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Analgesics and Pain Management Following Root Canal Therapy

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Abstract

Postoperative pain (POP) is a common outcome following root canal treatment (RCT). An accurate understanding of POP after RCT allows clinicians to predict and effectively manage POP through the prescription of analgesics. In this article, we review the common causes of POP and discuss the various available pharmacologic agents commonly prescribed to effectively manage it. We discuss nonsteroidal anti-inflammatory drugs, acetaminophen, opioids, and combination therapies with a specific emphasis on the pharmacology, indications, adverse drug reactions, and proper dosing of each agent. In addition, we look at geriatric and pregnant patients and discuss the unique physiology and associated changes in both pharmacokinetics and pharmacodynamics so as to properly and safely manage POP in these special populations.

Keywords: Analgesics, endodontics, pharmacology, postoperative pain

Introduction

Postoperative Pain

Postoperative pain (POP) is a normal and expected outcome following certain dental procedures. The fear of POP prevents many patients from getting the treatment they need. Management of POP is the cornerstone in all aspects of dentistry and is an important service that we, as clinicians, provide to our patients. One procedure associated with a high level of patient fear and anxiety is root canal treatment (RCT). An accurate understanding of pain following RCT will allow clinicians to predict and effectively manage POP. In this article, we review the common causes of POP and discuss the various available pharmacologic agents commonly prescribed to effectively manage it.

The principal method of dealing with pain of endodontic origin is through removal of the offending source, generally a bacterial infection causing inflammation in the affected roots. RCT involves the removal of the affected pulpal tissue, disinfection of the canals, cleaning and shaping of the canals, and ultimately sealing with gutta-percha. Despite constant advancements in the field of endodontics, POP is commonly reported in up to 40% of patients following RCT.[1] Fortunately, most patients only experience a mild discomfort that minimally affects their daily routine. However, following RCT, up to 6% of patients experience more severe pain that is consistent with a postoperative flare-up.[2] POP is most intense in the first 48 h following RCT and progressively decreases over the next few days. Studies have demonstrated that in more than 90% of patients who undergo RCT, their POP was fully or partially relieved after one week.[3,4] There are several notable predictive and causative factors related to POP following RCT as described in Table 1.

POP following RCT is generally transient and mild and is most often effectively managed with over-the-counter (OTC) drugs. However, in cases of a postoperative flare-up, surgical endodontics, or complications during treatment, more potent analgesics may be required. Here, we discuss three categories of analgesics that are commonly prescribed for the management of POP following RCT.

Nonsteroidal Anti-inflammatory Drugs

Nonsteroidal anti-inflammatory drugs (NSAIDs) are a category of analgesics that are widely used for dental pain because of their pronounced anti-inflammatory action that directly combat the main cause of POP - acute inflammation of the periradicular tissues.[5] They are a highly effective class of analgesics and are the drugs of choice for patients experiencing POP if there are

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Table 1.
Predictive and Causative Factors of POP64,65,74–76,66–73

Predictive factors	Causative factors
1. Older age	1. Acute inflammation of periradicular tissues caused by microorganisms
2. Female sex	2. Presence of periapical pathology
3. Molars, particularly mandibular molars	3. Inadequate cleaning and shaping
4. Presence of preoperative pain	4. Over-instrumentation of canals
5. Absence of a periapical radiolucency	5. Apical extrusion of debris
6. Lack of intracanal medication application	6. Missed canals
7. Single versus multiple visit treatments	7. Apical extrusion of irrigants and intracanal medication
8. Pulpal status*	8. Mechanical or chemical damage to periradicular tissues

*There are inconsistent findings about the relationship between POP and pulpal status
Abbreviations: POP, postoperative pain

