

Review

# Post-Operative Endodontic Pain Management: An Overview of Systematic Reviews on Post-Operatively Administered Oral Medications and Integrated Evidence-Based Clinical Recommendations

Federica Di Spirito <sup>1,\*</sup> , Giuseppe Scelza <sup>1</sup> , Roberto Fornara <sup>2</sup> , Francesco Giordano <sup>1</sup>, Donato Rosa <sup>1</sup> and Alessandra Amato <sup>1</sup>

<sup>1</sup> Department of Medicine, Surgery and Dentistry “Schola Medica Salernitana”, University of Salerno, Baronissi, 84081 Salerno, Italy; g.scelza4@studenti.unisa.it (G.S.); francescodrgiordano@gmail.com (F.G.); drosa@unisa.it (D.R.); aamato@unisa.it (A.A.)

<sup>2</sup> Private Practitioner, 20010 Milan, Italy; robertofornara01@gmail.com

\* Correspondence: fdi Spirito@unisa.it or dispiritof@yahoo.it

**Abstract:** Endodontic treatment comprises the overall management of pre-, intra- and post-operative symptoms, including post-operative endodontic pain, considered as a complication susceptible of chronicization. Post-operative pain is very common and highly unpreventable and has a multi-factorial etiology and a potential pathogenic link to the acute inflammation of the periapical area, secondary to localized chemical, mechanical, host and/or microbial damage occurring during endodontic treatment. Considering the multitude of heterogeneous technical and pharmacological approaches proposed to control post-operative endodontic pain, the present study primarily comprised an overview of systematic reviews of randomized clinical trials, summarizing findings on post-operatively administered oral medications for post-operative endodontic pain control, in order to note the most effective type and dosage of such drugs. Secondarily, a narrative review of the current evidence on technical solutions to be observed during endodontic treatment procedures, to control post-operative pain, was conducted to provide integrated evidence-based clinical recommendations for optimal post-operative endodontic pain management.

**Keywords:** endodontics; non-steroidal anti-inflammatory drugs; pain; root canal treatment; steroidal anti-inflammatory drugs



**Citation:** Di Spirito, F.; Scelza, G.; Fornara, R.; Giordano, F.; Rosa, D.; Amato, A. Post-Operative Endodontic Pain Management: An Overview of Systematic Reviews on Post-Operatively Administered Oral Medications and Integrated Evidence-Based Clinical Recommendations. *Healthcare* **2022**, *10*, 760. <https://doi.org/10.3390/healthcare10050760>

Academic Editors: Joseph Nissan and Gavriel Chaushu

Received: 13 February 2022

Accepted: 18 April 2022

Published: 19 April 2022

**Publisher's Note:** MDPI stays neutral with regard to jurisdictional claims in published maps and institutional affiliations.



**Copyright:** © 2022 by the authors. Licensee MDPI, Basel, Switzerland. This article is an open access article distributed under the terms and conditions of the Creative Commons Attribution (CC BY) license (<https://creativecommons.org/licenses/by/4.0/>).

## 1. Introduction

The majority of the patients visit the dental office because of more or less intense pain, mainly attributable to endodontic and periodontal causes, and most of all recognizing an endodontic origin; thus, it is essential for the clinicians to differentiate odontogenic from non-odontogenic pain [1]. Accordingly, endodontic pain management primarily depends on an accurate diagnosis of pain origin, aided by clinical exam and periapical and pulp tests, along with 2D and 3D radiographic examination [1,2].

Endodontic treatment comprises the overall management of pre-, intra- and post-operative symptoms, including post-operative endodontic pain, which is considered as a treatment complication susceptible of chronicization [3] and which represents patients' significant concern [4].

Post-operative pain is very common, affecting from 2.5% to almost 60% of subjects that have undergone endodontic treatments [5], and it shows a tendency to increase between 6 and 12 h after treatment, reaching a prevalence of about 40% in 24 h and falling to 11% one week after treatment [3,6]. Moreover, post-operative endodontic pain is highly unpreventable, being affected by a variety of factors related to the subject (such as age and

gender), to the treated tooth (including the pre-operative pulp status and type of tooth) and to the treatment performed (either primary root canal therapy or retreatment) [6].

Given that post-operative endodontic pain has a multi-factorial etiology and a potential pathogenic link to the acute inflammation of the periapical area, secondary to localized chemical, mechanical, host and/or microbial damage occurring during endodontic treatment [3–6], several strategies have been proposed to control post-operative endodontic pain, comprising technical features and solutions to be observed when performing endodontic treatment [5,7–30], along with occlusal reduction [31–33], as well as adjunctive therapies, such as lower-laser therapy [34,35], cryotherapy [36–38], phototherapy [39], topical medicaments administration and systemic drug therapy [6,40,41].

Considering the multitude of heterogeneous technical and pharmacological approaches proposed to control post-operative endodontic pain, the primary aim of the study was to summarize relevant systematic reviews of randomized controlled trials on post-operative oral medications administered in subjects that have undergone primary root canal therapy and retreatment, in order to note the type and dosage most effective in post-operative endodontic pain control. The secondary aim of the study was to integrate such findings with comprehensive evidence-based clinical recommendations for post-operative endodontic pain management, reviewing current evidence on technical solutions to be observed during endodontic treatment procedures for post-operative endodontic pain control.

## 2. Materials and Methods

The present study comprises an overview of systematic reviews of systematic reviews, summarizing findings on post-operatively administered oral medications for post-operative endodontic pain control in order to note the most effective type and dosage, and a narrative review of current evidence, highlighting technical solutions to be observed during endodontic treatment procedures to control post-operative pain in order to provide integrated evidence-based clinical recommendations for optimal post-operative endodontic pain management. Both the overview of systematic reviews and review protocols are described below.

### 2.1. Overview of the Systematic Reviews of Systematic Reviews Protocol

The overview of systematic reviews was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) statement [42], which is freely available online (<http://www.prisma-statement.org/>, accessed on 28 September 2021), and the overview of systematic reviews protocol was developed before the analysis.

The focused question identified for the present overview of systematic reviews, as well as search strategies and selection criteria currently applied, were compliant with the PICO model [43] (<https://linkeddata.cochrane.org/pico-ontology>; accessed on 28 September 2021).

The question of the overview of systematic reviews was “Which type and dosage of oral medication administered after non-surgical initial treatment and retreatment is more effective to control post-operative endodontic pain?”, focusing on:

P—Population: subjects who completed non-surgical initial endodontic treatment or retreatment and experienced post-operative endodontic pain;

I—Intervention: post-operative administration of oral medications to treat post-operative endodontic pain;

C—Comparison: among different post-operatively administered types of oral medications and with placebo;

O—Outcome: reduction/resolution of post-operative endodontic pain.

