We are IntechOpen, the world's leading publisher of Open Access books Built by scientists, for scientists

4,500
Open access books available

118,000
International authors and editors

130M
Downloads

Our authors are among the

154
Countries delivered to

TOP 1%
most cited scientists

12.2%
Contributors from top 500 universities

WEB OF SCIENCE™

Selection of our books indexed in the Book Citation Index in Web of Science™ Core Collection (BKCI)

Interested in publishing with us?
Contact book.department@intechopen.com

Numbers displayed above are based on latest data collected.
For more information visit www.intechopen.com

Chapter 6

Analgesics Use in Dentistry

Shaip Krasniqi and Armond Daci

Additional information is available at the end of the chapter

http://dx.doi.org/10.5772/66600

Abstract

Pain is a protective warning sign activated by tissue damage during different pathological processes. The clinical manifestation of pain is individual, multifactorial and very complex and requires the implementation of sound pharmacological approaches. The treatment of odontogenic pain is focused not only in the relief of pain but also in the suppression of causes of pain, mainly the inflammation. Acting as inhibitors of pain mechanism, analgesics are used for symptomatic treatment of pain. There are several groups of analgesic drugs used in dentistry practice and most frequent are nonsteroidal anti-inflammatory drugs (NSAIDs) and aniline analgesics. The contemporary strategies for the treatment of odontogenic pain are focused in analgesic drug combinations, which are more effective and have a better safety profile. Ibuprofen and acetaminophen agents are considered gold standard of dental analgesia for mild to moderate intensity of pain, while in moderate to severe pain the use of individual opioid analgesics or combination of opioid and nonopioid analgesics is recommended. The treatment of pain in children and elderly patients is associated with some limitations accompanied with safety concerns and dose reduction. Treatment of pain in dentistry is focused in achieving the satisfactory level of analgesia at low doses possible.

Keywords: dental pain, analgesics, NSAIDs, dentistry, opioids

1. Introduction

Pain has accompanied humans since their appearance on earth. Different natural remedies with analgesic properties date back to ancient Egypt and Greeks, including Dioscorides and Hippocrates who prescribed the use of willow bark with salicylic acid as the main ingredient. In the late nineteenth century, three prototypes of today's modern nonopioid

INTECH
open science | open minds

© 2017 The Author(s). Licensee InTech. This chapter is distributed under the terms of the Creative Commons Attribution License (http://creativecommons.org/licenses/by/3.0), which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited.

antipyretic analgesics were discovered: acetaminophen and aspirin (formulated in 1895 by Frederick Bayer and Felix Hoffman) and phenazon, which still make up about 50% of the market of antipyretic analgesics worldwide [1]. Opiates such as morphine, which are derived from the opium poppy, were also used for thousands of years. Later on codeine, as a naturally methylated morphine, was isolated in France in 1830 by Jean-Pierre Robiquet. In 1937, German scientists Max Bockmuhl and Gustav Ehrhart synthesized methadone [2].

Pain is a subjective symptom signaling a requirement to act urgently and is usually associated with other subjective feelings such as anxiety, anger and discomfort. The expression of nature and intensity of pain is a subject of different patient-related characteristics. There are several patient factors having an impact in the patient's interpretation of pain, such as gender, age, physiological factors and drug abuse history, neuropathic and other disease and psychological profile of individual humans [3].

Dental pain (toothache or odontalgia) is a common subjective complaint of dental patients following the different interventional procedures and dental diseases. Dental pain presents one of the most common causes (approximately 12%) of patients seeking emergency treatment in dental healthcare in the United States [4].

Odontogenic pain is a complex cascade process initiated from dental tissue damage and accompanied with heterogeneous neuronal stimuli as a consequence of neurovascular, neuroinflammation and morphologic reactions [5].

The development of new analgesics is a very dynamic process and nowadays clinicians have a greater range of agents in order to select the most efficient and safe analgesic therapy. Taking into consideration the period 1960–2009, 59 analgesics have been introduced and their use still remains important [6].

Analgesics are considered one of the most important drugs groups in dental practice considering the prescription rate, clinical efficacy, cost-effectiveness and safety profile of this drug group. According to this level of importance in dental clinical practice, there are different approaches to develop treatment algorithm and guidelines for dental pain treatment in order to rationalize the use of analgesics. The rationalization of analgesics use is an ongoing challenge, since some analgesics are over-the-counter (OTC) drugs and can be taken without medical prescription.

The management of dental pain in clinical practice is a complex part of dental care and requires high-level knowledge of analgesic pharmacology and implementing the standards of rational use.

There is a valuable evidence for significant relationship between nonrational use of analgesics and diminution of drug therapy, increased adverse drug reactions and socioeconomic consequences [7, 8].

Nevertheless, prescription of analgesic drugs for dental indications is often accompanied with challenges, which diminish the treatment success and increase the potential risk for serious adverse effects.

There are several reasons for the decrease in clinical efficacy of analgesic therapy, including the lack of real assessment and monitoring of pain by dentistry doctor, nonadequate quantification of subjective pain experienced by patients, lack of updated pharmacological knowledge of dental pain treatments, experience scarcity in safety profile of analgesic and insufficient knowledge regarding analgesic combinations. There is evidence that prescription errors with analgesic medicaments are substantially high and are a major cause of manifestations of analgesics side effects [9]. The percentage of analgesic-related prescription errors, as reported by Smith et al., is relatively high, with 29% in adult patients and in pediatric patients it is even higher at 59%. From total prescription percentage, 14% were serious or severe analgesic prescription errors with high harmful potential for patients, mainly in pediatric patients [10].

The prescription of analgesic drugs and treatment of dental pain is more complex when it is accompanied with other health disorders and diseases. In these cases, quantification of pain and its evaluation and treatment is a convoluted clinical challenge. The main complex challenges are patients with diabetes and other chronic diseases, patients with renal and hepatic insufficiency and patients with opioid addictive disorders [11, 12].

Pain has an impact in the quality of life of patients with complaints for prolonged experience of pain, it increases healthcare costs and it is a risk for progress to chronic pain with negative reflection in health and mental status of patients [13]. The experience of prolonged pain brings healthcare workers under more complex situations and the selection of appropriate pain treatment is more difficult [14].

Rational prescription of analgesics in dentistry involves the selection of appropriate pain reliever, right clinical indication, selection of adequate dosage and route of administration and implementation of cost-effectiveness and risk-benefits standards.

Hence, information with the objective of elaborating an analgesic's utilization patterns is considered as of high relevance in order to optimize the pain treatment in dentistry.

2. Dental indications for analgesic use

Odontogenic pain due to periapical and pulpal disease is considered as the most frequent in dental health settings [15] and it is a warning sign and subjective perception of altered pulpodentinal tissue and periapical tissue. These two can be distinguished one from the other and this perception has an impact on the appropriate selection of analgesic drugs.

According to the course of clinical manifestation of the dental pain, it can be classified as acute or chronic and/or with and without malignant disease. Acute pain lasts from several hours to a number of days, while chronic pain can be present for several months and, if primary dental care is not applied, pain can last for years.

Acute pain is usually a reflection symptom of several clinical conditions such as dental trauma, inflammatory conditions of dental tissue and other related tissue structures, including the temporomandibular and masticatory muscle damages. There are several painful dental conditions indicating the analgesic use.

The characteristic of odontogenic pain is so-called referred pain, which means that the damage located in one part of dental tissue can be projected to another dental tissue. Dental referred pain is a complex clinical phenomenon, which requires a highly experienced dentist to diagnose and locate the primary source of pain [16].

The majority of clinical indications of analgesic prescriptions relate to the treatment of acute and chronic dental pain and adjunctive intraoperative and postoperative pain. Moreover, in dental practice associated procedures such as dental extractions require the use of pain reliever therapy [17].

In addition to the understanding of primary mechanism of pain, the dental clinician needs to quantify the perceived intensity of pain. These are preconditions to develop an effective strategy for the selection of efficacious and safe analgesic treatment. According to anticipated pain intensity, the dental pain can be mild, moderate and severe. This classification of dental pain intensity is crucial in the selection procedure of analgesic therapy for satisfactory relief of pain. In patients with mild dental pain, the first lines of analgesics are the nonsteroidal anti-inflammatory drugs (NSAIDs). NSAIDs can be prescribed in over-the-counter doses and in some cases in combination with other analgesics such as paracetamol [18].

The drug of choice from NSAIDs group for the treatment of mild odontogenic pain is ibuprofen 200 mg or naproxen 200–225 mg individual dose. In patients with persistent mild dental pain, the combination of ibuprofen or naproxen with paracetamol is more effective than individual NSAID agents. Where NSAIDs are contraindicated, the appropriate choice is 500–1000 mg of paracetamol.

Acetyl salicylic acid is not the drug of choice for treatment of dental pain due to its interference with platelet aggregation and patients with heart disease receiving this drug should be treated with precautions.

In patients with moderate dental pain, the analgesic of choice is a NSAID used in pharmacological full doses. NSAIDs can be individually administered or in combination with aniline derivatives, such as mefenamic acid and meclofenamic acid. In some patients where NSAIDs are not effective in combination with paracetamol, a weak opioid analgesic can be considered. The individual dose of ibuprofen is 400 mg, while that of the naproxen is 500–550 mg. In patients where pain is not controlled effectively, the addition of full dose of paracetamol is recommended. If pain is still present, the addition of weak opioid agents in full doses is advised, i.e., codeine 30 mg, hydrocodone 5 mg [19].

In patients with severe dental pain, the pharmacological treatment consists usually of combinations of strong opioid analgesics with high doses of NSAID agents, with or without aniline derivatives. In such patients, treatment of pain should be under close supervision of the dental doctor due to a higher probability of adverse drug reactions. The first choice of drug is hydrocodone 10 mg, oxycodone 5 mg, codeine 60 mg, or tramadol 50–75 mg. Due to high potential of abuse, tramadol is not the drug of choice for the treatment of severe odontogenic pain. In patients with unsatisfactory level of pain control, the combination of full dose opioid agents and NSAIDs is recommended [20].

