g., nonsteroidal anti-inflammatory drugs, acetaminophen) and opioid analgesics. Acetaminophen and nonsteroidal anti-inflammatory medications are first line pharmacologic therapies for pain management. Use of opioids for pediatric dental patients should be rare, and steps to mitigate opioid misuse are discussed.

This document was developed through a collaborative effort of the American Academy of Pediatric Dentistry Councils on Clinical Affairs and Scientific Affairs to offer updated information and guidance on pain management in infants, children, adolescents, and individuals with special health care needs.

KEYWORDS: FACIAL PAIN; TOOTHACHE; PAIN MANAGEMENT; ACUTE PAIN; CHRONIC PAIN; PAIN, POSTOPERATIVE

ABBREVIATIONS
Purpose
The American Academy of Pediatric Dentistry (AAPD) recognizes that infants, children, adolescents, and individuals with special health care needs can and do experience pain due to dental/orofacial injury, infection, and dental procedures, and that inadequate pain management may have significant physical and psychological consequences for the patient. Appreciation of pediatric pain can help practitioners develop clinical approaches to prevent or substantially relieve dental pain. When pharmacological intervention is necessary to manage pain, the practitioner must understand the consequences, morbidities, and toxicities associated with the use of specific therapeutic agents. These recommendations are intended to provide dental professionals and other stakeholders with current best practices for pain management in pediatric dentistry.

Methods
This document was developed by the Council on Clinical Affairs and adopted in 2018. It is based on a review of current dental and medical literature pertaining to pain management in pediatric dental patients. Review of existing federal and professional pain management guidelines and consensus statements were used to assist with this document. An electronic search was conducted in the PubMed®/MEDLINE database using the terms: dental pain management, pediatric pain assessment, pre-emptive analgesia, paracetamol, pediatric and acetaminophen, adolescent and acetaminophen, pediatric and nonsteroidal anti-inflammatory drugs (NSAIDs), adolescent and NSAIDs, pediatric and opioids, adolescent and opioids, opioid risk, adolescent orofacial pain, pediatric and adolescent chronic pain, non-pharmacologic pain management; fields: all; limits: within the last 10 years, humans, English, systematic review, and clinical trials. There were 3,698 articles that met these criteria. Papers for review were chosen from this list and from references within selected articles. When data did not appear sufficient or were inconclusive, recommendations were based upon expert and/or consensus opinion by experienced researchers and clinicians.
Background

Pain is defined by the International Association of the Study of Pain as “an unpleasant sensory and emotional experience associated with, or resembling that associated with, actual or potential tissue damage.”\textsuperscript{2} Their expanded definition includes six items that provide further context to the complex topic of pain: pain is always a personal experience; pain is different from nociception; pain is learned through life experiences; a person’s report of pain should be respected; pain can have adverse effects on function and well-being; and verbal description is one of several behaviors used to express pain.\textsuperscript{2}

Intraoral pain presenting as a toothache is a common source of orofacial pain in children.\textsuperscript{3} An estimated 95 percent of orofacial pain results from odontogenic causes\textsuperscript{4} and, according to a recent systematic review and meta-analysis, an overall pooled prevalence of toothache in children and adolescents was 36.2 percent.\textsuperscript{3} Pain experienced during dental procedures can be distressing for the provider, the child, and his parents and can also lead to difficult behavior, dental fear, and avoidance behavior in the child.\textsuperscript{5} Moreover, pain experience in childhood may shape future pain experiences in adulthood.\textsuperscript{6}

Pain from dental pulp arises when functional nerves are stimulated by bacteria or trauma.\textsuperscript{7} Periodontal pain occurs when infectious or traumatic insults to the gingiva, periodontal ligament, and alveolar bone stimulate free nerve endings.\textsuperscript{7} Other sources of orofacial pain include temporomandibular disorders (e.g., joint pain, masticatory muscle pain), headaches (e.g., migraine, tension type), or other non-odontogenic causes (e.g., pathologic jaw lesions, oral ulcers, neuralgia). Pain may be divided into diagnostic categories such as somatic, visceral, and neuropathic.\textsuperscript{8} Pain encountered in dentistry is typically inflammatory and categorized as somatic (i.e., periodontal, alveolar, mucosal) or visceral (i.e., pulpal) pain.\textsuperscript{7}