#### 2.1.1. Overview of the Systematic Reviews Search Strategy

The Cochrane Database of Systematic Reviews and MEDLINE/PubMed were electronically searched for systematic reviews with or without meta-analyses until 30 September

2021, by two independent reviewers (F.D.S. and G.S.), using the following search terms combined by Boolean operators:

1. endodontic pain OR post-endodontic pain OR postendodontic pain OR endodontic post-operative pain OR endodontic postoperative pain.  
AND
2. oral medicines OR oral drugs OR oral medications OR oral medicaments OR oral administration OR orally administered medicines OR orally administered drugs OR orally administered medications OR orally administered medicaments OR treatment OR therapy OR management OR approach OR strategies.  
AND
3. Systematic Review OR Meta-analysis.

#### 2.1.2. Overview of the Systematic Reviews Study Selection and Eligibility Criteria

Retrieved citations were recorded, and duplicates were eliminated. Titles and abstracts of all the studies initially identified through the electronic search were independently screened by the two reviewers (F.D.S. and G.S.). Full-texts were also independently reviewed for ambiguous abstracts and for articles considered appropriate to the purpose of the present study and potentially eligible for the present overview of systematic reviews, according to the inclusion and non-inclusion criteria, reported in Table 1.

Disagreements between reviewers were solved through discussion and consensus.

Reference lists of included articles were also manually searched for additional potentially relevant systematic reviews with or without meta-analyses; identified titles and abstracts were screened, and full-texts were reviewed, as described above. In case of missing information or full-text unavailability, no attempt to contact authors was performed.

#### 2.1.3. Data Extraction of the Articles Included in the Overview of Systematic Reviews

Data extraction was independently conducted through a standardized data extraction form by the two reviewers (F.D.S. and G.S.), who solved disagreements by discussion and consensus.

The following data were recorded for each of the systematic reviews with or without a meta-analysis included in the present overview of systematic reviews: authors, year and journal of publication; trial's number; characteristics of the trial's population concerning the total number, age and gender of enrolled subjects; characteristics of the non-surgical endodontic treatment received (initial or re-treatment); post-operative endodontic pain assessment method and related follow-up period; characteristics of the trial's intervention and comparison regarding the type, dosage and duration of post-operatively administered oral medications and a comparison against drugs or a placebo; trials' statistically significant results concerning post-operative endodontic pain control.

#### 2.1.4. Quality Assessment and Data Synthesis of the Articles Included in the Overview of Systematic Reviews

Included systematic reviews were assessed for quality through the Assessing the Methodological Quality of Systematic Reviews 2 (AMSTAR 2) tool [43], freely available online (<https://amstar.ca>, accessed on 29 September 2021).

Two authors (F.D.S., G.S.) qualitatively synthesized the characteristics of the trial's population, intervention and comparison and reported significant results of each systematic review included in the present overview of systematic reviews.

**Table 1.** This is a table. Systematic reviews' eligibility criteria concerning sources, design and characteristics of the studies included regarding population, intervention, comparison and outcome(s).

Systematic Reviews Eligibility	Inclusion Criteria	Non-Inclusion Criteria
Sources Databases Language Publication status Publication date Text availability	Electronic and Manual English language Published or in press or ahead of print No restrictions Full-text access	None Non-English language Submitted No restrictions Abstractonly
Design	Systematic Reviews exclusively including Randomized Clinical Trials (RCTs) with or without a meta-analysis	Systematic Reviews also including ;prospective, retrospective, case-control, cross-sectional, case series, case reports or pre-clinical in vivo in vitro studies, as well as conference papers, oral communications, books and chapters Subjects who did not complete endodontic treatment or retreatment Subjects with periodontal pain Subjects with endodontic–periodontal lesions
Characteristics of the studies included in the eligible systematic reviews RCTs Population Study sample size Age Gender Treatments	Subjects who completed endodontic treatment or retreatment with post-operative endodontic pain No restrictions Adulthood Old age No restrictions Non-surgical endodontic initial treatment and retreatment	Subjects with disorders altering either pain perception or post-operatively administered oral medications effectiveness in post-operative endodontic pain control Subjects with oral cancer and osteonecrosis of the jaw Subjects with dental phobia No restrictions Childhood No restrictions Surgical endodontic treatment Other therapies or treatments Parenteral
Intervention Route of administration Timing of administration Type of medicaments	Pharmacological therapy Oral Post-operative administration Anti-inflammatory drugs (any) Analgesics (any)	Topical (intracanal, intraligamentary, supraperiosteal, intraosseous) Pre-operative administration In-between sessions administration Antibiotics Combined premedication and post-operative pharmacological pain treatment
Comparison	Placebo use Other type of medicaments	Pre- and intra-operative endodontic pain control Periodontal pain control
Outcome(S) Pain evaluation method	Post-operative endodontic pain control Visual Analogue Scale (VAS)	

VAS: Visual Analogue Scale; RCT: Randomized Clinical Trials.

## 2.2. Review Protocol

The narrative review question, also compliant with the PICO model [44], was “Which technical features and solutions to be observed during non-surgical initial endodontic treatment or retreatment procedures are more effective to control post-operative endodontic pain?”, identifying:

P—Population: subjects who completed non-surgical initial endodontic treatment or re-treatment;

I—Intervention: technical features and solutions to be observed during primary root canal treatment or retreatment procedures;

C—Comparison: among different technical features and solutions;

O—Outcome: reduced post-operative endodontic pain incidence, severity and duration.

### Review Search Strategy and Eligibility Criteria

The narrative review was accomplished through a further electronic literature search, independently performed by two reviewers (F.D.S. and G.S.).

MEDLINE/PubMed and the Cochrane Database of Systematic Reviews were searched for trials and observational studies, as well as for systematic reviews, with or without meta-analyses, reviews and book chapters, until 30 September 2021, employing the following same search terms:

1. endodontic pain OR post-operative endodontic pain OR postendodontic pain OR endodontic post-operative pain OR endodontic postoperative pain.

AND

2. endodontic treatment OR procedure OR therapy OR irrigation OR instrumentation OR obturation.