2.1. Factors influencing the analgesic selection

There are several factors that play a crucial role in the selection of analgesic drugs in dental pain treatment including:

1. Pathophysiological pain mechanism. This is a predictive factor in analgesic choice. Mechanisms include cancer metastases, postoperative dental pain, nerve root infiltration, nerve root infiltration, neuropathic pain, etc.
2. Patient age. The selection of analgesic is also determined by patient age. The administration of analgesics in children and elderly patients differs from adults patients. The use of a number of analgesics in children is limited due to unmaturated metabolism processes. The elderly usually require a restriction of analgesic dose due to decreased potential of metabolism and/or excretion with reflection in pharmacokinetics and pharmacodynamic of drugs.
3. Route of administration. This is determined by the general health condition of the patient, patient's characteristics of disease, bioavailability and pharmaceutical formulation of the analgesic. Oral use of analgesics is recommended where it is possible. Controlled release of pharmaceutical formulations is more suitable for chronic pain than fast release forms.
4. Patients-related features. There are several conditions, which may affect the success of analgesic treatment in dental patients. The placebo effect should be considered carefully by dental doctors. Initially, the dental doctors should address the potential renal and hepatic toxic effect, including the gastrointestinal disturbances which may impact the pharmacokinetic and safety profile.

Experienced dental clinicians select a safe and effective analgesic therapy using individual drugs or different analgesic combinations to treat dental pain based on individual conditions. This selection in dental practice is not always simple due to numerous confounding factors related to the mechanism and clinical manifestation of pain [21].

3. Utilization pattern of analgesic use

Drug utilization studies are useful quantitative tools for feedback information of analgesic use and for identifying the measures for quality improvement of dental pain therapy. There is an increase in the rate of prescription of analgesics. The most popular analgesic drug group is NSAIDs, followed by acetaminophen, while opioid analgesics are reserved for high intensity dental pain. There is an increase in the prescribing of opioid analgesics or their combination with nonopioid analgesics in nontraumatic dental condition-related visits with more severe pain in the emergency departments [22, 23]. In one recent published study with a large cohort of patients, opioids such as hydrocodone (78%), followed by oxycodone (15.4%), propoxyphene (3.5%) and codeine (1.6%) were reported to be the most frequently prescribed analgesics after surgical extraction of teeth which requires dental care.

However, recently different studies reported a drop by 5.6% in the prescribing of opioids [24, 25]. Taking this into consideration, more should be done to prevent opioid abuse and dentists play an important role in this regard, helping to minimize opioid abuse by careful patient education and appropriate prescribing practice [26]. In mild to moderate acute dental pain, acetaminophen and NSAIDs are the most appropriate choices. COX-2 inhibitors may be considered for patients at risk of gastrointestinal disease or those taking blood thinners such as warfarin. Also, prescribers must be aware to decrease the use of maximum recommended doses and advocate shorter duration of treatment [27]. Ibuprofen was found to dominate over other analgesics [28–31]. This also applies to pediatric dentistry, whereby ibuprofen and paracetamol predominate in prescription rates [32].

However, there are controversial studies, which show that diclofenac or paracetamol may offer improved benefits. Moreover, in patients undergoing third molar surgery, nimesulide followed by diclofenac, ketoprofen and ibuprofen were the most prescribed NSAIDs.

In general, this difference in prescribing may be influenced by different practitioners in different countries, less reported side effects of medications and their effectiveness in different indications [33, 34].

3.1. Prescription and nonprescription analgesics in dental use

The use of analgesics in general practice is regulated by marketing authorization instructions of drug regulatory agencies of the respective states. The number of analgesics in over-the-counter (OTC) drug group is permanently increasing and the consequence of this is the loss of active monitoring from health professionals.

Pain is a common factor for seeking dental advice but may also occur after different interventions. The dentist is responsible to create strategies for the management of different types of pain from the dental, oral, facial, or postoperative procedures. Nonopioid analgesics are available as "over-the-counter" medications and in U.S.A, 16 millions of these drugs are prescribed annually. There are fewer indications for opioids compared to nonopioid analgesics due to their side effects profile; these should be used with caution only in case of severe pain [21].

There are several OTC analgesics and the most used are ibuprofen, acetylsalicylic acid (aspirin), acetaminophen, ketoprofen and, recently, naproxen sodium. The main characteristic used to classify these analgesics within the OTC group is the dosage [35]. NSAIDs, including ibuprofen and naproxen, are used as nonprescription OTC analgesics in doses of 200–400 mg (1200 mg/d) and 440 mg (660 mg/d for maximum of 10 days), respectively. Also, acetaminophen is widely used as an OTC product which is used also in combination with hydrocodone, oxycodone, codeine and propoxyphene. Maximum doses of acetaminophen should not exceed 4000 mg and particular attention is paid to alcohol users, in whom this drug can cause hepatotoxicity [36, 37]. In general, ibuprofen is normally safe and effective for patients who use OTC analgesic, but it has also been shown that in a small percentage of patients who use OTC analgesics maximum doses are exceeded. More sophisticated research analyses are needed in this area to improve our understanding of dosing patterns of nonprescription

analgesics. This requires improved patient education about nonprescription analgesic use and prevention of possible adverse events [38, 39]. In OTC NSAID analgesic users, more caution is necessary in the elderly or in patients with rheumatoid arthritis who are already taking NSAIDs, or low dose aspirin, ACEI or diuretics. The shortest duration of treatment is required and the lowest effective doses of NSAIDs are crucial in their efficacy and safety [40]. Due to this, close medical supervision is advisable.

4. Nonsteroidal anti-inflammatory drugs (NSAIDs), opioids and their mechanism of action

NSAIDs exhibit their analgesic effect due to the inhibition of prostaglandin synthesis at the peripheral nerve endings, while opioids demonstrate their effect in central nervous system through its depression [41]. NSAIDs mechanism of action is through the inhibition of prostaglandin and thromboxane (eicosanoids) biosynthesis by inhibition of cyclooxygenase activity (COX-1 discovered by John Vane or COX-2 from Daniel Simmons) in reversible or irreversible fashion and dose-dependent manner competition of arachidonic acid. In the past four decades, many new drugs such as piroxicam, flurbiprofen, diclofenac, naproxen, ibuprofen, etoricoxib and celecoxib were introduced based on their COX activity. Their mechanism of action depends on whether they inhibit COX-1, COX-2, or both, which are responsible for the synthesis of different prostaglandins found in pathological situations (COX-2 is more expressed in inflammatory conditions). However, this inhibition also results in the loss of some protective effects of prostaglandins with respect to the gastrointestinal (COX-1), cardiovascular, platelet and renal function [42]. Taking this into consideration, COX-1 inhibitors are more prone to cause gastrointestinal bleeding, which can be prevented by a switch to COX-2 inhibitors. However, short-term use of the latter is recommended based on their cardiovascular side effects which results from the imbalance of PGI_2 as antithrombic mediator and as one of the most important prostanoid in regulating homeostasis of the cardiovascular system and also TXA_2 as prothrombic mediator [43–45]. Recently, there has been an increasing interest in their effects extended beyond COX enzymes and fascinating results have been shown in different pathologies such as cancer through major cellular signaling pathways, which mediate inflammatory response [46, 47].

Opioid mechanism of action is mediated via their affinity for μ, κ, δ and opioid receptor like-1 (ORL-1) which are G-protein-coupled opioid receptors acting on GABAergic neurotransmission, in CNS and throughout the body, by acting as agonists, weak agonists and partial agonists. These responses are mainly mediated from Gi proteins by closing N-type voltage-operated calcium channels and opening calcium-dependent inwardly rectifying potassium channels, which result in hyperpolarization and reduction in neuronal excitability. Another mediated effect is the decrease of intracellular cAMP, which modulates the release of substance P, a nociceptive neurotransmitter [48].

These receptors are activated also by endogenous ligands such as endorphins. It is shown that their action is also dose mediated by showing better efficacy when the dose increased.

However, side effects should be taken into consideration. Most significant opioid effects are mediated through μ and κ receptors including for morphine and other semisynthetic and synthetic drugs such as meperidine, methadone, hydrocodone, oxycodone, fentanyl, buprenorphine, pentazocine and tramadol.

5. Principles of dental pain management

5.1. In adult patients

Pain management in dental practice is usually an unpredicted challenge and is highly related to individual patient response to pain, the expectations of the patient, pathophysiological mechanism of pain and selection of analgesic drugs. Pain relief is a very important precondition during interventional dental treatment and ensures a trustful and comfortable relationship between patients and the dental doctor [49].

Almost all dental procedures are accompanied by pain of different intensity, nature and length and treatment of pain pre- or postdental intervention is an integral part of dental treatment [27]. Efficient pain treatment during dentistry healthcare is mandatory for the achievement of desirable clinical outcome and successful dental clinical treatment. Usually in the preparation phase of patient, before the initiation of dentistry interventions, the use of local anesthesia ensures the control of patient pain [50].

The clinical evidence shows that local anesthesia results in the relief of pain during intraoperative dental period and shortly for postoperative pain and dental doctor should consider effective pain management during all stages of dental treatment. As the dental pathological process usually involves inflammation, the effect of local anesthesia is reduced due to prostaglandins interference with tetrodotoxin-resistant receptors, which diminishes the nerve responses to local anesthesia [51].

For effective dental pain management, dental doctors should address attention to disease, patient and finally to available nonpharmacological and pharmacologically effective treatment options.

The dental doctor should initially assess the pathological process of dental tissue in order to understand the mechanism of disease and to predict the health status of the patient. It is very important to define the etiology of the pathological process, especially to determine the eventual inflammatory response [52].

There is reported evidence that premedication with NSAIDs drugs such as ibuprofen or indomethacin significantly increases the level of alveolar nerve block anesthesia in dental interventions (78 and 62%) compared to placebo (32%) [53]. During the process of soft tissue trauma, a pain response occurs and this warrants the measures for pain treatment.

In dental operative procedure, preoperative administration of medication, including analgesic drugs, is recommended in order to diminish postoperative pain and to reduce the need for postoperative analgesic.

An effective strategy for dental pain treatment is based on the dynamic process of creation of a logical treatment map, which is built by the methodology of conceptualization to visualize the relationship between patient symptoms, dental interventions, therapeutic treatment and patient's needs and expectations.