Pain management includes pharmacologic and nonpharmacologic strategies to treat both acute and chronic pain. Due to the increased appreciation for pediatric pain and because of the national opioid crisis, recommendations for professional education and approaches for therapeutic management are being reviewed at the national, state, and local levels.\textsuperscript{9-12}
Understanding nociception (i.e., pain processing) is essential for the management of pain. Following tissue injury, infection, or invasive treatment, thermal, mechanical, and chemical stimuli activate receptors on free nerve endings in vital structures in the orofacial region. In turn, sensory signals travel along afferent trigeminal nerve fibers and relay information to the brainstem and higher structures involved with the perception of pain. Under normal conditions the perception of pain persists until the stimulus is removed. Sensitization of central and peripheral nervous system circuits occurs following significant tissue damage or prolonged neuronal stimulation. Terminal nerve endings at the site of tissue injury exhibit an enhanced neuronal response to noxious stimuli in the peripheral nervous system. This local increase in nerve membrane excitability is referred to as peripheral sensitization. The exaggerated response to stimuli in the region of tissue damage is called primary hyperalgesia.

Central sensitization refers to enhanced functional status of pain circuits and pain processing at the level of the central nervous system (CNS). Both secondary hyperalgesia, which is an increase in pain intensity to noxious stimuli outside of the area of tissue damage, and allodynia, which refers to pain perception following innocuous stimuli such as light touch, are characteristics of central sensitization. Modulation of pain pathways occurs through CNS excitatory and inhibitory processes. Ascending facilitating and descending inhibitory processes enhance or suppress the pain experience, respectively. Both pharmacologic and nonpharmacologic methods target these processes to alter pain processing.

Pain assessment is an integral component of the dental history and comprehensive evaluation. When symptoms or signs of orofacial/dental pain are evident, a detailed pain assessment helps the dentist to derive a clinical diagnosis, develop a prioritized treatment plan, and better estimate analgesic requirements for the patient. Pain is difficult to measure due to its subjectivity, especially in children, and often relies on the report of parents or caregivers. In clinical practice, pain assessment is largely non-standardized and based on signs and symptoms rather than specific tools.
Pain can be assessed using self-report, behavioral (vocalization, facial expression, body movement), and biological (heart rate, transcutaneous oxygen, sweating, stress response) measures. Direct questioning or a structured, comprehensive pain assessment can be clinically beneficial for pediatric and adolescent patients. Conducting a structured interview begins with asking specific questions regarding pain onset, provoking factors, palliative factors, quality or character, region or location, severity or intensity, timing or duration, and impact on daily activities. Obtaining information through self-report can be aided by asking the child to make comparisons, using temporal anchors and facilitating communication through objects or gestures. Assessing behavioral reactions and physiological reactions to pain are required in non-verbal patients, young patients, and patients with special health care needs. Pain experienced by children with special health care needs or developmental disabilities is more challenging to assess accurately, and assessment may benefit from the utilization of scales that rely on observations such as vocalization, facial expressions, and body movements. Validated instruments available for assessing pain in verbal or nonverbal patients include: Wong-Baker FACES®, Faces Pain Scale (Revised), visual analogue scale (VAS), numeric rating scale (NRS), Faces, Legs, Activity, Cry, and Consolability score (FLACC), Revised Faces, Legs, Activity, Cry and Consolability (r-FLACC), and the McGill Pain Questionnaire. Additionally, ethnic, cultural, and language factors may influence the expression and assessment of pain.

Pain also may be categorized as acute or chronic. Acute pain that fails to respond to treatment may become chronic over time. Chronic pain refers to pain that is dysfunctional and persists beyond the time for typical tissue healing. Chronic pain is a costly public health problem that is difficult to treat. Temporomandibular disorder (TMD) is an example of a chronic pain condition encountered in dentistry.