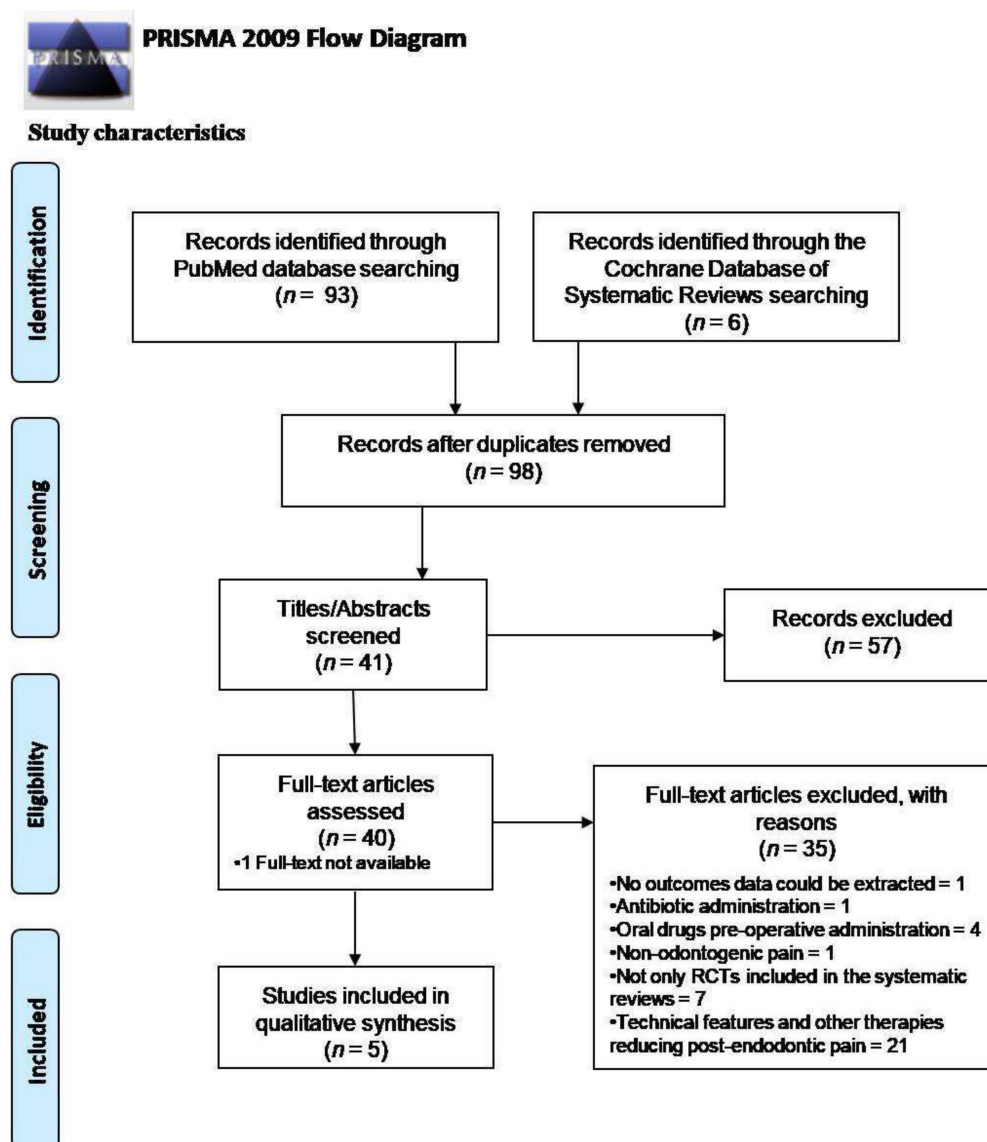
Studies investigating pre- and post-operative, either local or systemic, pharmacological approaches were excluded from the review, as well as those reporting adjunctive therapies, such as topical medicaments administration, lower-laser therapy, cryotherapy, phototherapy and similar.

### 3. Results

#### 3.1. Overview of Systematic Reviews: Study Selection

A total of 99 potentially relevant titles/abstracts were obtained from the literature search, of whom 93 were from MEDLINE/PubMed, and six were from the Cochrane Database of Systematic Reviews. One duplicate was removed, and after the titles/abstracts screening, 58 records were excluded, specifically 57 because they were not pertinent and 1 because no full-text was available; consequently, 40 potentially eligible full-text articles were assessed. Based on the eligibility criteria reported in Table 1, seven systematic reviews also including observational or preclinical or in vitro studies besides RCTs, 21 concerning technical features and other therapies reducing post-operative endodontic pain, four studies evaluating pre-operatively administered oral medications and one also comprising antibiotic prescription were not considered in the present analysis; one study evaluating non-odontogenic pain was removed, and one article was excluded because no outcomes data could be extracted.

Finally, five studies were included in the present overview of systematic reviews [4,45–48]. Figure 1 shows the study selection flow-chart.



**Figure 1.** This is a figure. PRISMA flow chart of the study.

### 3.2. Overview of Systematic Reviews: Studies' Characteristics and Synthesis of the Reported Results

Out of the five systematic reviews included in the present overview of systematic reviews of systematic reviews, all considered exclusively RCTs and were published in the English language, four [4,46–48] also comprised meta-analyses and only one [47] declared funding.

Findings from a total of 44 trials, accounting for 2697 enrolled subjects between 15 and 68 years of age, were retrieved, all concerning completed non-surgical initial endodontic treatments, performed in single [47], single/multiple [4,46] or an unspecified [45,48] number of sessions, of both vital and non-vital teeth and with none reporting retreatments.

Post-operative endodontic pain was assessed at different time points through Visual Analogue Scales in four studies [4,45,47,48], while in one study, the method was not specified [46]; the follow-up period ranged from 1 h to 7 days after the endodontic treatment.

The type and dosage of the oral medications, post-operatively administered to control post-operative endodontic pain, as well as the comparison with drugs and/or a placebo were clearly reported in all the studies, while duration was never specified. Four studies [45–48] evaluated the efficacy of non-steroidal anti-inflammatory drugs (NSAIDs).

A detailed summary of the data recorded for each study is shown in Table 2, reporting the authors, year and journal of publication; the trial's number; characteristics of the trial's population (subjects number, age and gender) and of the endodontic treatment received (non-surgical initial endodontic treatment or retreatment of vital or non-vital teeth and the number of sessions); post-operative endodontic pain assessment method and follow-up period; characteristics of trial's intervention and comparison (type, dosage and duration); the trial's significant results.

**Table 2.** Characteristics of the included systematic reviews and summary of the reported statistically significant results on the efficacy of post-operative endodontic pain control of post-operatively administered oral medications.