Furthermore, there is available misleading information showing that naproxen sodium has a superior analgesic efficacy compared with ibuprofen at postdose interval from 1 to 12 h [28, 54, 55]. The important analgesic agents for use in dentistry are also para-aminophenol derivative such as paracetamol (acetaminophen). Administration of individual paracetamol is recommended in mild form of dental pain only when the NSAIDs are contraindicated. Otherwise, there is clinical evidence showing that ibuprofen in doses 200–512 mg versus paracetamol 600–1000 mg is superior in relief of postoperative pain. The novel strategy for pain treatment is the use of combination containing ibuprofen and paracetamol. This combination is more effective than the effect of individual analgesic when taken at 6 h after dental intervention.

The evidence shows that the most frequent doses of respective analgesics prescribed in clinical practice are 400 mg for ibuprofen and 1000 mg for paracetamol [56]. For more intensive pain when the administration of individual NSAID analgesic or combination of NSAID and paracetamol are not effective, the administration of an opioid and NSAIDs is recommended. The analgesic effect achieved by this drug combination is higher than the doubling of dose of either analgesic administered alone [57].

There are several possibilities of combinations of nonnarcotic and narcotic analgesics, which might be effective for the treatment of dental pain. The mostly used analgesic combinations in dental pain management are acetaminophen-codeine (300 mg + 30 mg), oxycodone-ibuprofen (5 mg + 400 mg), or hydrocodone-acetaminophen (5 mg + 325 mg or 7.5 mg + 500 mg) [58]. The main paradigm for treatment of dental pain is the appropriate selection of effective analgesic, at lower possible dose with the lowest probability for side effects (**Table 1**).

Type of pain in dentistry	Analgesic drug	Dosing (Adults)	Adverse effects
Acute dental pain	Ibuprofen Ketoprofen Diclofenac Flurbiprofen Naproxen Sodium Acetaminophen Celecoxib Codeine/ Acetaminophen	200–400 mg every 6–8 h 25–75 mg tbl every 6–8 h 50 mg tbl. 3 times daily 50–100 mg tab every 8 h 500 mg, followed by 250 mg every 6–8 h 500–1000 mg 3 times daily 200 mg 2 times daily 30–60/325–650 mg every 4–6 h	Gastric ulceration-bleeding, diarrhea, hepatotoxicity, allergy, skin rashes, urticaria, cardiovascular-MI, atherothrombosis, CHF, ischemic stroke; Opioid side effects-respiratory depression, dependence, etc.
Postoperative pain Periodontal surgery Orthodonic tooth movement Pain from pulpal or periapical tissues	Ibuprofen Ibuprofen/ Acetaminophen Naproxen	200–400 mg every 6–8 h (OTC) 400/1000 mg every 6–8 h 220 mg every 12 h (OTC)	NSAIDs associated side effects, however, OTC doses are better tolerated

Type of pain in dentistry	Analgesic drug	Dosing (Adults)	Adverse effects
Dental surgery—impacted third molar surgery and Dental surgery—dental root canal treatment	Diclofenac/ Paracetamol Ibuprofen/ Paracetamol	100/1000 mg single oral dose with 8 h observation 600/1000 mg 30 minutes before procedure or after surgery	Nausea, drowsiness headache
After third molar extraction Oral surgical or endodontic treatment Temporomandibular disorders Nontraumatic dental Conditions with severe pain	Hydrocodone Oxycodone Codeine Tramadol	10 mg every 4–6 h 5 mg every 6 h 60 mg every 6 h 50–75 mg 4–6 h	Nausea, sedation, dizziness, constipation, addiction, sleep disorders
Intensive dental pain	Oxycodone/ Ibuprofen Oxycodone/ Acetaminophen Hydrocodone/ Acetaminophen	5/400 mg every 6 h 5/500 mg every 6 h 5/325 mg or 7.5/500 mg every 4–6 h	Nausea, sedation, dizziness, constipation, addiction, sleep disorders

Table 1. General use of analgesic drugs in the different types of pain in dentistry.

5.2. Elderly patients

The strategy for dental pain treatment in elderly patients is generally the same as treatment of pain in general adult population with some differences due to age-related changes principally in physiology and pharmacokinetics in this group of patients. Clinical practice shows that elderly patients are more prone to feel the pain than adult patients and frequently are undertreated.

In the management of dental pain the clinician should consider several factors:

- Age-related pharmacokinetic changes with reduced capacities of absorption, distribution, metabolism and excretion of drugs in general and analgesics in particular. This is the main reason why it is recommended that in elderly patients the dose of drugs should be reduced generally at three-fourths of dose of adult patients [59].
- Decreased pharmacodynamic capacities of drugs due to age-related physiological changes expressed as alterations in receptor affinity, receptors number and postreceptor signaling pathways, which have an impact in the development of drug tolerance and dependency [60].
- Multiple comorbidities, which require a higher number of drugs (polypharmacy) for pharmacological treatment with increased risk of drug interactions and side effects.
- The frequency and intensity of pain reported by elderly patients might be reduced and not correspond with real pain assessment, especially when they suffer from dementia and other neurodegenerative diseases.
- Patient adherence to drug therapy of elderly patients is usually decreased and support from family and nursing health care personnel should be considered.

The strategy of dental pain relief in elderly patients should be based on several principles and initially we should select the available nonpharmacological measure for pain treatment. If nonpharmacological options are ineffective we need to carefully select the appropriate analgesic drug considering the risk/benefit ratio. After selection of appropriate analgesic the initiation of therapy should start with dose titration starting with lowest dose increasing slowly to effective safe dose. The analgesic therapy should be monitored closely by dental clinicians in order to achieve a successful pain relief and to prevent the possible side effects. The course of analgesic therapy should be as short as possible and also need to be stopped in case of any sign of infectivity and persistency of pain.

For pain relief in elderly patients, the recommended analgesic drug is paracetamol. In case of hepatic or renal functional disorders, dose adaptation is recommended, while in terminal hepatic insufficiency, the administration of paracetamol is contraindicated, in this case the use of NSAIDs is preferred, but these patients need close monitoring. NSAID should be given to elderly patients in the lowest effective dose and in short periods of time in order to avoid the possible side effects of these analgesic drugs. In case of severe dental pain, the use of opioid analgesic is indicated. Usually, oral opioids in the lowest possible doses, such are tramadol and some others, are used. In order to use the opioid analgesic drugs in the lowest doses, the combination of paracetamol and tramadol or codeine is recommended. In elderly patients with intensive dental pain, the strong opioid of choice is morphine [61].

5.3. Children

In clinical pediatric care, effective pain management is a standard routine approach and is mandatory in the modern concept of health care. It is accepted that the basic mechanism of pain in infants and children is substantially similar to adults with some exception in neonates related to some differences in physiological mechanism of pain, which is characterized with slower and less precise conduction of pain but without significant differences in pain perception [62].

Modern pain management for children addressing the medical conditions and surgical interventions and postoperative period has substantially advanced over the last two decades.

Advanced pain management strategy is based on two main directions, including the interventional pharmacological and nonpharmacological approach. The interventional pharmacological approach consists of the use of NSAIDs and other analgesics administered via different routes of administration (i.v. bolus administration, continuous infusion, rectal, transdermal and other routes of administration); local anesthetics, epidural anesthesia and peripheral nerve blockade. Nonpharmacological measures consist of health education of children and psychological approach to release the perception of fear and other behavioral problems in children patients, breathing techniques, hypnosis, transcutaneous electrical nerve stimulation, guided imagery, acupuncture, relaxation and other techniques to relieve the pain [63].

Pain management strategy in children consists of several principles, which reflect the differences between children and adult pain treatments. The strategy of pain relief should focus on the prevention of pain and this ensures better treatment success before painful procedures.

Usually this starts with preparing the child and the family in advance, in order to reduce fear and anxiety before intervention and applying patient-controlled analgesia (PCA). In case of major surgical interventions the treatment of predicted pain after treatment in children can continue with oral analgesics depending on patient needs.

Dental clinicians should assess the pain intensity using the appropriate children pain scale. It is recommended to use the FLACC scale for pain measurement in pediatric patients aged 1 month to 3 years, while for children above 3–7 years the Wong-Baker pain rating scale is used (**Figure 1**), which has demonstrated to be more sensitive compared to visual analogue scale. For children above 7 years, the Visual Analogue/Numerical Rating Scale is used. A universal measuring tool does not exist but according to a systematic review FACES scale demonstrated to be effective in children from 3 to 12 years in which gradient of emotions cartoons are chosen by children based on their level of pain. There is also another measurement, such as Oucher pain scale, which does not differ much from the others, but it is more specific in different racial face expressions such as Caucasian, African American, Hispanic, First Nations Boy and Girl and Asian Boy and Girl [64–69].

Figure 1. Wong-Baker faces pain rating scale explains to the person that each face is for a person who has no pain (hurt), some, or a lot of pain by asking the person to choose that best describes how much pain he has.

Multimodal and multiapproach therapy is the cornerstone of pain management in children. This technique uses different analgesia and nonpharmacological complementary approach in order to enhance the pain control and minimize drug-induced adverse effects. This method supports the use of combined nonopioid (NSAIDS, other analgesic agents, local anesthetics, alpha$_2$-adrenergic agonists, voltage-gated calcium channel alpha-$_2$ delta-proteins) and opioid analgesics and other agents in smaller doses in order to prevent the clinical manifestations of drugs side effects [70]. Dosage calculations of analgesics for children are based on mg/kg body weight administered by intravenous, oral and rectal route, while intramuscular injections should be avoided. It is recommended that severe pain is treated by infusions, PCA and other routes of continuous analgesic administration.

Pain treatment options in neonates and premature infants should avoid the use of opioid analgesics. However, in cases when there is no other option, opioid analgesics should be closely monitored in intensive care units. In this group of infants, opioids are more prone to develop dependency and depression of cardiorespiratory functions.