**Pain management**

*Pre-emptive pain management*

Pre-emptive pain management refers to the administration of an anesthetic agent, medication, or technique prior to a surgical event with the goal of decreasing pain. Goals of pre-emptive pain management include attenuating central sensitization, decreasing postoperative pain, improving recovery, and reducing postoperative analgesic consumption. Postoperative pain
management in pediatric patients has been suboptimal in large part because parents frequently do not adequately treat pain that is experienced at home and fear of adverse events. Pain after dental treatment under general anesthesia frequently is related to the total number of teeth treated. Nearly 50 percent of patients undergoing dental rehabilitation describe moderate to severe pain, and data supports pre-emptive measures to optimize pain control for a variety of dental and surgical procedures.

Achieving profound anesthesia prior to initiating invasive treatment decreases central sensitization. Topical anesthetics are used in dentistry to minimize pain; however, these medicaments alone may not be sufficient for dental procedures. Topical anesthetics and over-the-counter products containing benzocaine have been used for minor procedures and to manage oral pain, teething, and ulcers. However, benzocaine use in children has been linked to methemoglobinemia, a life-threatening condition. In 2018, the U.S. Food and Drug Administration (FDA) issued a post-market warning against the use of these products for children younger than two years and that the products must have warning labels regarding methemoglobinemia. Local anesthetic administration techniques, the anesthetic properties, and the needle used during injection. Distraction techniques made at the time of the injection (e.g. jiggling the patient’s cheek, applying pressure to the palate with a mirror handle) take advantage of Aβ-fiber signal dominance and can significantly reduce the intensity of pain-related C-fiber signaling. Buffering or decreasing acidity of local anesthetic using sodium bicarbonate can decrease injection site pain and postoperative discomfort by increasing the pH of the anesthetic. A recent systematic review demonstrated lower pain scores following inferior alveolar block injections in children when buffered versus non-buffered local anesthesia was used; however, there was no difference in observer-reported pain behavior. Finally, decreasing anesthetic delivery rate also has demonstrated pain reduction during injection.

The use of pre-emptive analgesics in conjunction with local anesthetics has been shown to increase the ability to achieve pulpal anesthesia in patients with irreversible pulpitis when compared with placebo and to suppress the intensity of injection pain and reduce pain following extractions. The pre-emptive analgesics most commonly used in dentistry are NSAIDs (e.g., ibuprofen) and acetaminophen, either alone or in combination. Analgesics with sedative properties are often
administered during the pre-, peri-, or post-operative periods when moderate to severe pain is anticipated.49-52

Use of local anesthesia during general anesthesia
Although pain is not experienced during general anesthesia, central sensitization occurs when peripheral nerves are stimulated.23,53 Operating without local anesthesia may result in priming of CNS neurons and increased future pain sensitivity.6 Central sensitization is minimized with preemptive analgesia or anesthesia. For this reason, regional block or infiltration anesthesia is commonly performed prior to surgical procedures to decrease postoperative pain.15,55 However, pharmacologic and cardiac considerations, along with avoiding the numb sensation and potential for self-inflicted oral trauma, are reasons providers may choose not to provide local anesthesia during general anesthesia.55,56

Non-pharmacologic approaches to pain management
Studies suggest that nonpharmacologic interventions may be effective alone or as adjuncts to pharmacological interventions in managing procedure-related pain, anxiety, and distress with minimal risk of adverse effects.57-60 Fear and anxiety activate circuits within the CNS that facilitate pain.28 Creating a safe, friendly environment may help a child feel more comfortable and less stressed.60,61 The American Academy of Pediatrics (AAP) and the American Pain Society recommend that providers reduce distress-producing stimulation and provide a calm environment for procedures to improve pain management.10 Individual studies have shown the efficacy of psychologic techniques, including preparation and information, parent coaching or training, suggestion, memory alteration or change, and coping self-statements.62-64

Distraction and imagery
Distraction is an effective method of pain management in the pediatric population.26,65 It can be cognitive (e.g., counting, non-procedural talk) or behavioral (e.g., videos, games), both of which aim to shift attention away from pain. Distraction techniques such as bubbles, counting, conversation, music, television, toys, and video games may be used by health care providers or the child’s caregiver.60,61 Strong evidence supports the efficacy of distraction techniques for needle-related pain and distress in children and adolescents.66 Distraction is significantly effective when
measuring pulse rates, respiratory rates, and self-reported pain. Distraction techniques may be of great use with patients with special needs who have shortened attention spans and cannot understand verbal reasoning or reassurance. Distraction, hypnosis, combined cognitive behavior therapy (CBT), and breathing interventions have been effective in reducing children’s needle-related pain or distress, or both.