Intervention Oral Medication Type Dosage Duration Comparison Placebo Others	Author, Year Reference [] Journal Funding	Trials <i>n</i>	Population N. F/M Age (y.o.)	Characteristics of the Non-Surgical Endodontic Treatment Received Vital and Non-Vital Teeth Primary Root Canal Ther- apy/Retreatment N. of Sessions	Method to Assess/Grade post-Operative Pain VAS Others Follow-Up Period	Outcome(s) Statistically Significant ( <i>p</i> < 0.05) Pain Reduction
SAIDs Betamethasone 2 mg Dexamethasone 4 mg Dexamethasone 0.75 mg Duration: n.a. Comparison: placebo	Shamszadeh, 2018 [31] J Endod No Funding	4	166 F/M: n.a. >15 y.o.	Vital and Non-vital teeth Primary root canal therapy N. of sessions: single and multiple	VAS Follow-up period for Dexamethasone: 6, 24 h Follow-up period for Betamethasone: 6, 12, 24 h	Pain scores at 6 h: SAIDs < placebo (95% CI, −0.51; <i>p</i> = 0.000) Pain scores at 12 h: SAIDs < placebo (95% CI, −1.71 to −0.46; <i>p</i> = 0.001) Pain scores at 24 h: SAIDs < placebo (CI, −1.34 to −0.56; <i>p</i> = 0.000)
NSAIDs Ibuprofen 400 mg Ibuprofen 400 mg + alprazolam 0.5 mg Ketorolac 10 mg Flurbiprofen 50 mg Naproxen 500 mg Ibuprofen 200 mg + paracetamol 325 mg + 40 mg caffeine Meloxicam 15 mg Piroxicam 20 mg Ibuprofen 600 mg Salicylic acid 650 mg Paracetamol 650 mg Ketoprofen 50 mg Paracetamol 325 mg + codeine 60 mg	Smith, 2017 [47] J Endod Funding: Depart- ment of Endodon- tology Les Morgan Endow- ment and resident research	9 11	499 F/M: n.a. 18–80 y.o. 706 F/M. n.a. 18–68 y.o.	Vital and Non-vital teeth Primary root canal therapy N. of sessions: single Vital and Non-vital teeth Primary root canal therapy N. of sessions: n.a.	VAS Follow-up period for Alprazolam, Naproxen, Ibuprofen, Salicylic acid: baseline, 6, 12, 24 h Follow-up period for Ketorolac, Flurbiprofen: baseline, 6, 24 h Follow-up period for Piroxicam, Ibuprofen: baseline, 24 h 10 point, 100 mm, 170 mm Heft Parker VAS	Pain scores at 6 h: Ibuprofen 600 mg < placebo (ES = 10.50, <i>p</i> = 0.037) Pain scores: Ibuprofen 600 mg + paracetamol 1000 mg < placebo

Table 2. Cont.

Intervention Oral Medication Type Dosage Duration Comparison Placebo Others	Author, Year Reference    Journal Funding	Trials <i>n</i>	Population N. F/M Age (y.o.)	Characteristics of the Non-Surgical Endodontic Treatment Received Vital and Non-Vital Teeth Primary Root Canal Ther- apy/Retreatment N. of Sessions	Method to Assess/Grade post-Operative Pain VAS Others Follow-Up Period	Outcome(s) Statistically Significant ( <i>p</i> < 0.05) Pain Reduction
Ibuprofen 600 mg + paracetamol 1000 mg Duration: n.a Comparison: placebo Ibuprofen 400 mg Ibuprofen 400 + Alprazolam 0.5 mg Flurbiprofen (Loading dose 100 mg, subsequent 50 mg) Tramadol (Loading dose 100 mg subsequent 100 mg) Flurbiprofen + tramadol (Loading dose 100 mg subsequent 50/100 mg) Paracetamol 1000 mg Ibuprofen 600 + paracetamol 1000 mg Mefenamic acid 500 + paracetamol 1000 mg Diclofenac K 50 + paracetamol 1000 mg Dexamethasone 4 mg Dexamethason 0.75 mg Ibuprofen + paracetamol 400/325 mg DiclofenacSodium + paracetamol 50/500 mg Tramadol 100 mg Paracetamol 325+ ibuprofen 200+ caffeine 40 mg Naproxen 500 mg Ibuprofen 600 mg Pentazocine + naloxone 50/0.5 mg Indomethacin 75 mg Ibuprofen 150 mg Ibuprofen 150 + paracetamol 250 mg Duration: n.a. Comparison: placebo	grant from the American Associa- tion of Endodon- tists Founda- tion Zanjir, 2020 [48] J Endod No funding	9 11			Numerical rating scale 0 to 11 Follow-up period for Ibuprofen 400 mg, Ibuprofen 400 + Alprazolam 0.5 mg: 6, 12, 24, 48, 72 h Follow-up period for Flurbiprofen:6, 24, 48 h Follow-up period for Paracetamol 1000 mg Ibuprofen 600 + paracetamol 1000 mg Mefenamic acid 500 + paracetamol 1000 mg: 1, 2, 3, 4, 6, 8 h Follow-up period for DiclofenacSodium + paracetamol 50/500 mg Tramadol 100 mg Paracetamol 325+ ibuprofen 200+ caffeine 40 mg Naproxen 500 mg: 6, 12, 24 h [14,45] Follow-up period for Dexamethasone 4 mg and 0.75 mg: 8, 24, 48 h Follow-up period for Naproxen 500 mg Ibuprofen 600 mg: 0, 6, 12, 24, 48 h Follow-up period for Ibuprofen 150 mg Ibuprofen 150 + paracetamol 250 mg: 0 to 5 days	(ES = 34.89, <i>p</i> = 0.000) Pain scores at 6–8 h: NSAIDs + paracetamol< placebo(MD = −22; 95% CrI = −38 to −7.2) NSAIDs < placebo (MD = −22; 95% CrI = −38 to −7.2) NSAIDs < placebo (MD = −21; 95% CrI = −34 to −7.6) Pain scores at 12 h: Only NSAIDs were effective in decreasing postoperative pain (MD = −28; 95%CrI = −49 to −7) Pain scores at 24 h: Only NSAIDs were effective in decreasing postoperative pain (MD = −15; 95%CrI = −27 to −2.3) Pain scores at 48 h: No pain reduction



Table 2. Cont.