The mainstream in pharmacological pain treatment consists of administration of NSAIDs, paracetamol. Usually it is recommended to use paracetamol (infant dose is 10–15 mg/kg/dose every 6–8 h, pediatric oral dose 10–15 mg/kg/dose every 4 h), ibuprofen (10 mg/kg/dose every 6 h) and diclofenac (1 mg/kg/tds or 1.5 mg/kg/bd, maximum daily dose is 3 mg/kg). While naproxen (2 years or older: 5 mg/kg orally twice a day; 12 years or older: 220 mg orally every 8–12 h) is indicated more in inflammatory diseases. In modalities of analgesic therapy combinations the dosage of individual analgesics are decreased.

For more intensive pain the use of opioids is recommended. Codeine (0.5–1 mg/kg every 4–6 h) is a weak opioid analgesic and to increase the analgesic effect it is often combined with paracetamol. However, FDA alerts about odeine use in children and it should be used with careful monitoring only in patients from which benefits outweigh the risks [71]. Another opioid analgesic for treatment of mild to severe dental pain in children is tramadol (1–1.5 mg/kg). For severe dental pain, the use of morphine (0.2–0.5 mg/kg q4–6 h) is recommended. Other alternatives to morphine are also considered, including fentanyl, hydromorphone, methadone and other opioid agents.

Other approaches to pain treatment of dental pain in children include the use of regional analgesia such as local anesthetic instillation, wound anesthetic infiltration, topical regional analgesia (lignocaine gel), peripheral nerve block and other methods. Dental pain management in children is complex and further improvements are needed to improve the efficacy and safety of pain treatment [72].

5.4. Analgesic use in renal and hepatic insufficiency

There is an increased risk for renal dysfunction in patients undergoing analgesic treatment, although moderate use is not associated with increased risk of renal disease or dysfunction [73]. Patients with renal failure should be carefully considered due to the increased risk of side effects in dental treatment and also when analgesic therapy is indicated. This requires consultation with the nephrologists or hepatologists for the grade of the disease and an important monitoring for clinical parameters which need to be observed. Regarding medication, dose adjustments need to be considered as an important step to reduce side effects or toxicity. For NSAIDs dose reduction or avoidance is also indicated in more advanced stages of renal failure. In aspirin, acetaminophen and ibuprofen treatment indications prolongation of dosing interval is recommended; however, dose reduction is recommended for diclofenac and naproxen. When the GFR is <10 mL/min avoidance need to be considered, excluding acetaminophen in intervals of 8–12 h. On the other side narcotic analgesics (morphine, fentanyl, codeine) are metabolized by the liver and usually do not require dose adjustment [74, 75]. But special caution should also be exercised in patients with end-stage renal disease without dialysis whereby the use of opioids such as codeine, dihydrocodeine, dextropropocyphene and hydrocodone is not recommended (tramadol may be used with caution). Also, only short-term treatment must be prescribed for morphine, diamorphine, or dose reduction in fentanyl by 25–50% or methadone 50–70% with specialist advice on prescribing and special care in the elderly due to highly variable pharmacokinetics [76, 77].

Due to pharmacokinetic changes in the elderly and reduced renal and metabolism capacity, acetaminophen is the drug of choice for the control of mild to moderate pain in doses of 500–1000 mg every 4 h. Moreover the overuse of this drug is related with side effects including acute liver failure, hepatotoxicity and in rare cases nephrotoxicity. Taking this into consideration, chronic dosing needs to be avoided in patients with decreased liver function or cirrhosis [78, 79]. In cirrhotic patients, NSAIDs should be avoided or used with extreme caution due to increased risk of gastrointestinal bleeding and risk of hepatotoxicity or acute hepatic decompensation or risk of renal failure.

For opioids, low dose of tramadol is considered as second choice in this group of patients after acetaminophen [80].

Opioid side effects are more common in hepatic impairment due to prolongation of their effects. Conversely, fentanyl and methadone pharmacokinetic is less affected by hepatic impairment. Fentanyl is recommended more than methadone. And also hydromorphone, morphine and oxicodone are other choices that are recommended with caution [81]. Consultation with specialist and also titration should be done slowly, monitoring of drug concentrations and adverse effects are crucial steps in the use of analgesics in dental management for patients with impairment of renal or hepatic functions (**Table 2**).

Population	Analgesic drug	Dosing	Adverse effects
Elderly	Acetaminophen (First choice in mild to moderate pain)	500–1000 mg every 8 h (maximum 3 g)(reduce maximum dose 50–70% for adults with reduced hepatic function or alcohol abusers)	Gastric ulceration-bleeding; Abdominal pain; Hepatotoxicity and acute liver failure; Acute renal failure; Allergy; Skin, Rashes; Urticaria, Cardiovascular-Myrocardial infection, atherothrombosis, Chronic heart failure; Ischemic Stroke; More sensitive for opioids induced side effects. More pronounced drug interaction associated adverse effects.
	NSAIDs (Ibuprofen, Naproxen, Flurbiprofen, Ketorolac, Celecoxib)	Lowest effective dose for the shortest Possible time (It is recommended to use NSAIDss with PPIs to avoid gastrointestinal bleeding, or use celecoxib in patients with no significant risk factors for cardiovascular events)	
	Opioids (Oxycodone, Hydrocodone, Tramadol) (moderate to severe pain)	Oxycodone 2.5 mg every 6 h Hydrocodone 5 mg every 6 h Tramadol 25 mg daily with increase every 2–3 days with 25 mg up to 100 mg. (It recommended 25–50% dose reduction from recommended dosage in adults and shortest possible time)	
Children	Acetaminophen Ibuprofen (age 2–12) Naproxen (age 2–12)	10–15 mg/kg every 4–6 h 5–7 mg/kg every 8–12 h 5–10 mg/kg every 8–12 h	Acetaminophen hepatotoxicity in liver disorders Gastric irritation, ulceration, bleeding and perforation and clotting impairment from NSAIDs Codeine associated nausea, sedation, constipation, dependency.
	Codeine/Acetaminophen (3 days or less and only with careful monitoring and only in patients which benefits outweighs the risks)	0.5–1 mg/kg every 4–6 h	

Population	Analgesic drug	Dosing	Adverse effects
	Morphine (Only in severe dental pain)	0.2–0.5 mg/kg every 4–6 h	
Renal and hepatic insufficiency	Acetaminophen	500–1000 mg every 6–8 h (no need for adjustment in renal insufficiency, reduce dose up to 2 g daily n cirrhosis	Coagulopathies from liver disease; Acute renal injury; Hepatotoxicity; NSAIDs and Opioid-associated side effects.
	Ibuprofen	200–600 mg every 4–6 h (no need for adjustment in renal insufficiency, avoid or use with caution in hepatic insufficiency)	
	Dihidrocodeine	10–30 mg every 4–6 h (decrease dose 25% in renal insufficiency)	
	Fentanyl	12 mcg/h transdermal patch (only if patients have been taking other strong narcotic pain medicines for at least a week)	

Table 2. Use of analgesic drugs in dentistry in special populations.

6. Analgesic clinical efficacy and safety in dental pain management

Evidence-based medicine strongly supports the evaluation of analgesic efficacy and safety. The majority of this research uses the third-molar extraction model of acute dental pain to determine relief of pain intensity over time with different available analgesics. The clinical efficacy of dental analgesics is focused on comparison of individual analgesics and placebo and monotherapy analgesics with combined therapy.

Efficacy and safety of analgesic drugs is shown to be enhanced through the use in combination due to the reduction of single drug component. Usually, the choice of analgesic is based on personal preference. In systematic reviews for dental and general surgical randomized controlled trials with naproxen, diclofenac and rofecoxib, they were shown to be superior compared to placebo and also COX-2 inhibitors demonstrated equipotent efficacy relative to NSAIDs.

Moreover in dental and orthopedic pain, valdecoxib, celecoxib, ibuprofen and acetaminophen alone or with oxycodone demonstrated superiority of COX-2 inhibitors compared to acetaminophen, but not to ibuprofen alone. Also, oral ibuprofen is significantly superior to placebo and when the doses were maximal the effect were enhanced.

When compared to diclofenac, ibuprofen was less efficacious even after showing a reduction by at least 50% of pain for 100% of patients participated. Acetaminophen was also proven to be similarly efficacious in general and orthopedic surgery and less effective in dental surgery compared to NSAIDs. When it is combined with opioids such as codeine or oxycodone, it was shown to be superior compared to placebo; however, it was more prone to side effect. The same was proven with tramadol alone.

In general, NSAIDs demonstrate higher efficacy in dental pain and are considered as the main alternative and drug of choice for dental pain. However, even though opioids are relatively less effective, they may be considered when NSAIDs are contraindicated and also different combination could be administered for some patients that require adequate pain relief [82].

Common reported adverse events of NSAIDs are dyspepsia, gastric ulceration-bleeding, diarrhea from COX-1 inhibitors, cardiovascular disease (congestive heart failure, atherothrombosis, myocardial infarction, ischemic stroke), reduced renal perfusion, or nephrotic syndrome accompanied with edema, acute kidney failure in rare cases from COX-2 inhibitors. Ibuprofen use in normal doses is one of the drugs with least risk or alternative option as selective COX-2 inhibitors. Acetaminophen adverse effects resulting from their higher dosage, chronic use, or in patient with liver disease includes liver toxicity, prolongation of prothrombine time, urticaria or skin rashes and acute renal tubular necrosis. Severe hepatotoxicity was reported in patients with risk factors such as HIV, hepatitis C and chronic alcohol users. In postoperative pain, a single dose usage and rational prescribing is demonstrated to be safe.

Moreover, narcotic analgesics have more frequent adverse effects and many patients abandoned treatment which make them poor choice in dental pain. When contemplating surgery, it is recommended to suppress NSAID medication from 1–2 to 4–5 days, which also depends on the drug type and dose regimen. Analgesic combination, which contains NSAIDs, is recommended to be used with caution only in short course for the acute dental pain [41, 83–86]. These above-mentioned side effects usually tend not to occur with the occasional use of NSAIDs, which makes these drugs safe in dental practice. NSAID usage for more than 10 days should be consulted with the practitioner. Even though they are considered relatively safe within the recommended dosage for use of up to 10 days, cautions should be exercised in NSAIDs-exacerbated respiratory disease, asthma, patients with prior myocardial infarction who are receiving antithrombotic therapy and those with a history of renal disease [87, 88].