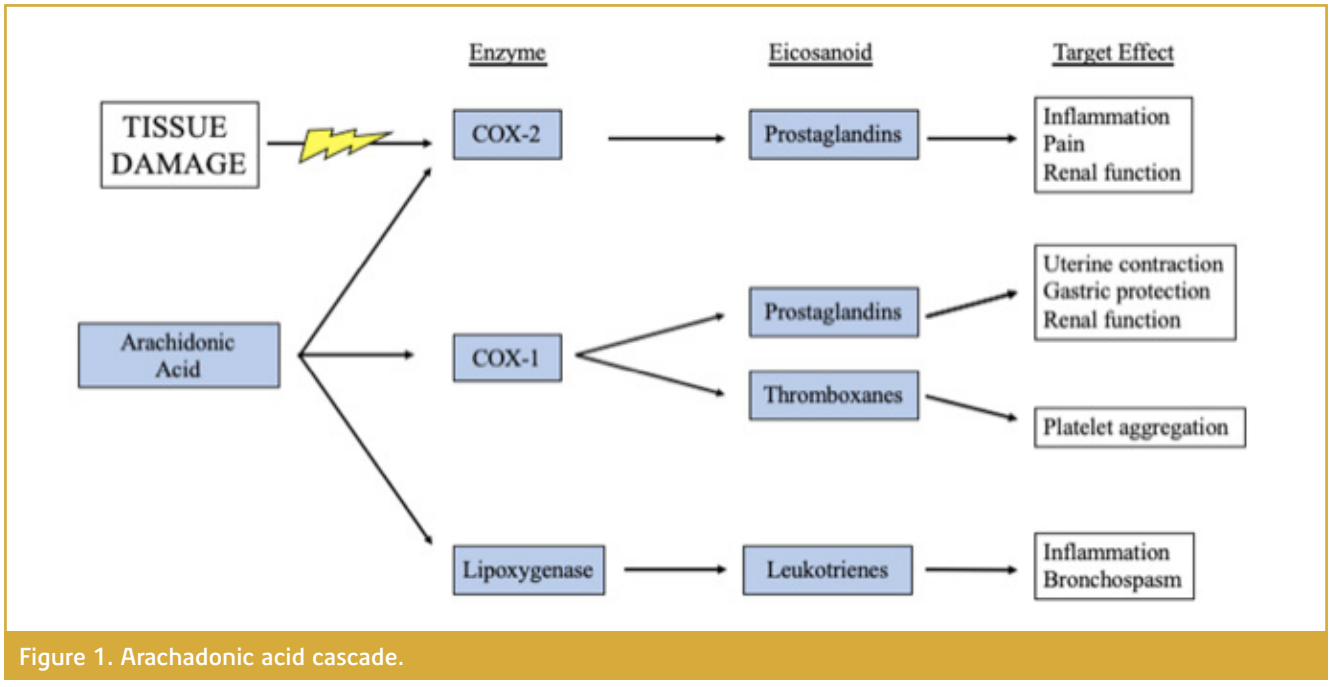

Figure 1. Arachadonic acid cascade.

no contraindications to their administration.[5,6] NSAIDs have various additional pharmacologic abilities including analgesic, antipyretic, anti-dysmenorrheal, and antiplatelet action.[7]

Main Points

- Postoperative pain (POP) is a common and expected outcome following root canal treatment.
- POP has several known predictive and causative factors, allowing clinicians to know when to expect and how to properly inform patients.
- Nonsteroidal anti-inflammatory drugs (NSAIDs) are the drugs of choice for patients experiencing POP if there are no contraindications to their administration.
- Acetaminophen is indicated for the management of mild to moderate pain and is the drug of choice in patients who cannot be prescribed NSAIDs, including children, elderly, and pregnant patients.
- In cases of expected severe POP, the addition of an opioid analgesic may be indicated and is generally prescribed in combination with a non-opioid analgesic.

The pharmacologic effects of NSAIDs are directly related to their mechanism of action. NSAIDs act on the arachidonic acid cascade (Figure 1) as they block the action of key enzymes within the cascade, the cyclooxygenase (COX) enzymes which exist in two isoforms, COX-1 and COX-2.[6] COX-1 is a constitutive enzyme that is always present without external stimuli, whereas COX-2 is an inducible enzyme that is only activated upon tissue damage and increases in case of inflammation.[7] COX-1 is considered "the good COX" as it results in the production of prostaglandins and thromboxanes, which have beneficial physiologic effects such as gastric protection, renal function, and platelet aggregation. Alternatively, COX-2 is considered "the bad COX" as it produces prostaglandins that result in pain and inflammation.[6]

Most NSAIDs reversibly bind with the COX enzymes, and their effects are only present for up to 24 h.[6] Acetylsalicylic acid (ASA) is a common NSAID used in geriatric patients and, among other indications, is taken as a primary or secondary prophylaxis against coronary artery disease through its

antiplatelet action. ASA differs from other NSAIDs as it irreversibly inhibits COX-1 and COX-2.[8] Generally, the blood-thinning properties of ASA are of no concern; however, a clinician may request the discontinuation of ASA for one week prior to surgery.[6]

NSAIDs block both COX-1 and COX-2 to varying degrees, with each target having different physiologic and pathophysiologic effects. The inhibition of COX-1 is associated with gastropathy, nephropathy, and prolonged bleeding time through its negative influence on the synthesis of beneficial prostaglandins and thromboxanes.[9] The inhibition of COX-2 is the objective as it will allow for the management of POP and the associated inflammation. Selective COX-2 inhibitors were developed in an attempt to avoid the undesired gastric, renal, and bleeding-associated side-effects of COX-1 inhibition while only disrupting the pain and inflammatory pathways.[10] These selective COX-2 inhibitors were prescribed regularly; however, its usage came under scrutiny when the inhibitors were shown to have a cardiovascular risk and increase the risk of thrombosis as well as various other cardiac conditions.[11] This led to most COX-2 inhibitors being taken off the market. Currently, the only selective COX-2 inhibitor available in Canada is celecoxib (Celebrex), a drug that also carries a potential risk of cardiotoxicity.[12]