Intervention Oral Medication Type Dosage Duration Comparison Placebo Others	Author, Year Reference    Journal Funding	Trials <i>n</i>	Population N. F/M Age (y.o.)	Characteristics of the Non-Surgical Endodontic Treatment Received Vital and Non-Vital Teeth Primary Root Canal Ther- apy/Retreat- ment N. of Sessions	Method to Assess/Grade post-Operative Pain VAS Others Follow-Up Period	Outcome(s) Statistically Significant ( <i>p</i> < 0.05) Pain Reduction
SAIDs NSAIDs and Paracetamol Opioid analgesics Tramadol 100 mg Flurbiprofen 50 mg every 6 h for 2 days Flurbiprofen 50 mg + tramadol 100 mg Ibuprofen 600 mg single dose Ibuprofen 600 mg + paracetamol 1000 mg Paracetamol 325 mg + ibuprofen 200 mg + caffeine 40 mg every 6 h for 2 days Naproxen 500 mg every 6 h for 2 days Ibuprofen 400 mg every 6 h for 2 days Alprazolam 0.5 mg + ibuprofen 400 mg Tramadol 37.5 mg + paracetamol 325 mg every 4 h for 3 days Duration: n.a. where not specified Comparison: placebo, codeine + paracetamol, each other	Santini, 2020 [45] Endod J No funding	5	266 18–68 y.o.	Vital and Non vital teeth Primary root canal therapy N. of sessions: n.a.	VAS Follow-up period for Ibuprofen (600 mg): 0, 1, 2, 3, 4, 6, 8 h Follow-up period for paracetamol + ibuprofen + caffeine, naproxen: 6, 12, 24 h Follow-up period for Ibuprofen (400 mg), alprazolam + ibuprofen Follow-up period for tramadol + paracetamol: 0, 6, 12, 24, 48, 72 h	Pain decreased in all groups over time Pain scores at 1 h: Reduction in pain scores in all groups ( <i>p</i> < 0.001) At 6, 12 and 24 h, pain was lower in the experimental groups than in the placebo ( <i>p</i> < 0.01) Pain scores at 4 h: Alprazolam + ibuprofen < other groups ( <i>p</i> < 0.0001) Ibuprofen/paracetamol < placebo ( <i>p</i> < 0.001) Pain scores at 6 h: Ibuprofen + alprazolam < Ibuprofen ( <i>p</i> = 0.018) and placebo ( <i>p</i> = 0.018) Pain scores at 8 h: Ibuprofen/paracetamol < placebo ( <i>p</i> < 0.001) Pain scores at 12 h: Ibuprofen + alprazolam < placebo ( <i>p</i> < 0.001)
NSAIDs and paracetamol Ibuprofen Meloxicam Piroxicam Diclofenac sodium Tramadol Novafen Naproxen Indomethacin	Shirvani, 2017 [46] J Oral Rehabil No funding	15	1060 >15 y.o.	Vital and Non-vital teeth Primary root canal therapy N. of sessions: single and multiple (2)	Method to assess/grade post-operative pain: n.a. Follow-up period: 0, 6, 12, 24 h	Pain scores immediately after the procedure: non-narcotic analgesics < placebo (MD of −0.50; 95% CI = −0.70,

Table 2. Cont.

Intervention Oral Medication Type Dosage Duration Comparison Placebo Others	Author, Year Reference [] Journal Funding	Trials <i>n</i>	Population N. F/M Age (y.o.)	Characteristics of the Non-Surgical Endodontic Treatment Received Vital and Non-Vital Teeth Primary Root Canal Ther- apy/Retreatment N. of Sessions	Method to Assess/Grade post-Operative Pain VAS Others Follow-Up Period	Outcome(s) Statistically Significant ( <i>p</i> < 0.05) Pain Reduction
Diclofenac sodium/Paracetamol Paracetamol/Ibuprofen Ibuprofen/Alprazolam Rofecoxib Etodolac Celecoxib Dosage: n.a. Duration: n.a. Comparison: placebo						<p>−0.30; <i>p</i> = 0.000)</p> <p>Pain scores at 6 h: non-narcotic analgesics &lt; placebo (MD of −0.76; 95%CI = −0.95, −0.56; <i>p</i> = 0.000)</p> <p>Pain scores at 12 h: non-narcotic analgesics &lt; placebo (MD of −1.15; 95% CI = −1.52, −0.78; <i>p</i> = 0.000)</p> <p>Pain scores at 24 h: non-narcotic analgesics &lt; placebo (MD of −0.65; 95% CI = −1.05, −0.26; <i>p</i> = 0.001)</p>

SAIDs = Steroidal anti-inflammatory drugs; NSAIDs = Non-steroidal anti-inflammatory drugs; n.a. = not available; VAS = Visual Analogue Scale; h = hours; MD = mean difference; EF = Effect size; CrI 95% = credible intervals, including with 95% probability that the treatment effect was evaluated in pairs in new trials.

No meta-analysis could be performed due to the high heterogeneity and incompleteness of the retrieved data.

### 3.3. Narrative Review: Study Screening Process and Included Studies

From literature research, a total of 127 articles were retrieved from MEDLINE/PubMed and six from the Cochrane Database of Systematic Reviews, and no duplicate elimination was necessary. After titles/abstract screening, 52 articles were removed because of not being pertinent. Full-text reading of potentially relevant articles was performed for 75 records, specifically 40 trials and observational studies, 24 systematic reviews (of whom 9 were with meta-analyses) and 11 narrative reviews. Finally, 22 systematic reviews with or without meta-analyses relevant to the topic and to the aim of providing clinical recommendations to control post-operative endodontic pain were obtained [5,22–41,49] along with 26 among trials, observational studies and reviews [7–12,14–21,50–62] that were compliant with the eligibility criteria.

## 4. Discussion

Several technical features and solutions [5,7–38] as well as systemic post-operative pharmacological therapies [4,6,40,41;46–48] have been proposed to control post-operative endodontic pain. Given the multi-factorial etiology of such a complication, a comprehensive approach, integrating both aspects, may be more effective and, therefore, recommended in the clinical management of post-operative endodontic pain. Accordingly, the current study presented an overview of systematic reviews of systematic reviews on oral medications post-operatively administered in subjects who completed either non-surgical endodontic initial treatment or retreatment, comparing them orally with each other and with a placebo, to note the most effective type and dosage for post-operative endodontic pain control and a narrative review, highlighting recent evidence on technical solutions to be observed during endodontic treatment procedures to control post-operative pain, in order to provide clinicians with integrated clinical recommendations for optimal post-operative endodontic pain management.

### 4.1. Oral Medications Post-Operatively Administered to Control Post-Operative Endodontic Pain

Previous systematic reviews have mostly analyzed single classes of oral medicaments, including steroidal (SAIDs) and non-steroidal anti-inflammatory drugs (NSAIDs), as well as opioid analgesics, not comparing one another and, thus, failing to provide conclusive results on the superiority of one over another approach. In addition, specific data regarding indications, timing and dosage of the post-operative endodontic oral medications prescription were often not clearly presented, thus not providing clinically relevant recommendations. Moreover, several reviews also evaluated antibiotics and pre-medications to control post-operative endodontic pain, which were both excluded from the present overview of systematic reviews of systematic reviews, because they contrasted with antibiotic stewardship standards proposed both by the American Dental Association [63] and the American Association of Endodontists [64] and with the attempt of avoiding polypharmacy [64], respectively, and they should, therefore, be considered not clinically advisable.

Systematic reviews reporting findings from subjects with cancer, osteonecrosis of the jaws or other systemic disorders possibly affecting pain perception or the efficacy of the investigated oral medications [65–68] were also not considered in the attempt to obtain generalizable data.