Strategies to lower risk events for gastrointestinal toxicity from NSAIDs include the use of the lowest dose, switch to acetaminophen or COX-2 inhibitors, or antiulcer cotherapy use (PPI, H2-blockers, antacids, prostaglandins). Cardiovascular-related adverse effects have resulted in rofecoxib and valdecoxib being withdrawn from the market. However, uses were for a long period of time and dose dependent or even in short course of treatments for 10 days after bypass surgery. Currently, celecoxib, etoricoxib, lumiraxocib and parecoxib, with better cardiovascular risk profiles, are still in the market. Hence, NSAIDs may increase the risk for myocardial infarction, in particular those with more COX-2 selectivity such as diclofenac. Taking this into consideration, avoiding COX-2 inhibitors and following treatment with antiulcer drugs is recommended in high risk patients [82]. Ibuprofen and naproxen are considered the safest NSAIDs. Overall risk from analgesic used in dentistry is low and importantly when they are used in acute dental pain. Moreover, the most serious safety concerns about the use of opioids are the side effect profile which includes respiratory depression, dependence, sedation, euphoria, constipation, cognitive dysfunction, pruritus, nausea and immunologic and endocrine effects, which are more prone from μ receptor activity. Dependence is another challenge and this occurs more in severe acute, chronic and terminal pain for longer than a week and after repeated administration. Furthermore, tolerance to opioids is developed when higher doses are used.

Selective κ agonist such as nalbuphine is shown to be safer even though this should never be given to a patient who is dependent. Important care is recommended for codeine metabolism from CYP2D6 ultrarapid metabolizers, which are more prone to morphine-induced side effects or for CYP2D6 deficient or patient who are on inhibitors of this cytochrome may not produce analgesic effect of hydrocodone and oxycodone. Methadone has potential to cause cardiac arrhythmia. Due to this pretreatment and periodic cardiograms are recommended for patients suspected for drug interactions or increasing methadone dosing. Important care should also be taken with conversion of one opioid to another from opioid conversion tables (for example, morphine to methadone). Regarding treatment of withdrawal, partial agonists such as buprenorphine is recommended [19, 89].

Recently, there have been important developments in the investigation of lower addictive potential opioids such as tamper-resistant extended release, also opioid abuse screening tools, genetic testing and fMRIs for patients at risk of opioid abuse while maintaining treatments for patients with appropriate management.

Even though recent research has shown that a number of potential predictors for personalization of therapy exist, there is still insufficient evidence for opioid prescribing from patient's characteristics. Data-based personalized prescribing of opioids for optimization of analgesic effectiveness and mitigate risks of opioid-related mortality and abuse is highly desirable with the potential to benefit patients by raising world clinical care and optimizing cost effectiveness of opioid analgesic therapy [90].

7. Analgesic monotherapy versus combined therapy in dental practice

Analgesic monotherapy and combined therapy is shown in different clinical situations such as reducing pain in surgical procedures, periodontal and endodontic procedures which is documented also from different clinical trials. Many NSAIDs which are used in dental pain includes ibuprofen, aspirin, diflunisal, etodolac, mefenamic acid, ketoprofen, ketorolac and flubiprofen. Ibuprofen is the most commonly used in acute pain and is often prescribed as the first choice analgesic associated with its anti-inflammatory actions in the dentistry practice. Paracetamol acts in the central nervous system and it possesses analgesic and antipyretic effects. It is the first choice for patients who cannot tolerate NSAIDs. Higher doses such as 1000 mg are more favorable in the context of its efficacy and were comparable with ibuprofen.

There is strong evidence that combined analgesics therapy lead to greater efficacy and fewer adverse events compared with monotherapy of analgesics in higher doses. Different randomized controlled trials that compared combinations of several analgesics (NSAIDs and acetaminophen) revealed that the combination of acetaminophen with different NSAID drugs was more effective than either acetaminophen or individual NSAID alone [18, 91, 92].

Currently there are many combinations of paracetamol with other NSAIDs such as ibuprofen, ketoprofen and diclofenac and they have resulted in providing superior analgesia than using the drug alone. Otherwise in the patients with moderate to severe pain induced by postoperative pain, the combination of lower doses of ibuprofen with paracetamol has not shown benefits when compared with ibuprofen used alone. This is an

indication that dosage choice is an important factor regarding its related combinations [93–95].

Naproxen is indicated in toothache and its pain relief efficacy is comparable with ibuprofen. It is comparable with etodolac, but less effective in swelling when compared with diclofenac when they were used in oral surgical procedures, including postoperative third molar surgery or orthodontic pain [96–98]. Diclofenac is used in moderate to severe pain following third molar extraction and it could be used in an intravenous form in risk population groups such as the elderly and renal insufficiency, postoperative anticoagulation which uses ketorolac as the only choice for the moderate to severe acute pain. Very similar effects were shown when transdermal diclofenac patches were used compared to oral administration [99, 100].

Due to safety concerns COX-2 selective inhibitors have been introduced as a safe alternative in dentistry practice with superior analgesic and inflammatory conditions in periodontal diseases and after oral surgery procedures. Etoricoxib and celecoxib groups were shown to be comparable to ibuprofen on its efficacy in the dental pulpal pain or postoperative pain relief, third molar surgery but superior toacetaminophene [101–103].

Their use is favorable in patients with upper-GI-complications, in the aspirin user for cardiovascular comorbidities, or those allergic to aspirin and perioperative settings due to their lack of properties over blood clotting. But they are limited to be used in such short periods including postoperative periods due to their cost effectiveness compared to other NSAIDs. Also, their long-term uses in the painful temporo mandibular joint disorders and chronic orofacial pain in the patients without cardiovascular risk factors could be considered as another therapeutic option [41, 104].

8. Significant drug interactions of analgesics

NSAIDs display major interactions when used alongside anticoagulant and antiplatelet effects of warfarin and clopidrogel, which results in enhancement of their effects and increased risk of bleeding. In this situation acetaminophen is an appropriate choice at the lowest possible dose, in short-term treatment only. Ibuprofen use in patients taking cardioprotective aspirin does not interfere with its antiplatelet activity, even though there are studies that demonstrate reduced cardioprotective benefits and increase gastrointestinal risk, in contrast to diclofenac or acetaminophen which did not influence effects of aspirin on platelet function [86]. Moreover, patients taking daily aspirin for cardiovascular disease prevention should avoid chronic use of ibuprofen and FDA recommends taking ibuprofen in intervals of more than 8 h before or more than 30 min after the immediate release of aspirin to reduce potential interaction in platelet function [40]. Concurrent use of NSAIDs with warfarin or corticosteroid may increase gastrointestinal risk. They also increase the risk of gastrointestinal ulceration in concomitant use with biphosphonates. Effects of antidiabetic sulfonylureas are increased with coadministration of NSAIDs.

A decrease of renal extraction of methotrexate is shown with the use of NSAIDs, which can bring to its toxicity. Also, the serum concentrations of lithium are raised and non-NSAID analgesic should be recommended. Additionally, fluconazole was shown to increase celecoxib concentration due to its metabolism inhibition.

Interactions with lesser significance are NSAIDs use with ACE inhibitors, diuretics, Ca-channel bBlockers and beta-blockers which results in diminished antihypertensive effects. However, short-term use does not pose a major risk in healthy individuals, but in hypertensive patients and especially in the elderly if the treatment will be continued for a long term a careful selection and close monitoring is required. Antacids were shown to decrease NSAIDs effects. NSAIDs are also found to interact with SSRIs (selective serotonin reuptake inhibitors) to increase the risk of bleeding including also upper gastrointestinal and postoperative bleeding [37, 105, 106]. Acetaminophen has very few drug interactions. Carbamazepine as metabolic inducer may decrease drug levels of acetaminophen. Its combination with alcohol or drugs that harm the liver may increase the risk for liver toxicity.

Dental practitioners should be aware of these interactions and use analgesic drug therapy within the limit of dosage or interval of use and in carefully considered combinations. Furthermore, they should avoid them when there is increased risk for toxicity [81, 107]. Narcotic analgesic interactions include antipsychotics (phenotiazines) which enhance their hypotensive effect and also CYP2D6 inhibitors (cimetidine, chlorpheniramine, fluoxetine and quinidine), which inhibit their effects including hydrocodone. Inhibitors or inducers of CYP3A4 cause clinical significant interactions when used with morphine, oxycodone and methadone by mediating opioid toxicity or impairment of pain treatment. Also, SSRIs and MAOIs effects are more associated with meperidine, methadone, tramadol, buprenorphine, oxycodone, hydrocodone, pentazocine and fentanyl, which may also result in the cause of the serotonin syndrome. Barbiturates may enhance their sedative effects. Also an increase of meperidine metabolism is induced by phenytoine. Taking this into consideration physicians should recognize and monitor patients carefully for drug interactions and possibly try to avoid polypharmacy [89, 108, 109].

9. Challenges of dental pain management

Safe and effective dental pain management strategy requires an understanding of several factors. Pain is perceived differently by individual patients, depending on their biogenetic profile, gender, age, sociocultural attitudes, comedical and psychiatric conditions and several other factors [110]. Due to ethical consideration there are limited scientific data for drug efficacy in dental pain management and this is why it is important to challenge the work of clinicians in daily clinical practice. Dental clinicians assign a comprehensive practice that involves the pharmacological, biological and psychosocial aspects of pain management in order to ensure effective low risk pain treatment. Therefore, they need to implement and coordinate the extrapolated evidence base, knowledge, personal clinical experience and close monitoring of patients to achieve the effective balance of pain treatment in dental patients [11].

In general more attention should be paid by dental practitioners to reducing opioid drug abuse and monitoring of prescription and nonprescription uses of analgesics, improvement of drug choice alone or in combination, new analgesic alternatives and adjustment in course of treatment according to clinical needs. Also, individualization of therapy and dosage needs to be done carefully in the risk groups mentioned above, coupled with the need for adequate monitoring of drug interactions.