Imagery guides the child’s attention away from the procedure by harnessing imagination and storytelling. Imagery in combination with distraction has been shown to decrease postoperative pain in children.

**Hypnotherapy**

Hypnotherapy aims to alter sensory experiences and dissociate from pain experiences, and hypnosis is best for children of school age or older. There is evidence hypnotherapy is effective in reducing needle-related pain and distress in children and adolescents; however, there is no evidence hypnotherapy alone is capable of producing an anesthetic effect necessary for invasive dental procedures.

**Virtual reality and smart phone applications**

The use of digital distraction can provide distraction and reduction in pain and distress for children undergoing painful procedures. The use of virtual reality, video games, and smartphone applications has shown a reduction in self-reported and observer-reported pain and distress during common procedures such as venipuncture and dental and burn treatments. Further studies are needed to assess the benefits of distraction with a tablet compared to audiovisual glasses during dental procedures.

**Other techniques**

Studies have shown efficacies for pediatric pain management with other techniques such as relaxation and breathing exercises, transcutaneous electrical nerve stimulation, acupuncture, counterstimulation, video modelling, and music therapies. Additional research is need on these interventions to measure their effectiveness.
Pharmacologic/therapeutic agents

Management of pain in children is changing rapidly as a result of improvements in the appreciation of pediatric pain and pharmacologic knowledge. However, randomized controlled trials are lacking in children so the use of many pain medications is considered off label. Acetaminophen and ibuprofen are recommended as first-line medication choices for the treatment of acute pain in children. Both have been shown to have good efficacy and safety and are also cost-effective analgesics. The use of opioids in children carries risks.

Non-opioid analgesics

Nonsteroidal anti-inflammatory drugs. NSAIDs are among the most commonly used class of drugs and have anti-inflammatory, analgesic, antipyretic, and antiplatelet properties. They inhibit prostaglandin synthesis, with specific action on cyclooxygenase (COX), the enzyme responsible for converting arachidonic acid into pro-inflammatory mediators that drive postoperative pain, swelling, and hyperalgesia. Representatives of the major categories of NSAIDs are salicylic acids (aspirin), acetic acids (ketorolac), propionic acids (ibuprofen, naproxen), and cyclooxygenase-2 selective (celecoxib). Ibuprofen in oral or intravenous (IV) form is a safe and commonly used analgesic and antipyretic agent in pediatrics. Ketorolac, an IV or intranasal NSAID, is useful in treating moderate to severe acute pain in patients unable or unwilling to swallow oral NSAIDs. Some adverse effects associated with NSAIDs include: rash, inhibition of bone growth and healing, gastritis with pain and bleeding, decreased renal blood flow and kidney dysfunction, reversible inhibition of platelet function, hepatic dysfunction, and increased incidence of cardiovascular events. A specific concern with NSAIDs is the potential to exacerbate asthma due to a shift in leukotrienes. Due to shared pathways, combined NSAIDs and corticosteroid (e.g. prednisone) use may increase the potential for gastrointestinal bleeding.

Acetaminophen (acetyl-para-aminophenol [APAP], paracetamol). Acetaminophen is an analgesic with efficacy for mild to moderate pain and an antipyretic. Unlike NSAIDs, acetaminophen is centrally acting and does not have anti-inflammatory effects or an effect on gastric mucosal lining or platelets. Its mechanism of action is the blockade of prostaglandin and substance P production. Allergic reactions are rare, but toxicity from overdose may result in acute liver failure. Acetaminophen can be administered in tablets, capsules, and liquid but also is available as oral
disintegrating tablets, oral disintegrating films, and rectal and IV forms. Rectal administration has somewhat higher bioavailability and faster onset than the oral route since it partially bypasses hepatic metabolism.