No data were retrieved differentiating vital from non-vital teeth, non-surgical initial endodontic treatment from retreatment and sessions number, neither in terms of post-operative endodontic pain incidence and severity nor management; thus, no specific recommendations could be formulated concerning pre-operative pulp conditions, the type of non-surgical endodontic treatment and single- vs. multiple-sessions procedures.

However, with regard to the type and dosage of post-operatively administered medications, steroidal anti-inflammatory drugs were shown to be effective in reducing pain intensity in the first 24 h after a primary root canal treatment. SAIDs' analgesic efficacy was shown to be potentially influenced by the type and dose of the drug; no significant difference was nonetheless reported between dexamethasone (4 mg) and betamethasone (2 mg) [31].

Nonsteroidal anti-inflammatory drugs were the most common oral medicaments post-operatively administered to control pain, with ibuprofen being the most prescribed and investigated. Ibuprofen (600 mg) alone and ibuprofen (600 mg) combined with acetaminophen (1000 mg) were reported to be significantly more effective in post-operative endodontic pain control when administered 6 h after endodontic treatment and may be, therefore, recommended as a first-choice treatment in the first hours following non-surgical endodontic treatment. In addition, emerging data support the evidence that ketoprofen (50 mg) as well as naproxen (500 mg) might be even more effective than ibuprofen (600 mg) alone 6 h post-operatively [47]. However, only low to moderate evidence supports such a recommendation [48]. Moreover, multiple-dose regimens seemed to be

more effective in pain control compared to single-dose, although no definite protocols were proposed [45].

The main limitation of this overview of systematic reviews of systematic reviews is the small number of included studies, ascribable to the restricted eligibility criteria, fitting the PICO-focused question. Other limitations include variability in post-operative endodontic pain assessment time points, excluding the possibility to quantitatively synthesize and compare the results from the included studies; a lack of information regarding indications and, especially, duration of the oral pharmacological therapies, perpetuating the empirical approach to oral drugs prescription to control post-operative endodontic pain and significant heterogeneity of the included systematic reviews, principally concerning the type and dosage of the post-operatively administered oral medications, which may not all be available at the same concentrations and combinations worldwide, thus reducing conclusions' generalizability.

However, to the authors' knowledge, this study was the first summarizing findings from systematic reviews of RCTs on different classes of oral drugs prescribed to control post-operative endodontic pain all together. In addition, the presented overview of systematic reviews of systematic reviews did not consider either pre-operatively administered oral medications or combined antibiotic prescriptions in the attempt to highlight the shorter therapy duration, thus excluding pre-medications, and to avoid unnecessary antibiotic treatment to control post-operative endodontic pain. Moreover, we aimed to identify the most effective type and dosage of post-operatively administered medications, not only limiting, at the most, therapy duration and complying with accepted standards for antibiotic stewardship, but also taking into account polypharmacy, which is especially relevant for patients' comorbidity and specific conditions [48,69–74]. In such a perspective, the correct pharmacological strategy should also reduce patients' concerns, on the one side, and optimize practitioners' time and efforts, on the other side, thus decreasing endodontic complications and emergencies, which may potentially require additional operative sessions, which should be even more avoided in the ongoing context of COVID-19 [75–79].

#### *4.2. Evidence-Based Clinical Recommendations for Post-Operative Endodontic Pain Management*

Pain following endodontic treatment may be secondary to anatomical factors, such as apical foramen position, pulp tissue localization in areas where it cannot be removed without proper care and root canals that can be omitted without instrumentation, as well as to technical factors affecting or occurring during the procedure, such as an inaccurate determination of the working length. The last could, in turn, lead to excessive instrumentation, with extrusion of root canal debris beyond the apical foramen during instrumentation, an extension of the filling beyond the apex and an incorrect use of irrigants, specifically sodium hypochlorite and hydrogen peroxide, potentially causing iatrogenic periapical discomfort [50,51]. Mechanical and chemical damages to the periapical tissues would also determine an inflammatory reaction that causes pain. The severity of the pain has been reported to be dependent on several aspects, including the intensity of the injury, the intensity of the tissue damage and the inflammatory response's intensity. The mechanical irritation that causes periapical inflammation includes over-instrumentation, irritants and drugs over the apical foramen and excessively extensive filling materials. Furthermore, the greater the amount of overextended material, the greater is the intensity of damage to the periapical tissues [62].

Pain after root canal treatment is a serious health problem that affects the quality of life in the short term and, sometimes, even in the long term. Root canal treatment is generally very effective in relieving tooth pain [50,52,53] when correctly performed. However, it has been reported that one in five patients, on average, receiving root canal treatment will experience a serious disturbance in their daily life due to post-operative endodontic pain [50] and that up to 10% of patients may refer to persistent pain until six months after endodontic treatment [51]. Indeed, endodontic therapy does not rely on biological consequences solely, but also on minimizing patient discomfort. The success of endodontic

treatments is based on eliminating microbes from the root canal and on creating a local environment favoring healing, by performing appropriate shaping, 3D cleaning and, finally, a 3D obturation [5,7–30,54,55].

Silva et al. compared rotary instruments with hand files and concluded that a lower incidence of post-operative pain was recorded when rotary systems were employed [56]. Furthermore, these authors highlighted that rotary systems may reduce the overall risk of complications throughout the procedure, favoring both less debris formation and bacteria extrusion [56].

Based on the evidence, no significant differences in post-operative endodontic pain incidence, severity or control capability were reported for a single session when compared to multiple sessions endodontics [57,58]. However, numerous studies have also reported inter-appointment pain, putatively secondary to the imbalance in the host–bacteria relationship, induced by intra-canal procedures [5]. In such particular circumstances, pain may be due to the pathogenic effect of specific bacteria, such as *Porphyromonas Endodontalis*, *Porphyromonas Gingivalis* and *Prevotella species*, as proposed by various studies [59–61], or it may be linked to an individual's host resistance [60]; it has been hypothesized that subjects who have a lesser ability to cope with infections may be more prone to develop clinical symptoms after endodontic procedures in infected root canals. Calcium hydroxide is considered an optimum root canal medication against microbes in multiple sessions treatments; such intra-canal medicaments have been found to be able to reduce the periapical infection, both decreasing the total count of those microbes present in the root canals and retarding the growth of new pathogens [49]. In addition to intracanal medications, several methods have been proposed to control pain occurring during endodontic treatment and resulting from inter-appointment exacerbations, comprising re-instrumentation, chirurgical incision, abscess drainage, occlusal reduction and systemically delivered medications [62].