NSAIDs have a vast array of both drug interactions (DIs) and adverse drug reactions (ADRs). The ADRs of NSAIDs are derived mainly from their action on the arachidonic acid cascade. The most common ADR reported is gastrointestinal (GI) bleeding and toxicity, which arises as a result of prostaglandin inhibition, decreasing their protective effect on the gastric mucosa. NSAIDs are, therefore, contraindicated in patients with a history of gastric ulcerations, and an alternative analgesic should instead be prescribed.[13] Another ADR, albeit rare, is an anaphylactoid reaction to NSAIDs. This anaphylactoid reaction is truly "allergy-like," sharing many symptoms of real allergies including, most severely, bronchospasm. These reactions occur as NSAIDs block the COX-1 and COX-2 lanes of the arachidonic acid cascade, resulting in the redirection of the cascade to produce harmful leukotrienes.[6,13] Therefore, NSAIDs are relatively contraindicated in patients with asthma as this redirection can initiate an asthma attack in susceptible individuals.

In addition to ADRs, NSAIDs have a plethora of DIs. A commonly discussed interaction is one that occurs between NSAIDs and antihypertensives, namely angiotensin-converting enzyme (ACE) inhibitors, beta-blockers, and diuretics. When taken together with antihypertensives, NSAIDs can reduce their effectiveness and may result in renal damage.[14] It has been suggested that an acute NSAID prescription may be acceptable in addition to these medications only if the NSAIDs are limited to a short course (i.e., four days or less).[15] Another common drug interaction occurs in diabetic patients with the concomitant use of NSAIDs and oral hypoglycemics as NSAIDs may induce hypoglycemia.[16] Finally, NSAID use in combination with several drugs has been linked to drug toxicity as NSAIDs can lead to elevated serum levels of certain drugs, including methotrexate, lithium, phenytoin, and calcium-channel blockers.[9] Additional contraindications and DIs can be found in Table 2.

Acetaminophen

Acetaminophen, also known as paracetamol or APAP, is another pharmacologic agent that is commonly used for POP. It has similar pharmacologic actions to NSAIDs (namely, analgesia and antipyresis) with a major key difference; acetaminophen has no peripheral anti-inflammatory action and is, therefore, not considered an NSAID. Acetaminophen is indicated for the management of mild to moderate pain and is the drug of choice in patients who cannot be prescribed NSAIDs, including children, elderly, and pregnant patients.[7,17,18] Although it is a highly safe drug, acetaminophen overdose has been indicated as the leading cause of acute liver failure within the northern hemisphere.[19]

Table 2.
***ADRs, Contraindications, and DIs with NSAIDs*[6,9,77]**

ADRs	**Dyspepsia**
	Gastric mucosal damage†
	Increased bleeding
	Possible nephrotoxicity
	Anaphylactoid reaction
Contraindications	Presence of gastric ulcers or gastrointestinal inflammatory disease$^{\Delta}$
	History of ASA-induced hypersensitivity
	Combination of ASA-induced asthma, nasal polyps, and allergic rhinitis
	Bleeding concerns
	Third trimester pregnancy
	Significant renal disease
	Children (for ASA only)
DIs	Oral hypoglycemics
	Low-dose ASA
	Antihypertensives*
	Antiplatelets or anticoagulants
	Alcohol
	Other NSAIDs
	Corticosteroids
	Methotrexateø
	Lithium
	Phenytoin
	Calcium-channel blockers
	Digitalis
	SSRIs
	Nephrotoxic agents•

† including ulceration and perforation
$^{\Delta}$ e.g., Crohn's disease, ulcerative colitis
* Including ACE-inhibitors, beta-blockers, and diuretics (may be co-administered if the NSAID prescription is limited to 4 days or less)
ø only a high dose is contraindicated, as in cancer therapy
• adefovir, aminoglycosides, cisplatin, foscarnet
Abbreviations: ADRs, adverse drug reactions; Dis, drug interactions; ASA, acetylsalicylic acid; NSAIDs, nonsteroidal anti-inflammatory drugs; SSRIs, selective serotonin reuptake inhibitors; ACE, angiotensin-converting enzyme

The mechanism of action of acetaminophen is not entirely understood; however, several hypotheses have been proposed. The current understanding pertaining to the antipyretic and analgesic actions of acetaminophen has to do with its selective action within the central nervous system (CNS). Contrary to the mechanism of NSAIDs, acetaminophen selectively inhibits the COX pathway within the brain, blocking central prostaglandin synthesis with none of the peripheral side effects of NSAID use, such as gastric ulceration or hemostatic imbalance.[20] It should be noted that the inhibition of the COX pathway occurs centrally not via the direct binding of the drug to the active site, but by reducing the active form of the COX enzyme, preventing it from functioning properly.[19] Furthermore, it has been shown that acetaminophen displays a peroxide-mediated COX inhibition as the inhibition of COX only occurs in areas of low peroxide concentration, such as the brain. This hypothesis supports the central action of acetaminophen as it demonstrates why the drug does not inhibit COX in areas with a higher peroxide concentration (i.e., peripherally).[21] Furthermore, a recently proposed mechanism for analgesia in acetaminophen involves its modulation of the endogenous cannabinoid system.[19]