Author details

Shaip Krasniqi[1] and Armond Daci[2]*

*Address all correspondence to: armond.daci@uni-pr.edu

1 Faculty of Medicine, Institute of Pharmacology and Toxicology and Clinical Pharmacology, University of Prishtina "Hasan Prishtina", Prishtina, Kosovo

2 Department of Pharmacy, Faculty of Medicine, University of Prishtina, Prishtina, Kosovo

References

[1] Brune K, Hinz B. History of Analgesics. In Encyclopedia of Pain. Berlin Heidelberg: Springer; 2013, pp. 1490–6. DOI: 10.1007/978-3-642-28753-4_1766

[2] Brune K. The early history of non-opioid analgesics. Acute Pain. 1997;1(1):33–40. DOI: 10.1016/S1366-0071(97)80033-2#_blank#Persistent link using digital object identifier

[3] Fainsinger RL, Nekolaichuk C, Lawlor P, Hagen N, Bercovitch M, Fisch M, Galloway L, Kaye G, Landman W, Spruyt O, Zhukovsky D. An international multicentre validation study of a pain classification system for cancer patients. European Journal of Cancer. 2010;46(16):2896–904. DOI: 10.1016/j.ejca.2010.04.017 DOI:10.1016/j.ejca.2010.04.017# doilink

[4] Anderson R, Thomas DW. 'Toothache stories': a qualitative investigation of why and how people seek emergency dental care. Community Dental Health. 2003;20(2):106–11.

[5] Trowbridge HO. Review of dental pain—histology and physiology. Journal of Endodontics. 1986;12(10):445–52. DOI: 10.1016/S0099-2399(86)80197-2 DOI:10.1016/S0099-2399(86)80197-2#_blank#Persistent link using digital object identifier

[6] Kissin I. The development of new analgesics over the past 50 years: a lack of real breakthrough drugs. Anesthesia & Analgesia. 2010;110(3):780–9. DOI: 10.1213/ANE.0b013e3181cde882

[7] Compton WM, Jones CM, Baldwin GT. Relationship between nonmedical prescription-opioid use and heroin use. New England Journal of Medicine. 2016;374(2):154–63. DOI: 10.1056/NEJMra1508490

[8] Scott NL, Miner JR. The safe and rational use of analgesics: non-opioid analgesics. Current Emergency and Hospital Medicine Reports. 2016;4(2):66–70. DOI: 10.1007/s40138-016-0102-5

[9] Van Doormaal JE, Van Den Bemt PM, Mol PG, Zaal RJ, Egberts AC, Haaijer-Ruskamp FM, Kosterink JG. Medication errors: the impact of prescribing and transcribing errors on preventable harm in hospitalised patients. Quality and Safety in Health Care. 2009;18(1):22–7. DOI: 10.1136/qshc.2007.023812

[10] Smith HS, Lesar TS. Analgesic prescribing errors and associated medication characteristics. The Journal of Pain. 2011;12(1):29–40. DOI: 10.1016/j.jpain.2010.04.007 DOI:10.1016/j.jpain.2010.04.007#doilink

[11] Savage SR, Kirsh KL, Passik SD. Challenges in using opioids to treat pain in persons with substance use disorders. Addiction Science & Clinical Practice. 2008;4(2):4.

[12] Nielsen FE, Gram-Hansen P, Christensen JH, Sørensen HT, Klausen IC, Ravn L. Reduced consumption of analgesics in patients with diabetes mellitus admitted to hospital for acute myocardial infarction. Pain. 1991;47(3):325–8. DOI: 10.1016/0304-3959(91)90223-K DOI:10.1016/0304-3959(91)90223-K#_blank#Persistent link using digital object identifier

[13] Casey CY, Greenberg MA, Nicassio PM, Harpin RE, Hubbard D. Transition from acute to chronic pain and disability: a model including cognitive, affective and trauma factors. Pain. 2008;134(1):69–79. DOI: 10.1016/j.pain.2007.03.032 DOI:10.1016/j.pain.2007.03.032#doilink

[14] McCarberg BH, Billington R. Consequences of neuropathic pain: quality-of-life issues and associated costs. The American Journal of Managed Care. 2006;12(9 Suppl): S263–8.

[15] Nalliah RP, Allareddy V, Elangovan S, Karimbux N, Lee MK, Gajendrareddy P, Allareddy V. Hospital emergency department visits attributed to pulpal and periapical disease in the United States in 2006. Journal of Endodontics. 2011;37(1):6–9. DOI: 10.1016/j.joen.2010.09.006 DOI:10.1016/j.joen.2010.09.006#doilink

[16] Murray GM. Referred pain, allodynia and hyperalgesia. The Journal of the American Dental Association. 2009;140(9):1122–4. DOI: 10.14219/jada.archive.2009.0339

[17] Hargreaves KM, Hutter JW. Endodontic pharmacology. In Cohen S, Burns R, eds. Pathways of the Pulp. St Louis: Mosby; 2002, pp. 665–82.

[18] Ong CK, Seymour RA, Lirk P, Merry AF. Combining paracetamol (acetaminophen) with nonsteroidal antiinflammatory drugs: a qualitative systematic review of analgesic efficacy for acute postoperative pain. Anesthesia & Analgesia. 2010;110(4):1170–9. DOI: 10.1213/ANE.0b013e3181cf9281

[19] Becker DE. Pain management: part 1: managing acute and postoperative dental pain. Anesthesia Progress. 2010;57(2):67–79. DOI: 10.2344/0003-3006-57.2.67

[20] Cairns BE, Kolta A, Whitney E, Craig K, Rei N, Lam DK, Lynch M, Sessle B, Lavigne G. The need for further research. Journal of the Canadian Dental Association. 2014;80:e49.

[21] Hargreaves K, Abbott PV. Drugs for pain management in dentistry. Australian Dental Journal. 2005;50(4 Suppl 2):S14–22.DOI: 10.1111/j.1834-7819.2005.tb00378.x

[22] Okunseri C, Okunseri E, Thorpe JM, Xiang Q, Szabo A. Medications prescribed in emergency departments for nontraumatic dental condition visits in the United States. Medical Care. 2012;50(6):508. DOI: 10.1097/MLR.0b013e318245a575 DOI:10.1097%2FMLR.0b013e318245a575#pmc_ext

[23] Okunseri C, Okunseri E, Xiang Q, Thorpe JM, Szabo A. Prescription of opioid and nonopioid analgesics for dental care in emergency departments: findings from the National Hospital Ambulatory Medical Care Survey. Journal of Public Health Dentistry. 2014;74(4):283–92. DOI: 10.1111/jphd.12055 DOI:10.1111%2Fjphd.12055#pmc_ext

[24] Levy B, Paulozzi L, Mack KA, Jones CM. Trends in opioid analgesic–prescribing rates by specialty, US, 2007–2012. American Journal of Preventive Medicine. 2015;49(3):409–13. DOI: 10.1016/j.amepre.2015.02.020 DOI:10.1016/j.amepre.2015.02.020#doilink

[25] Baker JA, Avorn J, Levin R, Bateman BT. Opioid prescribing after surgical extraction of teeth in Medicaid patients, 2000–2010. Journal of the American Medical Association. 2016;315(15):1653–4. DOI: 10.1001/jama.2015.19058.

[26] Denisco RC, Kenna GA, O'Neil MG, Kulich RJ, Moore PA, Kane WT, Mehta NR, Hersh EV, Katz NP. Prevention of prescription opioid abuse: the role of the dentist. The Journal of the American Dental Association. 2011;142(7):800–10. DOI: 10.14219/jada.archive.2011.0268

[27] Donaldson M, Goodchild JH. Appropriate analgesic prescribing for the general dentist. General Dentistry. 2009;58(4):291–7.

[28] Kulkarni MD, Baig MS, Hussaini SA, Doifode SM. Drug utilization pattern in OPD of government dental college and hospital, Aurangabad. International Journal of Basic & Clinical Pharmacology. 2013;2:69–70. DOI: 10.5455/2319-2003.ijbcp20130113

[29] Haliti NR, Haliti FR, Koçani FK, Gashi AA, Mrasori SI, Hyseni VI, Bytyqi SI, Krasniqi LL, Murtezani AF, Krasniqi SL. Surveillance of antibiotic and analgesic use in the Oral Surgery Department of the University Dentistry Clinical Center of Kosovo. Therapeutics and Clinical Risk Management. 2015;11:1497. DOI: 10.2147/TCRM.S87595 DOI:10.2147%2FTCRM.S87595#pmc_ext

[30] Pise ND, Kaikade SB. Drug utilization evaluation of analgesics in tertiary care dental hospital in Dhule district. International Journal of Biomedical Research. 2016;7(6):344–5. DOI: 10.7439/ijbr.v7i6.3324

[31] Moore PA, Nahouraii HS, Zovko JG, Wisniewski SR. Dental therapeutic practice patterns in the US II. Analgesics, corticosteroids and antibiotics. General Dentistry. 2005;54(3):201–7.

[32] Paudel KR, Sah NK, Jaiswal AK. Prevalence of pharmacotherapy in the department of paediatric dentistry. Kathmandu University Medical Journal. 2010;8(2):190–4. DOI: 10.3126/kumj.v8i2.3556

[33] Levrini L, Carraro M, Rizzo S, Salgarello S, Bertelli E, Pelliccioni GA, Garau V, Bandettini M, Caputi S, Lörincz A, Szûcs A. Prescriptions of NSAIDs to patients undergoing third molar surgery. Clinical Drug Investigation. 2008;28(10):657–68. DOI: 10.2165/00044011-200828100-00006

[34] Datta P, Datta PP. Drug utilization pattern in Oral Medicine Department of Saveetha Dental College, Tamil Nadu, India. National Journal of Medical Research. 2015;5(4):272–4.

[35] Analgesics in Dentistry. Available at: https://www.netcegroups.com/964/Course_55041.pdf 2013.