Given that post-operative pain is very common and highly unpreventable [47], patients should always be advised that pain may be felt after the procedure, and considering the multi-factorial etio-pathogenesis of post-operative endodontic pain, practitioners should always steer clear of iatrogenic injury. Indeed, dentists should respect the working length during shaping, cleaning and obturation, both during root canal treatment and retreatment, accomplishing a correct access cavity to find all the root canals, using a crown down technique and respecting the apical third, avoiding debris, irrigants, gutta-percha and sealer extrusion over the apex and, finally, performing a correct obturation.

## 5. Conclusions

Post-operative endodontic pain remains still often undervalued, although it may lead, if not correctly managed, to both local and central sensitization, with pain chronicization [80–83].

For effective endodontic pain management, the causative factors and treatment methods discussed above should be given due consideration to help the patient get rid of the unpleasant feeling of pain.

Therefore, patients should always be advised that pain may be felt after the procedure, and practitioners should, beyond correctly identifying odontogenic pain, diagnose its causes and, if possible, adapt clinical procedures according to the evidence-based findings. Moreover, the described clinical protocols, optimizing post-operative endodontic pain control, should be integrated with the presented recommendations on post-operatively administered oral medicaments, proposing the use of ibuprofen (600 mg) alone and combined with acetaminophen (1000 mg) as a first choice treatment, or ketoprofen (50 mg) as well as naproxen (500 mg) 6 h post-operatively [47], also in the perspective of minimizing drug intake, as it may be especially relevant in fragile and elderly subjects.

**Author Contributions:** Conceptualization, F.D.S., R.F. and F.G.; methodology, D.R. and A.A.; validation, R.F. and F.G.; investigation, F.D.S. and G.S.; data curation, R.F. and F.G.; writing—original draft preparation, F.D.S. and G.S.; writing—review and editing, F.D.S., G.S. and D.R.; supervision, A.A. All authors have read and agreed to the published version of the manuscript.

**Funding:** No external funding.

**Institutional Review Board Statement:** Not applicable.

**Informed Consent Statement:** Not applicable.

**Data Availability Statement:** Medline (PubMed) and Scopus databases.

**Conflicts of Interest:** The authors declare no conflict of interest.

## References

- Rosenberg, P.A. Clinical strategies for managing endodontic pain. *Endod. Top.* **2002**, *3*, 78–92. [[CrossRef](#)]
- Guevara Perez, S.V.; de la Rosa Castolo, G.; Thollon, L.; Behr, M. A 3D characterization method of geometric variation in edentulous mandibles. *Morphologie* **2018**, *102*, 255–262. [[CrossRef](#)] [[PubMed](#)]
- Iqbal, A. The Factors Responsible for Endodontic Treatment Failure in the Permanent Dentitions of the Patients Reported to the College of Dentistry, the University of Aljouf, Kingdom of Saudi Arabia. *J. Clin. Diagn. Res.* **2016**, *10*, 146–148. [[CrossRef](#)] [[PubMed](#)]
- Gotler, M.; Bar-Gil, B.; Ashkenazi, M. Postoperative Pain after Root Canal Treatment: A Prospective Cohort Study. *Int. J. Dent.* **2012**, *2012*, 310467. [[CrossRef](#)]
- Sathorn, C.; Parashos, P.; Messer, H. The prevalence of postoperative pain and flare-up in single- and multiple-visit endodontic treatment: A systematic review. *Int. Endod. J.* **2008**, *41*, 91–99. [[CrossRef](#)]
- Iranmanesh, F.; Parirokh, M.; Haghdoost, A.A.; Abbott, P.V. Effect of Corticosteroids on Pain Relief Following Root Canal Treatment: A Systematic Review. *Iran. Endod. J.* **2017**, *12*, 123–130. [[CrossRef](#)]
- Amato, M.; Pantaleo, G.; Abdellatif, D.; Blasi, A.; Gagliani, M.; Iandolo, A. An in vitro evaluation of the degree of pulp tissue dissolution through different root canal irrigation protocols. *J. Conserv. Dent.* **2018**, *21*, 175–179. [[CrossRef](#)]
- Iandolo, A.; Abdellatif, D.; Amato, M.; Pantaleo, G.; Blasi, A.; Franco, V.; Mds, P.N. Dentinal tubule penetration and root canal cleanliness following ultrasonic activation of intracanal-heated sodium hypochlorite. *Aust. Endod. J.* **2020**, *46*, 204–209. [[CrossRef](#)]
- Iandolo, A.; Amato, M.; Dagna, A.; Poggio, C.; Abdellatif, D.; Franco, V.; Pantaleo, G. Intracanal heating of sodium hypochlorite: Scanning electron microscope evaluation of root canal walls. *J. Conserv. Dent.* **2018**, *21*, 569–573. [[CrossRef](#)]
- Iandolo, A.; Pantaleo, G.; Malvano, M.; Simeone, M.; Amato, M. Nonsurgical management of complex endodontic cases with several periapical lesions: A case series. *G. Ital. Endod.* **2016**, *30*, 101–103. [[CrossRef](#)]
- Iandolo, A.; Simeone, M.; Riccitiello, F. The preparation of coronal isthmus is a fundamental step for long term success. *G. Ital. Endod.* **2012**, *26*, 150–154. [[CrossRef](#)]
- Iandolo, A.; Dagna, A.; Poggio, C.; Capar, I.; Amato, A.; Abdellatif, D. Evaluation of the actual chlorine concentration and the required time for pulp dissolution using different sodium hypochlorite irrigating solutions. *J. Conserv. Dent.* **2019**, *22*, 108–113. [[CrossRef](#)] [[PubMed](#)]
- Iandolo, A.; Ametrano, G.; Amato, M.; Rengo, S.; Simeone, M. IG-File: A novel tool to improve root canal cleaning and measurement of the apical foramen. *G. Ital. Endod.* **2011**, *25*, 72–81. [[CrossRef](#)]
- Di Lorenzo, P.; Niola, M.; Buccelli, C.; Re, D.; Cortese, A.; Pantaleo, G.; Amato, M. Professional responsibility in dentistry: Analysis of an interdepartmental case study. *Dent. Cadmos* **2015**, *83*, 324–3405. [[CrossRef](#)]
- Amato, M.; Iandolo, A.; Pantaleo, G.; Abdellatif, D.; Simeone, M.; Lizio, A.; Giudice, R.L.; Giudice, G.L. The IG- file use to Gauge the Apical Diameter in Endodontics: An In Vitro Study. *Open Dent. J.* **2018**, *12*, 638–646. [[CrossRef](#)]
- Iandolo, A.; Simeone, M.; Orefice, S.; Rengo, S. 3D cleaning, a perfected technique: Thermal profile assessment of heated NaOCl. *G. Ital. Endod.* **2017**, *31*, 58–61. [[CrossRef](#)]
- Iandolo, A.; Abdellatif, D.; Pantaleo, G.; Sammartino, P.; Amato, A. Conservative shaping combined with three-dimensional cleaning can be a powerful tool: Case series. *J. Conserv. Dent.* **2020**, *23*, 648–652. [[CrossRef](#)]
- Rengo, C.; Spagnuolo, G.; Ametrano, G.; Goracci, C.; Nappo, A.; Rengo, S.; Ferrari, M. Marginal leakage of bulk fill composites in Class II restorations: A microCT and digital microscope analysis. *Int. J. Adhes. Adhes.* **2015**, *60*, 123–129. [[CrossRef](#)]
- Iandolo, A.; Amato, A.; Martina, S.; Abdellatif, D.; Pantaleo, G. Management of severe curvatures in root canal treatment with the new generation of rotating files using a safe and predictable protocol. *Open Dent. J.* **2020**, *14*, 421–425. [[CrossRef](#)]
- Amato, M.; Pantaleo, G.; Abdellatif, D.; Blasi, A.; Lo Giudice, R.; Iandolo, A. Evaluation of cyclic fatigue resistance of modern Nickel-Titanium rotary instruments with continuous rotation. *G. Ital. Endod.* **2017**, *31*, 78–82. [[CrossRef](#)]
- Iandolo, A.; Abdellatif, D.; Barbosa, A.F.A.; Scelza, G.; Gasparro, R.; Sammartino, P.; Silva, E.J.N.L. Confocal laser scanning microscopy evaluation of roots subjected to activation protocol in endodontic microsurgery. *Aust. Endod. J.* **2021**. [[CrossRef](#)]
- RahbaniNobar, B.; Dianat, O.; RahbaniNobar, B.; Shirvani, A.; Zargar, N.; Kazem, M.; Tordik, P. Effect of Rotary and Reciprocating Instrumentation Motions on Postoperative Pain Incidence in Non-Surgical Endodontic Treatments: A Systematic Review and Meta-Analysis. *Eur. Endod. J.* **2021**, *6*, 3–14. [[CrossRef](#)]
- Susila, A.; Minu, J. Activated Irrigation vs. Conventional non-activated Irrigation in Endodontics—A Systematic Review. *Eur. Endod. J.* **2019**, *4*, 96–110. [[CrossRef](#)] [[PubMed](#)]