The major risk associated with acetaminophen is liver toxicity, which is important in patients with liver cirrhosis and in those with a history of alcohol abuse. This risk involves how acetaminophen is metabolized in the liver. Acetaminophen is mostly (95%) metabolized in the liver through a process called glucuronidation or sulfation and produces non-toxic metabolites. The remaining amount of acetaminophen (5%) is metabolized by an enzyme of the cytochrome P450 (CYP450) class of enzymes and forms the toxic metabolite N-acetyl-p-benzoquinone imine (NAPQI).[22] Under normal physiologic doses, this toxic metabolite is quickly conjugated with glutathione via its sulfhydryl groups and safely gets excreted by the kidneys[7]. In cases of liver failure or alcohol abuse, glutathione stores are depleted, thereby allowing large amounts of NAPQI to build up which can lead to irreversible liver damage, including liver necrosis and apoptosis. Hence, patients exhibiting signs of liver impairment or a history of alcohol abuse must have their liver function assessed before being able to be prescribed acetaminophen.[7,22]

Opioids

Opioid analgesics are a class of centrally acting agents that are effective at managing moderate to severe POP and other types of pain.[6] Although a very powerful and useful tool in treating pain, opioids should only be prescribed as a last resort when dealing with POP. It is important to note that moderate to severe POP following RCT is rare, and an opioid prescription is unlikely to be indicated. Restricting opioids as a last-line measure arose because of the overwhelming evidence that prescribing them for acute dental pain may significantly contribute to the opioid epidemic.[5] In individuals who have a susceptibility to substance misuse, a single prescription can potentially lead to a lifetime of addiction.[23] Additionally, medications that include an opioid agent are among the drugs that produce the most frequent acute adverse events seen in both pediatric and middle-aged populations.[24] It is our duty as responsible clinicians to slow the progression of the opioid crisis by limiting our prescribing of opioids to the few, rare instances where they are truly indicated.

Opioids act on the CNS via various opiate cell receptors found in the neuronal cells, including mu (μ), delta (δ), and kappa (k) receptors. Within the CNS, they act by inhibiting the release of neurotransmitters, thereby centrally modulating the pain response.[25] It should be noted that opioid analgesics have actions on both pre and postsynaptic targets and are therefore able to effectively modulate pain at multiple levels.[26] However, pain symptoms are only managed through the central modulation of pain perception, and there is no direct targeting of the actual cause of POP (i.e., the local inflammatory response).[27]

Opioids have many pharmacologic effects; however, their main effect is analgesia by modulating both the pain threshold and pain reaction as previously described. The majority of opioid effects are dose dependent and are summarized in Table 3. These dose-dependent effects produce several contraindications caused by the exacerbation of a depressed physiologic state. Historically, opioids have been contraindicated in patients with chronic respiratory conditions because of the exacerbation of respiratory depression; however, recent evidence opposes this by suggesting that their use in these patients is beneficial.[28]

Table 3.
***ADRs and Contraindications of Opioids*[6,78,79]**

ADRs	CNS depression including sedation and decreased cognition
	Nausea
	Vomiting
	Constipation
	Respiratory depression
	Mood alteration including euphoria and/or dysphoria
	Pruritus
	Meiosis
	Convulsions
	Potential for tolerance, physical dependence, and addiction
	Potential to cause serotonin syndrome when combined
Contraindications	Severe chronic respiratory disease (e.g., COPD, emphysema)
	Severe inflammatory bowel disease (e.g., Crohn's disease, ulcerative colitis)
	Allergy to opioid agents
	Co-administration with other serotonergic agents
	Family or personal history of substance abuse (discuss with physician)
	Concurrent use of CNS depressants (e.g., alcohol)

Abbreviations: ADRs, adverse drug reactions; Dis, drug interactions; CNS, central nervous system; COPD, chronic obstructive pulmonary disease

Although much debate exists on this subject, most of the related studies involve patients requiring pain control in palliative care; and, as such, it is highly recommended to avoid prescribing opioids to patients with chronic respiratory conditions such as asthma and chronic obstructive pulmonary disease (COPD) experiencing POP. Another contraindication involves opioid-induced constipation, a highly common ADR that arises from opioids inhibiting gastric emptying and peristaltic action in the GI tract.[29] Therefore, opioids are contraindicated in patients with inflammatory bowel disease as their use may lead to the development of dangerous conditions, such as toxic megacolon and narcotic bowel syndrome because of the constipation it causes.[30] Concurrent alcohol use is another contraindication as alcohol has been implicated as a contributing factor in many opioid overdose deaths.[31] This interaction is caused by both alcohol and exogenous opioids depressing the CNS, which has the potential to produce significant respiratory depression.[32] If a patient has an allergic reaction to morphine, codeine, oxycodone, or hydromorphone; any other opioid within this class is relatively contraindicated depending on the severity of the allergy; however, an opioid of another class may be prescribed.[6,33]