**Opioid analgesics**

Opioid analgesics historically have been used to produce profound pain relief in all age groups. Opioid analgesics are considered for acute moderate to severe pain refractory to other therapies. However, opioids only interrupt the nociceptive pathway to inhibit pain perception and do not target inflammation, which is an integral part of managing dental pain. Common uses in pediatric patients include pain associated with cancer, sickle cell disease, osteogenesis imperfecta, epidermolysis bullosa, and neuromuscular disease. Limited studies are available regarding postoperative opioid use in pediatric dentistry, perhaps because it is rare that pediatric dental patients require opioid analgesics following dental treatment. However, opioid/nonopioid combination medications followed by oxycodone and morphine were the most common analgesics prescribed to children during post-operative emergency room encounters. Major concerns of opioid analgesics in the pediatric population are efficacy, safety, misuse, and accidental deaths.

Opioids interact differentially with μ, κ, and δ receptors in the central nervous system. Opioid agonists act on receptors located in the brain, spinal cord, and digestive tract. Activation of opioid receptors can cause respiratory depression, pupil constriction (miosis), euphoria, sedation, physical dependence, endocrine disruption, and suppression of opiate withdrawal. Pruritus (itching) may occur due to histamine release that accompanies some opioid analgesics. Naloxone is a μ opioid receptor competitive antagonist usually administered parenterally to counter opioid overdose. Pain medicine specialists (e.g. pain physicians, anesthesiologists) are experienced in continuing, tapering, or discontinuation of opioids in patients who are actively prescribed opioids for cancer or other pain.

Codeine has more adverse effects and limited efficacy for dental pain when compared to over-the-counter analgesics. Codeine, tramadol, and hydrocodone, and to a lesser extent oxycodone and fentanyl, are broken down in the liver to active metabolites by the highly variable cytochrome
enzyme, CYP2D6. Some opioid analgesics are ineffective in certain children due to poor drug metabolism. Yet, other patients known as hyper-metabolizers hydrolyze prodrugs to their active forms too quickly, potentially resulting in overdose, respiratory depression, and even death. The FDA and AAP issued warnings and safety communications on codeine and tramadol over the past few years because of this. Hydrocodone and oxycodone also rely on cytochrome p450 metabolism and have the potential for similar adverse effects. Although systematic reviews have demonstrated that these medications provide appropriate analgesia when compared to placebo, evidence is not convincing they outperform non-opioid analgesics, and safety concerns exist. In 2017, the FDA issued a warning specifically for codeine and tramadol, stating they are no longer considered safe to use in all patients less than 12 years of age. Deaths have occurred in children using these medicines for post tonsillectomy and/or adenoidectomy pain management, general pain, sore or strep throat pain, and cold and cough. The FDA warns that in the 12-17-year age group, these medications should not be used in high-risk patients (e.g., those with obesity, obstructive sleep apnea, lung tissue disease). Furthermore, tramadol and codeine should not be used if breastfeeding since active metabolites are present in breastmilk.

Although morphine causes respiratory depression and histamine release, it consistently provides rapid relief of severe pain for 2-3 hours. To that point, the potency of all opioids is compared to morphine using a morphine milligram equivalent dose. Considering the variability of drug metabolism, safety concerns, and the experience of pain, the “right dose” for everyone does not exist. For example, fentanyl is 100 times more potent than morphine, ultra-short acting, and used for invasive procedures and sedations. Chest wall rigidity is a well-known adverse reaction to fentanyl. Rapidly-acting oxycodone has a longer half-life than morphine and is more potent. Oxycodone is available as a single agent or is combined with aspirin, ibuprofen, or acetaminophen. It comes in tablets, capsules, oral solution, and oral concentrate, and use is considered off label in children.
Opioid concerns and Centers for Disease Control and Prevention (CDC) and World Health Organization (WHO) recommendations. Trends in opioid overdose, opioid misuse, and concerns for opioid addiction prompted the CDC and the WHO to issue guidelines for prescribing opioids for chronic pain. The CDC guideline focuses on adults while the WHO guideline relates specifically to children. Although chronic pain is the focus of the guidelines, both aims to improve prescribing practices and to ultimately benefit patient safety, emotional well-being, and quality of life. The topics covered in the guidelines include limiting opioids for moderate to severe pain, restricting opioid prescriptions to three days, providing concurrent pharmacologic and non-pharmacologic therapy, and following accepted protocols for procurement, storage, and the disposal of unused opioids. The CDC guideline also advises against overlapping benzodiazepines and opioids prescriptions because of the increased potential for respiratory depression.