[36] Dionne RA, Berthold CW. Therapeutic uses of non-steroidal anti-inflammatory drugs in dentistry. Critical Reviews in Oral Biology & Medicine. 2001;12(4):315–30. DOI: 10.1177/10454411010120040301

[37] Hersh EV, Pinto A, Moore PA. Adverse drug interactions involving common prescription and over-the-counter analgesic agents. Clinical Therapeutics. 2007;29(11):2477–97. DOI: 10.1016/j.clinthera.2007.12.003 DOI:10.1016/j.clinthera.2007.12.003#_blank#-Persistent link using digital object identifier

[38] Heard KJ, Ries NL, Dart RC, Bogdan GM, Zallen RD, Daly F. Overuse of non-prescription analgesics by dental clinic patients. BMC Oral Health. 2008;8(1):1. DOI: 10.1186/1472-6831-8-33

[39] Lavonas EJ, Fries JF, Furst DE, Rothman KJ, Stergachis A, Vaida AJ, Zelterman D, Reynolds KM, Green JL, Dart RC. Comparative risks of non-prescription analgesics: a structured topic review and research priorities. Expert Opinion on Drug Safety. 2012;11(1):33–44. 10.1517/14740338.2012.629782

[40] Moore N, Pollack C, Butkerait P. Adverse drug reactions and drug–drug interactions with over-the-counter NSAIDs. Therapeutics and Clinical Risk Management. 2015;11:1061. DOI: 10.2147/TCRM.S79135 DOI:10.2147%2FTCRM.S79135#pmc_ext

[41] Poveda Roda R, Bagán JV, Jiménez Soriano Y, Gallud Romero L. Use of nonsteroidal antiinflammatory drugs in dental practice: a review. Medicina Oral, Patología Oral y Cirugía Bucal (Internet). 2007;12(1):10–8.

[42] Botting RM. Inhibitors of cyclooxygenases: mechanisms, selectivity and uses. Journal of Physiology and Pharmacology. 2006;57:113.

[43] Kawabe JI, Ushikubi F, Hasebe N. Prostacyclin in vascular diseases-recent insights and future perspectives. Circulation Journal. 2010;74(5):836–43. DOI: 10.1253/circj.CJ-10-0195

[44] Kearney PM, Baigent C, Godwin J, Halls H, Emberson JR, Patrono C. Do selective cyclooxygenase-2 inhibitors and traditional non-steroidal anti-inflammatory drugs increase

the risk of atherothrombosis? Meta-analysis of randomised trials. British Medical Journal. 2006;332(7553):1302–8. DOI: http://dx.doi.org/10.1136/bmj.332.7553.1302

[45] Dogne JM, Hanson J, Supuran C, Pratico D. Coxibs and cardiovascular side-effects: from light to shadow. Current Pharmaceutical Design. 2006;12(8):971–5.DOI: http://dx.doi.org/10.2174/138161206776055949

[46] Ng K, Meyerhardt JA, Chan AT, Sato K, Chan JA, Niedzwiecki D, Saltz LB, Mayer RJ, Benson AB, Schaefer PL, Whittom R. Aspirin and COX-2 inhibitor use in patients with stage III colon cancer. Journal of the National Cancer Institute. 2015;107(1):dju345. DOI: 10.1093/jnci/dju345

[47] de Pedro M, Baeza S, Escudero MT, Dierssen-Sotos T, Gómez-Acebo I, Pollán M, Llorca J. Effect of COX-2 inhibitors and other non-steroidal inflammatory drugs on breast cancer risk: a meta-analysis. Breast Cancer Research and Treatment. 2015;149(2):525–36. DOI: 10.1007/s10549-015-3267-9

[48] Al-Hasani R, Bruchas MR. Molecular mechanisms of opioid receptor-dependent signaling and behavior. The Journal of the American Society of Anesthesiologists. 2011;115 (6):1363–81. DOI: 10.1097/ALN.0b013e318238bba6.

[49] Walton RE, Reader AF Local anesthesia. In Walton RE, Torabinejad M, eds. Principles and Practice of Endodontics, 3rd ed. Philadelphia: W.B. Saunders Company; 2002, pp. 99–117.

[50] Malamed SF. Handbook of Local Anesthesia, 6th Edition. Published by Mosby, MO, USA. 2012, pp 432.

[51] Henry MA, Hargreaves KM. Peripheral mechanisms of odontogenic pain. Dental Clinics of North America. 2007;51(1):19–44. DOI: 10.1016/j.cden.2006.09.007

[52] Rood JP, Pateromichelakis S. Inflammation and peripheral nerve sensitisation. British Journal of Oral Surgery. 1981;19(1):67–72. DOI: 10.1016/0007-117X(81)90023-8 DOI:10.1016/0007-117X(81)90023-8#_blank#Persistent link using digital object identifier

[53] Parirokh M, Ashouri R, Rekabi AR, Nakhaee N, Pardakhti A, Askarifard S, Abbott PV. The effect of premedication with ibuprofen and indomethacin on the success of inferior alveolar nerve block for teeth with irreversible pulpitis. Journal of Endodontics. 2010;36 (9):1450–4. DOI: 10.1016/j.joen.2010.05.007 DOI:10.1016/j.joen.2010.05.007#doilink

[54] Kalyvas DG, Tarenidou M. Influence of nonsteroidal anti-inflammatory drugs on osseointegration. Journal of Oral Science. 2008;50(3):239–46. DOI: 10.2334/josnusd.50.239

[55] Kiersch TA, Halladay SC, Koschik M. A double-blind, randomized study of naproxen sodium, ibuprofen and placebo in postoperative dental pain. Clinical Therapeutics. 1992;15(5):845–54.

[56] Bailey E, Worthington HV, van Wijk A, Yates JM, Coulthard P, Afzal Z. Ibuprofen and/or paracetamol (acetaminophen) for pain relief after surgical removal of lower wisdom

teeth. Cochrane Database of Systematic Reviews 2013; 12:1–55. DOI:10.1002/14651858.CD004624.pub2.

[57] Wideman GL, Keffer M, Morris E, Doyle Jr RT, Jiang JG, Beaver WT. Analgesic efficacy of a combination of hydrocodone with Ibuprofen in postoperative pain. Clinical Pharmacology and Therapeutics. 1999;65(1):66–76. DOI: 10.1016/S0009-9236(99)70123-2

[58] Wynn RL. Narcotic analgesics for dental pain: available products, strengths and formulations. General Dentistry. 2000;49(2):126–8.

[59] Cusack BJ. Pharmacokinetics in older persons. The American Journal of Geriatric Pharmacotherapy. 2004;2(4):274–302. DOI: 10.1016/j.amjopharm.2004.12.005 DOI:10.1016/j.amjopharm.2004.12.005#_blank#Persistent link using digital object identifier

[60] Guay DR, Artz MB, Hanlon JT, Schmader KE. The Pharmacology of Aging. Brocklehurst's Textbook of Geriatric Medicine and Gerontology. New York, NY: Churchill Livingstone; 2003, pp. 155–61.

[61] Huanga AR, Mallet L. Prescribing opioids in older people. Maturitas. 2013;74(2):123–9. DOI: 10.1016/j.maturitas.2012.11.002.

[62] Anand KJ. Consensus statement for the prevention and management of pain in the newborn. Archives of Pediatrics & Adolescent Medicine. 2001;155(2):173–80. DOI: 10.1001/archpedi.155.2.173

[63] Shim YS, Kim AH, Jeon EY, An SY. Dental fear & anxiety and dental pain in children and adolescents: a systemic review. Journal of Dental Anesthesia and Pain Medicine. 2015;15(2):53–61. DOI:http://dx.doi.org/10.17245/jdapm.2015.15.2.53

[64] Khatri A, Kalra N. A comparison of two pain scales in the assessment of dental pain in East Delhi children. ISRN Dentistry. 2012; 247351:1–8. DOI: 10.5402/2012/247351

[65] Azarpazhooh A, Chong V, Chuk M, Dosanjh A, Lee Y, Norsen H, Toth K. The dental utility of pain-assessment tools: an evidence-based report. Community Dentistry 2011. retrieved from: https://www.dentistry.utoronto.ca/system/files/w3_2011.pdf

[66] Shindova M, Belcheva A. Pain assessment methods among pediatric patients in medical and dental research. Medical Biology Studies, Clinical Studies, Social Medicine and Health Care. 2016; 6(1):16–23.

[67] Manworren RC, Hynan LS. Clinical validation of FLACC: preverbal patient pain scale. Pediatric Nursing. 2003 ;29(2):140.

[68] Garra G, Singer AJ, Taira BR, Chohan J, Cardoz H, Chisena E, Thode HC. Validation of the Wong-Baker FACES pain rating scale in pediatric emergency department patients. Academic Emergency Medicine. 2010;17(1):50–4. DOI: 10.1111/j.1553-2712.2009.00620.x

[69] Hjermstad MJ, Fayers PM, Haugen DF, Caraceni A, Hanks GW, Loge JH, Fainsinger R, Aass N, Kaasa S, European Palliative Care Research Collaborative (EPCRC). Studies

comparing Numerical Rating Scales, Verbal Rating Scales and Visual Analogue Scales for assessment of pain intensity in adults: a systematic literature review. Journal of Pain and Symptom Management. 2011;41(6):1073–93. DOI: 10.1016/j.jpainsymman.2010.08.016 DOI:10.1016/j.jpainsymman.2010.08.016#doilink

[70] Yaster M. Multimodal analgesia in children. European Journal of Anaesthesiology (EJA). 2010;27(10):851–7. DOI: 10.1097/EJA.0b013e328338c4af

[71] Weaver JM. New FDA black box warning for codeine: how will this affect dentists? Anesthesia Progress. 2013;60(2):35.

[72] Coric A, Banozic A, Klaric M, Vukojevic K, Puljak L. Dental fear and anxiety in older children: an association with parental dental anxiety and effective pain coping strategies. Journal of Pain Research. 2014;7:515–21. DOI: 10.2147/JPR.S67692.

[73] Rexrode KM, Buring JE, Glynn RJ, Stampfer MJ, Youngman LD, Gaziano JM. Analgesic use and renal function in men. Journal of the American Medical Association. 2001;286 (3):315–21. DOI: 10.1001/jama.286.3.315.

[74] Hamid MJ, Dummer CD, Pinto LS. Systemic conditions, oral findings and dental management of chronic renal failure patients: general considerations and case report. Brazilian Dental Journal. 2006;17(2):166–70. DOI:10.1590/S0103-64402006000200016

[75] Cerveró AJ, Bagán JV, Soriano YJ, Roda RP. Dental management in renal failure: patients on dialysis. Medicina Oral, Patología Oral y Cirugía Bucal. 2008;13(7):E419–26.