Although these are powerful analgesics, the major concern surrounding opioid use and the opioid crisis is the danger of repeated administration, which causes cellular alterations, including both pharmacodynamic and pharmacokinetic changes. These changes can lead to tolerance, thereby requiring increasing doses to be administered to produce the same effect. With continued administration, a physical dependence can occur wherein continuous opioid receptor occupancy is required to avoid the negative withdrawal symptoms.[34] The other additional issues that may arise with opioid administration are the possibility of misuse, abuse, and diversion which all greatly influence the opioid crisis.[5] The guidelines released by the Royal College of Dental Surgeons of Ontario (RCDSO) in 2015 support the use of non-opioid analgesics for the management of dental pain and provide a list of questions to be answered to determine if an opioid prescription is appropriate. These questions include, "Is the patient's pain well-documented?", "Is the patient currently taking an opioid?", "Does the patient's medical and social histories suggest signs of substance misuse, abuse, and/or diversion?", and "Does the benefits of prescribing an opioid outweigh the risks?"[35] These guidelines enforce the need to limit opioid prescriptions and to properly screen patients to have an adequate knowledge of their health and psychological status before prescribing opioids.

Combination of NSAIDs and Acetaminophen

The majority of recent research on analgesia for POP and dental pain in general has focused on the combination of NSAIDs and acetaminophen. Multiple studies support the idea that a combination of NSAIDs and acetaminophen is more effective than the administration of either agent on its own.[24,36,37] In addition, it has been demonstrated that the analgesia associated with the use of NSAIDs in combination with acetaminophen is equal or superior to that of opioid-containing medications.[24] The emergence of the efficacy of this combination has provided an invaluable tool to all clinicians as there is now a level of pain-relieving analgesics between first-line analgesics and opioid-containing combinations.

When the administration of these drugs is combined, they act synergistically as opposed to merely having an additive effect.[38] Furthermore, the combination of acetaminophen and an NSAID provides the most favorable risk-benefit balance as it maximizes analgesic efficacy and minimizes any adverse effects that are associated with stronger analgesics (namely, opioids).[24,36] Adverse effects are still possible with this combination; however, the risk of experiencing them is minimized as long as the maximum daily dose of either agent is not exceeded.[36]

One caveat regarding the combination of NSAIDs and acetaminophen is analgesic nephropathy or kidney injury caused by analgesic medications. Analgesic nephropathy has been shown to be associated with a combination of OTC analgesics, including NSAIDs and acetaminophen.[39–41] However, further research is required to determine its true effect on renal function.

Prescribing for POP

The prescription of analgesics for POP following RCT is not black or white. It is not acceptable for clinicians to prescribe the same postoperative pain management plan for every patient. Analgesia recommendation and prescription should vary depending on the expected pain severity on the basis of the procedure performed. Patient factors such as the presence of any medication contraindications, age, pregnancy, and a history of substance abuse should be considered. All clinicians should adopt a patient-centered approach when dealing with POP as all the patients deserve effective and timely pain relief.

The POP expected following RCT is generally mild to moderate and can usually be managed with OTC medications such as NSAIDs, acetaminophen, or a combination of the two. If a greater severity of pain is expected based on specific procedural factors, a stronger, more effective analgesic such as an opioid may be indicated. In addition to altering the analgesic agent, factors such as the timing and scheduling of dosing can be modified. The potential use of a long-acting local anesthetic (LA), such as bupivacaine, can also be considered.

Mild POP Expected

Mild POP is to be expected following most invasive dental procedures, including RCT. As such, patients should be instructed to anticipate the pain, and OTC analgesics should be recommended. The most commonly prescribed analgesics are ibuprofen and acetaminophen. If ibuprofen is not contraindicated, it should be prescribed at a dose of 200–400 mg every 4–6 h, to a daily maximum of 2.4 g.[23] If ibuprofen is contraindicated for any reason, acetaminophen is indicated and should be prescribed at a dose of 500–1000 mg every 4–6 h, up to a daily maximum of 4 g.[42] In the majority of patients with mild POP, this regimen should be sufficient.

Moderate POP Expected

Moderate POP can occasionally be expected, such as in the case of surgical endodontics, but it also acts as a "next step" analgesic regimen for when the mild POP regimen is insufficient. If NSAIDs are not contraindicated, 400–600 mg of ibuprofen every 6 h for the initial 24 h, followed by 400 mg every 4–6 h thereafter should be prescribed.[23] If NSAIDs are contraindicated, the clinician may consider adding an opioid to acetaminophen. In this case, an opioid (oxycodone or codeine, discussed below) may be added to 650 mg of acetaminophen and taken every 6 h for the initial 24 h, followed by 500–1000 mg of acetaminophen every 6 h.[42]

It is possible that the moderate POP regimen may be inadequate, especially in patients experiencing a moderate to severe level of POP. In these patients (when NSAIDs are not contraindicated), the combination of ibuprofen and acetaminophen plays an important role as these drugs are an intermediate step between a single OTC analgesic and the addition of an opioid. A combination of 400–600 mg of ibuprofen and 500–1000 mg of acetaminophen every 6 h for the initial 24 h, followed by 400 mg of ibuprofen and 500 mg of acetaminophen every 6 h, as needed for pain should be prescribed.[36] In patients experiencing moderate to severe POP and for those in whom the use of NSAIDs is contraindicated, the clinician should treat the situation as severe POP, and a longer course of an opioid combination may be indicated.