Deaths due to opioid overdoses reached record highs prompting the CDC to declare an opioid epidemic in 2011. The pediatric mortality rate for opioid poisoning increased nearly threefold from 1999 to 2016, with nearly 9,000 children and adolescents in the United States dying as a result of opioids. A trend towards increased pediatric emergency department visits due to opioid ingestion and a greater than five-fold increase in overdose death rates in the 15-24-year age group also have been demonstrated. Risky use of opioids among children and adolescents is a growing trend, and the concern for opioid use disorder in adolescents is significant. Since commercial opioids often are combined with acetaminophen, the potential for hepatotoxicity is an accompanying concern. In 2016, the AAP released a policy statement that recommended timely intervention to curb opioid use disorder with the goal of eliminating long-term medical, psychiatric, and social consequences of ongoing substance abuse.

Opioid risk mitigation involves recognizing drug-seeking behavior. To address the potential risk of opioid misuse, screening patients prior to prescribing opioids has been advocated as standard practice. However, a standardized assessment for adolescents has not been identified. Therefore, at a minimum, a thorough review of medical history including analgesics used in the past is indicated before prescribing. Despite the fact that screening of parents is recommended by the AAP, this is not a common practice. Nonetheless, screening is essential for identifying
children at risk of opioid exposure in the home. Children of parents who abuse opioids are at an increased risk for neglect and often suffer from parental instability and lack of structure in the home.\textsuperscript{110}

For professionals who suspect patients have misuse issues, the FDA, National Institutes of Health, National Institute on Drug Abuse, the American Dental Association, and state prescription drug monitoring programs have resources available to review the history of prescriptions for controlled substances which may decrease their diversion.\textsuperscript{111} Transparent discussion about the potential for physical and/or psychological dependence is a critical component of safe opioid practices in the adolescent population.\textsuperscript{80,112} Furthermore, discussion regarding the proper disposal of unused controlled medications is key to reducing availability/diversion of opioids.\textsuperscript{80,112} Safeguarding of opioids stored in offices for sedation can be accomplished by following security requirements for dispensers of controlled substances.\textsuperscript{113}

**Recommendations**

Infants, children, and adolescents can and do experience pain due to dental/orofacial injury, infection, and dental procedures. Inadequate pain management may have significant physical and psychological consequences for the patient. Adherence to the following recommendations can help practitioners prevent or substantially relieve pediatric dental pain and minimize risk of associated morbidities. Practitioners should:

1. assess pain for all patients as part of the dental history.
2. avoid sensitization by using techniques to minimize stimulation and tissue damage when providing dental treatment.
3. achieve profound anesthesia prior to invasive treatment.
4. use pre-emptive analgesia when moderate to severe postoperative pain is anticipated.
5. manage odontogenic and non-odontogenic pain with combined nonpharmacologic (e.g., distraction) and pharmacologic pain management.
6. use APAP/NSAIDs as first-line pharmacologic therapy for pain management.
7. use caution and carefully assess benefits and risks of adverse events when considering prescribing opioids for pain management in children and adolescents.
8. minimize the risk of opioid misuse by screening patients and parents regarding previous/current opioid use before prescribing opioid analgesics.

9. utilize prescription monitoring databases and inform parents to properly discard unused medications to avoid diversion of controlled substances.

10. inform parents of risks associated with prescribed and over-the-counter analgesic medications and anticipate and manage adverse effects (e.g., asthma and NSAIDs, sedation and opioids.)

11. seek expert consultation for patients with chronic pain or other complicated pain condition.

12. be familiar with analgesic properties of agents when used in conjunction with sedation or general anesthesia.

13. strongly advise against opioids in high-risk patients (e.g., obesity, obstructive sleep apnea, lung tissue disease, benzodiazepines use).

14. use an alternating schedule of APAP and NSAIDs for multi-modal pain management if single-agent therapy is ineffective.

References


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