[76] Murtagh FE, Chai MO, Donohoe P, Edmonds PM, Higginson IJ. The use of opioid analgesia in end-stage renal disease patients managed without dialysis: recommendations for practice. Journal of Pain & Palliative Care Pharmacotherapy. 2007;21(2):5–16.

[77] Niscola P, Scaramucci L, Vischini G, Giovannini M, Ferrannini M, Massa P, Tatangelo P, Galletti M, Palumbo R. The use of major analgesics in patients with renal dysfunction. Current Drug Targets. 2010;11(6):752–8. DOI: 10.2174/138945010791170879

[78] Ouanounou A, Haas DA. Pharmacotherapy for the elderly dental patient. Journal (Canadian Dental Association). 2015;80:f18.

[79] Mazer M, Perrone J. Acetaminophen-induced nephrotoxicity: pathophysiology, clinical manifestations and management. Journal of Medical Toxicology. 2008;4(1):2–6. DOI: 10.1007/BF03160941

[80] Martínez SR, Serna JT, Silvestre FJ. Dental management in patients with cirrhosis. Gastroenterología y Hepatología (English Edition). 2016;39(3):224–32.DOI: 10.1016/j.gastre.2016.02.020 DOI:10.1016/j.gastre.2016.02.020#doilink

[81] Smith H, Bruckenthal P. Implications of opioid analgesia for medically complicated patients. Drugs & Aging. 2010;27(5):417–33. DOI: 10.2165/11536540-000000000-00000

[82] Ong CK, Seymour RA. An evidence-based update of the use of analgesics in dentistry. Periodontology 2000. 2008;46(1):143–64.

[83] Cicconetti A, Bartoli A, Ripari F, Ripari A. COX-2 selective inhibitors: a literature review of analgesic efficacy and safety in oral-maxillofacial surgery. Oral Surgery, Oral Medicine, Oral Pathology, Oral Radiology and Endodontology. 2004;97(2):139–46. DOI: 10.1016/j.tripleo.2003.08.032 DOI:10.1016/j.tripleo.2003.08.032#doilink

[84] Au AH, Choi SW, Cheung CW, Leung YY. The efficacy and clinical safety of various analgesic combinations for post-operative pain after third molar surgery: a systematic review and meta-analysis. Plos One. 2015;10(6):e0127611. DOI: 10.1371/journal.pone.0127611

[85] Guggenheimer J, Moore PA. The therapeutic applications of and risks associated with acetaminophen use: a review and update. The Journal of the American Dental Association. 2011;142(1):38–44. DOI: 10.14219/jada.archive.2011.0026 DOI:10.14219/jada.archive.2011.0026#doilink

[86] Branco FP, Pinheiro ML, Volpato MC, De Andrade ED. Analgesic choice in dentistry. Part I: the mechanism of action. Brazilian Journal of Oral Sciences. 2005;4(14):762–65.

[87] Pinheiro ML, Cristina M andrade VE, Branco PF. Analgesic choice in dentistry Part II: the toxicity. Brazilian Journal of Oral Sciences. 2005; 4(14):880–83.

[88] Aminoshariae A, Kulild JC, Donaldson M. Short-term use of nonsteroidal anti-inflammatory drugs and adverse effects: an updated systematic review. The Journal of the American Dental Association. 2016;147(2):98–110. DOI: 10.1016/j.adaj.2015.07.020 DOI:10.1016/j.adaj.2015.07.020#doilink

[89] Trescot AM. Opioid pharmacology and pharmacokinetics. In Controlled Substance Management in Chronic Pain. Springer International Publishing, USA. 2016, pp. 45–62. DOI:14 10.1007/978-3-319-30964-4_4

[90] Bruehl S, Apkarian AV, Ballantyne JC, Berger A, Borsook D, Chen WG, Farrar JT, Haythornthwaite JA, Horn SD, Iadarola MJ, Inturrisi CE. Personalized medicine and opioid analgesic prescribing for chronic pain: opportunities and challenges. The Journal of Pain. 2013;14(2):103–13. DOI: http://dx.doi.org/10.1016/j.jpain.2012.10.016 DOI:10.1016/j.jpain.2012.10.016#doilink

[91] Dionne R. Additive analgesia without opioid side effects. Compendium of Continuing Education in Dentistry (Jamesburg, NJ: 1995). 2000;21(7):572–4.

[92] Paudel KR. Therapeutic practice preference in dentistry: antibiotics, analgesics and antiseptics. Asian Journal of Medical Sciences (E-ISSN 2091-0576; P-ISSN 2467-9100). 2014;4(4):17–23.

[93] Spivakovsky S. Will adding acetaminophen (paracetamol) to ibuprofen be more effective in relieving postoperative pain on symptomatic necrotic teeth? Evidence-Based Dentistry. 2012;13(4):105. DOI: 10.1038/sj.ebd.6400889

[94] Alexander L, Hall E, Eriksson L, Rohlin M. The combination of non-selective NSAID 400 mg and paracetamol 1000 mg is more effective than each drug alone for treatment of acute pain. A systematic review. Swedish Dental Journal. 2013;38(1):1–4.

[95] Bailey E, Worthington H, Coulthard P. Ibuprofen and/or paracetamol (acetaminophen) for pain relief after surgical removal of lower wisdom teeth, a Cochrane systematic review. British Dental Journal. 2014;216(8):451–5. DOI: 10.1038/sj.bdj.2014.330

[96] Akbulut N, Üstüner E, Atakan C, Çölok G. Comparison of the effect of naproxen, etodolac and diclofenac on postoperative sequels following third molar surgery: a randomised, double-blind, crossover study. Medicina Oral, Patologia Oral Y Cirugia Bucal. 2014;19(2): e149. DOI: 10.4317/medoral.19518 DOI:10.4317%2Fmedoral.19518#pmc_ext

[97] Kara İM, Polat S, İnce F, Gümüş C. Analgesic and anti-inflammatory effects of oxaprozin and naproxen sodium after removal of impacted lower third molars: a randomized, double-blind, placebo-controlled crossover study. Journal of Oral and Maxillofacial Surgery. 2010;68(5):1018–24. DOI: 10.1016/j.joms.2009.09.094 DOI:10.1016/j.joms.2009.09.094#doilink

[98] Polat O, Karaman AI, Durmus E. Effects of preoperative ibuprofen and naproxen sodium on orthodontic pain. The Angle Orthodontist. 2005;75(5):791–6.

[99] Christensen K, Daniels S, Bandy D, Ernst CC, Hamilton DA, Mermelstein FH, Wang J, Carr DB. A double-blind placebo-controlled comparison of a novel formulation of intravenous diclofenac and ketorolac for postoperative third molar extraction pain. Anesthesia Progress. 2011;58(2):73–81. DOI: 10.2344/0003-3006-58.2.73

[100] Bhaskar H, Kapoor P. Comparison of transdermal diclofenac patch with oral diclofenac as an analgesic modality following multiple premolar extractions in orthodontic patients: a cross over efficacy trial. Contemporary Clinical Dentistry. 2010;1(3):158. DOI: 10.4103/0976-237X.72783

[101] Tschoppe P, Kielbassa AM. The role of COX-2 in dentistry. Past or future? Swiss Monthly Record for Dentistry=Swiss Monthly magazine of dentistry and stomatology/SSO. 2005;116(9):880–6.

[102] May N, Epstein J, Osborne B. Selective COX-2 inhibitors: a review of their therapeutic potential and safety in dentistry. Oral Surgery, Oral Medicine, Oral Pathology, Oral Radiology and Endodontology. 2001;92(4):399–405. DOI: 10.1067/moe.2001.115127 DOI:10.1067/moe.2001.115127#doilink

[103] Madani ZS, Moghadamnia AA, Panahi A, Mir AP. Analgesic effect of etoricoxib compared to ibuprofen on post endodontic pain. Oral Health and Dental Management. 2013;12:511. DOI: 10.4172/2247-2452.1000511

[104] Murnion BP. Combination analgesics in adults. Australian Prescriber. 2010;33(4). DOI:10.18773/austprescr.2010.056

[105] Der Khatchadourian Z, Moreno-Hay I, de Leeuw R. Nonsteroidal anti-inflammatory drugs and antihypertensives: how do they relate? Oral Surgery, Oral Medicine, Oral Pathology and Oral Radiology. 2014;117(6):697–703. DOI: 10.1016/j.oooo.2014.02.028 DOI:10.1016/j.oooo.2014.02.028#doilink

[106] Hersh EV, Moore PA. Adverse drug interactions in dentistry. Periodontology 2000. 2008;46(1):109–42. DOI: 10.1111/j.1600-0757.2008.00224.x

[107] Moore PA, Hersh EV. Principles of pain management in dentistry. The ADA Practical Guide to Substance Use Disorders and Safe Prescribing. 2015;5:31.

[108] Kotlinska-Lemieszek A, Klepstad P, Haugen DF. Clinically significant drug–drug interactions involving opioid analgesics used for pain treatment in patients with cancer: a systematic review. Drug Design, Development and Therapy. 2015;9:52–55. DOI: 10.2147/DDDT.S86983 DOI:10.2147%2FDDDT.S86983#pmc_ext

[109] Weinstock RJ, Johnson MP. Review of top 10 prescribed drugs and their interaction with dental treatment. Dental Clinics of North America. 2016;60(2):421–34. DOI:http://dx.doi.org/10.1016/j.cden.2015.11.005 DOI:10.1016/j.cden.2015.11.005#doilink

[110] Kim H, Neubert JK, San Miguel A, Xu K, Krishnaraju RK, Iadarola MJ, Goldman D, Dionne RA. Genetic influence on variability in human acute experimental pain sensitivity associated with gender, ethnicity and psychological temperament. Pain. 2004;109 (3):488–96. DOI: 10.1016/j.pain.2004.02.027 DOI:10.1016/j.pain.2004.02.027#doilink

IntechOpen

IntechOpen

IntechOpen