Severe POP Expected

As previously discussed, severe POP is rarely expected following routine RCT, and this condition would most likely occur in the case of complicated surgical endodontics. In the case of severe POP, the addition of an opioid analgesic may be indicated and is generally prescribed in combination with a non-opioid analgesic. Two of the most commonly prescribed opioids are codeine and oxycodone, and these are combined with acetaminophen or ibuprofen. If the addition of an opioid is indicated for POP, the combination opioid analgesic should only be prescribed for a maximum of 48 h, and the continuation of a non-opioid analgesic course should be continued thereafter. Furthermore, the opioid should be added to the existing analgesic regimen, either the combination of ibuprofen and acetaminophen or only acetaminophen if NSAIDs are contraindicated.

Codeine is a very common opioid used in dentistry because of its ease of administration and combination with a non-opioid. It is commonly combined with 300 mg of acetaminophen and 15 mg of caffeine and is available as codeine phosphate in doses of 8 mg, 15 mg, 30 mg, or 60 mg. These combinations are marketed and prescribed in North America as Tylenol® #1 to #4 respectively, based on the codeine dosage. The effective oral-dose range of codeine that provides analgesia is 30–90 mg; however, increasing the dose beyond 60 mg produces intolerable side-effects such as nausea and vomiting.[43] Therefore, for most patients, a combination of 600 or 650 mg of either a non-opioid in combination with 30/60 mg of codeine is sufficient to provide some additive analgesia.[5] It is also worth noting that there are genetic polymorphisms of the enzyme that metabolizes codeine into its functional form, morphine, the enzyme cytochrome P450 2D6 (CYP2D6). Up to 10% of the population are considered "poor metabolizers" because the low levels of CYP2D6 and the administration of codeine will lead to insufficient analgesia.[44] In contrast, 1%–2% of the population are "ultra-rapid metabolizers" and are at a high risk of morphine toxicity and overdose because of the extremely rapid conversion of codeine into morphine because of the presence of excessive CYP2D6.[45]

Oxycodone is another frequently prescribed opioid and is combined with acetaminophen or aspirin. Oxycodone is more effective than codeine as it has a higher morphine equivalent than codeine (1.5–2 versus 0.15), making it an upwards of 10 times more potent.[46] When combined with acetaminophen, the oxycodone combination is marketed and prescribed as Percocet®; and when combined with aspirin, it is called Percodan®. Percocet® contains 325 mg of acetaminophen and comes in various strengths based on the amount of oxycodone present; 2.5 mg, 5 mg, 7.5 mg, and 10 mg. The recommended dosing is 5 mg of oxycodone in combination with 325 mg of acetaminophen every 6 h for the first 24–48 h postoperatively.[5] Following this period, the patient should be instructed to continue with an appropriate non-opioid analgesic regimen. The recommended analgesic prescriptions for the varying levels of anticipated acute postoperative pain are described in Table 4.

Additional Considerations for Postoperative Analgesia

1. Administer an initial loading dose immediately (e.g., double the maintenance dose) to reach therapeutic serum levels more quickly.[6]
2. Consider preoperative, perioperative, or immediate postoperative dosing of analgesics.[6]
3. Prescribe an analgesic agent on a regular basis for the first one to two days (e.g., every 4 h) and then switch to an "as required" basis (prn).[6,20]
4. Administer a long-acting LA (e.g., bupivacaine) right before the completion of the procedure.[47]

Special Populations

Geriatric Patients

Geriatric patients have been shown to comprise a large proportion of those undergoing RCT, with up to 26% of all endodontically treated patients in the US being 65 years or older.[48] This figure is largely because of the increased life expectancy as a result of advances in medicine, as well as the fact that geriatric individuals tend to exhibit more untreated periapical diseases.[49,50] Maintaining a healthy dentition is critical in ensuring the overall health of these individuals, and there is an increasing desire from this population to preserve their teeth through endodontic treatments.[51,52]

The geriatric population provides a challenge with regard to relieving POP because of the many physiologic changes that accompany aging as well as the widespread incidence

Table 4.
Recommended Prescriptions of Analgesics for Anticipated Acute Postoperative Pain[5,23,36,42,80,81]

Anticipated severity	If NSAIDs are tolerated	If NSAIDs are contraindicated
Mild (routine endodontics)	Ibuprofen 200–400 mg q.4–6 h	APAP 500*–1000 mg q.4–6 h
Moderate (surgical endodontics) or Inadequate pain relief	Ibuprofen 400–600 mg q.6 h for the initial 24 h Followed by Ibuprofen 400 mg q.4–6 h prn pain	APAP 650 mg with an opioid Oxycodone 2.5 mg or codeine 30 mg q.6 h for initial 24 h Followed by APAP 500–1000 mg q.6 h prn pain
	If inadequate Ibuprofen 400–600 mg + APAP 500/650 mg q.6 h for the initial 24 h Followed by Ibuprofen 400 + APAP 500 mg q.6 h prn pain	
Severe (complex surgical endodontics) or Inadequate pain relief	Ibuprofen 400–600 mg + APAP 650 mg with an opioid Oxycodone 5 mg or codeine 30/60 mg q.6 h for initial 24–48 h Followed by Ibuprofen 400 + APAP 500 mg q.6 h	APAP 650 mg with an opioid Oxycodone 5 mg or codeine 30/60 mg q.6 h for initial 24–48 h Followed by APAP 500–1000 mg q.6 h prn pain

* Dosing depends on APAP preparation: APAP is available as 325 mg (regular strength) or 500 mg (extra strength) formulations with minimum dosing ranging from 325–500 mg depending on the formulation
Ibuprofen daily maximum is 2400 mg
APAP daily maximum is 4000 mg for healthy adults; limit should be reduced for those with impaired liver function or a history of alcoholism
Abbreviations: APAP, acetaminophen (i.e., Tylenol, paracetamol); prn, as required; q, every

Table 5.
Recommendations for the Use of Analgesics in Geriatric Patients[17]

General	Eliminate the source of pain The analgesic prescription is based on the patient's pain severity and medical history
Acetaminophen	Analgesic of choice in otherwise healthy geriatric patients Dosing of 500–1000 mg q.4–6h to a daily maximum of 4 g/day
NSAIDs	Best avoided in geriatric patients because of the high incidence of gastrointestinal issues If required, prescribe the lowest effective dose for the shortest possible duration
Opioids	Best avoided in geriatric patients because of its association with profound ADRs and prolonged duration of action If required, reduce dosing and shortest possible duration

Abbreviations: ADRs, adverse drug reactions; NSAIDs, nonsteroidal anti-inflammatory drugs; q, every

of polypharmacy. Normal physiologic changes reported in literature include changes to the CNS, cardiovascular, gastrointestinal, respiratory, renal, and immune systems.[17,53,54] These physiologic changes are associated with an alteration of the pharmacokinetics of medications, including changes in absorption, distribution, biotransformation, and elimination of the drug.[17] The alteration of its properties require pharmacologic agents and associated dosing to be individualized according to the condition of the geriatric patients. Hence, the prescription of analgesics to manage POP needs to be modified so that it can be safely given to these patients (Table 5).

Another major obstacle present in the geriatric patient population is polypharmacy or the prescription and use of multiple drugs in the management of concomitant multiple diseases. On average, a geriatric patient will be taking four to five prescription drugs in addition to two to three OTC medications at a given time.[55] The issue with polypharmacy involves the increased rates of ADRs and DIs among this population. Clinicians should conduct regular medication and medical history reviews before initiating a pharmacologic intervention, including the prescription of analgesics for the management of POP. Close monitoring of geriatric patients with polypharmacy is required to limit and quickly resolve any ADRs or DIs that may arise.[17]

In general, the physiologic and pharmacokinetic changes discussed previously result in geriatric patients requiring a reduced dose of any analgesic agent.[17] Within this population, acetaminophen is the drug of choice for mild to moderate POP because of its superior tolerability profile and avoidance of the ADRs associated with NSAID use, namely GI bleeding. Acetaminophen can safely be prescribed at a dose of 500–1000 mg every 4 h to a maximum of 4 g/day.[17,36] It should be noted that liver function must be assessed in patients with a compromised liver to avoid potentially irreversible liver damage.[7,22] Studies have demonstrated a potential interaction between acetaminophen and the oral anticoagulant warfarin, and it is recommended to halve the acetaminophen dose in these patients.[56,57]

The use of NSAIDs is highly common in the geriatric population because of the high prevalence of chronic, painful conditions such as arthritis.[17] The main issue with NSAIDs is that they are highly lipid-soluble and protein-binding. These properties result in both the widespread systemic distribution and increased storage within the additional adipose tissue

Table 6.
Summary of Analgesic Use in Pregnant Patients[18,82,83]

Analgesic	FDA category	Safe during pregnancy	Safe during breastfeeding
Acetaminophen	B	Yes	Yes
Aspirin	C/D	Avoid in 3rd trimester	Avoid
Diflunisal	C/D	Avoid in 3rd trimester	Avoid
Ibuprofen	B/D	Avoid in 3rd trimester	Yes (unless contraindicated)
Ketorolac	B/D	Avoid in 3rd trimester	Avoid
Ketoprofen	B/D	Avoid in 3rd trimester	Avoid
Naproxen	B/D	Avoid in 3rd trimester	Avoid
Codeine	C	Use with caution (low dose)	Caution, avoid
Oxycodone	B	Yes (low dose, short duration)	Caution, avoid
Meperidine	B	Yes (low dose, short duration)	Caution, avoid

Abbreviations: FDA, Food and Drug Administration

present in this population.[5-8] This, in addition to an impaired renal function, may inadvertently lead to an excessive drug serum level and can result in possible toxicity.[17] Gastric ulceration is another concern when prescribing NSAIDs to geriatric patients. As previously discussed, GI bleeding is a common ADR of NSAIDs and should, therefore, be avoided in patients with a history of GI ulceration.[13]

Opioid use within the geriatric population is associated with an increase in both the depth and duration of its effects, including sedation, dizziness, respiratory depression, and constipation.[6,56] Opioids display a narrow therapeutic index because of hepatic and renal systems impairment, the potentiating ADRs, and the potential toxicity.[17] Therefore, opioids should be generally avoided within this population and only used when absolutely required. If its use is indicated, a general guideline is to halve the recommended adult dose.[56]

Pregnant Patients

Pregnant patients also present with an altered physiologic condition that requires modification in the prescription and dosing of analgesics. These changes occur in a variety of body systems, including the cardiovascular, respiratory, GI, renal, and hematologic systems. These changes have implications on the pharmacokinetics of various drugs as well as the potential teratogenic effects of the drugs on the developing fetus.[18,59] Although clinicians should limit prescribing analgesics to pregnant patients, this cannot be avoided altogether as inadequately managed pain in pregnant patients carries its own risks. In general, medications should be prescribed to pregnant patients when the potential benefit to the mother is maximum and the potential risk to the fetus minimum.[18] Studies indicate that all drugs have the ability to cross the placenta and, therefore, affect the developing fetus.[60] Fetal organ development occurs primarily in the first trimester (first 90 days), and it is during this phase that the fetus is at the highest risk for teratogenesis. It is best to avoid all medications during the first trimester; and as a general rule, it is recommended to prescribe the lowest possible dose for the shortest possible duration.[18]

To communicate the potential risk of drugs during pregnancy, the US Food and Drug Administration (FDA) created a graded classification of ranking for drugs based on their risk to the developing fetus, and these drugs are labeled category A, B, C, D, and X.[61] Briefly, categories A and B can be administered to pregnant mothers as no fetal harm has been found.[59,61] Category C is more of a gray area in terms of prescribing as adverse effects have been identified in animals; however, no adequate or well-controlled studies exist in humans. In this case, it is considered acceptable to prescribe a category C drug if the benefits outweigh the risks.[18] Category D and X drugs should be avoided at all costs as they are associated with clear and deleterious teratogenic effects.

Analgesics vary in terms of their FDA categories related to their safety during pregnancy and breastfeeding. A brief summary of this can be found in Table 6.[31,79, 80] The most commonly prescribed analgesic and the drug of choice for pregnant mothers is acetaminophen. Acetaminophen is an FDA category B drug and is not associated with any teratogenicity.[18] The recommended dosing for acetaminophen in an otherwise healthy pregnant mother is 500–1000 mg, 4 times a day (QID) to a maximum of 3 g per day.[60,62]

The next category of analgesics to consider is NSAIDs, including ibuprofen and naproxen which are two of the most commonly prescribed NSAIDs for POP. Both of these medications are category B during the first and second trimesters; however, these are downgraded to a category D during the third trimester. This change in classification results from the role of NSAIDs on the modulation of prostaglandin synthesis. Prostaglandins are critical in the induction of labor and by blocking their production, NSAIDs can effectively prolong labor.[59] There are also concerns regarding prostaglandin inhibitors causing premature closure of the fetal ductus arteriosus, resulting in subsequent fetal pulmonary hypertension.[59,62]

Opioid analgesics can also be prescribed to pregnant mothers; however, they should be prescribed cautiously and only when truly indicated. Within this category, oxycodone is considered the safest opioid as it has a category B ranking; and other opioids, such as codeine, should be avoided.[18] Codeine has been given a category C ranking because of its association with congenital defects, including heart defects and cleft lip or palate.[61,63] As with the other analgesics, the prescription of opioids should only be for a low dose and for the shortest duration possible and be prescribed only in patients with moderate to severe POP. Prolonged use and high-dose opioid prescriptions are associated with an increased incidence of risks when taken late in pregnancy, including fetal opioid dependence, respiratory depression, and delayed growth.[18,59]

Postoperative pain (POP) is a common outcome following root canal treatment (RCT). In this article, we review the common causes of POP and discuss the various drugs commonly given after endodontic treatment. The pharmacology of the main drug categories, namely, the nonsteroidal anti-inflammatory drugs, acetaminophen and opioids, was reviewed as well as the ADRs and Dis of these agents.

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