24. Martins, C.M.; da Silva Machado, N.E.; Giopatto, B.V.; de Souza Batista, V.E.; Marsicano, J.A.; Mori, G.G. Post-operative pain after using sodium hypochlorite and chlorhexidine as irrigation solutions in endodontics: Systematic review and meta-analysis of randomised clinical trials. *Indian J. Dent. Res.* **2020**, *31*, 774–781. [[CrossRef](#)] [[PubMed](#)]
25. Anjaneyulu, K.; Nivedhitha, M.S. Influence of calcium hydroxide on the post-treatment pain in Endodontics: A systematic review. *J. Conserv. Dent.* **2014**, *17*, 200–207. [[CrossRef](#)]
26. Sun, C.; Sun, J.; Tan, M.; Hu, B.; Gao, X.; Song, J. Pain after root canal treatment with different instruments: A systematic review and meta-analysis. *Oral Dis.* **2018**, *24*, 908–919. [[CrossRef](#)]
27. Yaylali, I.E.; Demirci, G.K.; Kurnaz, S.; Celik, G.; Kaya, B.U.; Tunca, Y.M. Does Maintaining Apical Patency during Instrumentation Increase Postoperative Pain or Flare-up Rate after Nonsurgical Root Canal Treatment? A Systematic Review of Randomized Controlled Trials. *J. Endod.* **2018**, *44*, 1228–1236. [[CrossRef](#)]
28. Nunes, G.P.; Delbem, A.C.B.; Gomes, J.M.L.; Lemos, C.A.A.; Pellizzer, E.P. Postoperative pain in endodontic retreatment of one visit versus multiple visits: A systematic review and meta-analysis of randomized controlled trials. *Clin. Oral Investig.* **2021**, *25*, 455–468. [[CrossRef](#)]
29. Ibrahim, A.M.; Zakhary, S.Y.; Amin, S.A.W. Calcium hydroxide intracanal medication effects on pain and flare-up: A systematic review and meta-analysis. *Restor. Dent. Endod.* **2020**, *45*, e26. [[CrossRef](#)]
30. Martins, C.M.; De Souza Batista, V.E.; Andolfatto Souza, A.C.; Andrada, A.C.; Mori, G.G.; Gomes Filho, J.E. Reciprocating kinematics leads to lower incidences of postoperative pain than rotary kinematics after endodontic treatment: A systematic review and meta-analysis of randomized controlled trial. *J. Conserv. Dent.* **2019**, *22*, 320–331. [[CrossRef](#)]
31. Shamszadeh, S.; Shirvani, A.; Asgary, S. Does occlusal reduction reduce post-operative endodontic pain? A systematic review and meta-analysis. *J. Oral Rehabil.* **2020**, *47*, 528–535. [[CrossRef](#)]
32. Chagas Carvalho Alves, N.; RaianeMamede Veloso, S.; de Andrade Silva, S.; de Almeida, A.C.; Tavares VelozoTelles, C.; Romeiro, K.; Monteiro, G.Q.D.M.; de Albuquerque, D.S. Influence of occlusal reduction on pain after endodontic treatment: A systematic review and meta-analysis. *Sci. Rep.* **2021**, *11*, 14019. [[CrossRef](#)] [[PubMed](#)]
33. Lauritano, D.; Moreo, G.; Carinci, F.; Della Vella, F.; Di Spirito, F.; Sbordone, L.; Petruzzi, M. Cleaning efficacy of the XP-Endo<sup>®</sup> Finisher instrument compared to other irrigation activation procedures: A systematic review. *Appl. Sci.* **2019**, *9*, 5001. [[CrossRef](#)]
34. Chen, Y.; Chen, X.L.; Zou, X.L.; Chen, S.Z.; Zou, J.; Wang, Y. Efficacy of low-level laser therapy in pain management after root canal treatment or retreatment: A systematic review. *Lasers Med. Sci.* **2019**, *34*, 1305–1316. [[CrossRef](#)] [[PubMed](#)]
35. Guerreiro, M.Y.R.; Monteiro, L.P.B.; de Castro, R.F.; Magno, M.B.; Maia, L.C.; da Silva Brandão, J.M. Effect of low-level laser therapy on postoperative endodontic pain: An updated systematic review. *Complement. Ther. Med.* **2021**, *57*, 102638. [[CrossRef](#)] [[PubMed](#)]
36. Gupta, A.; Aggarwal, V.; Gurawa, A.; Mehta, N.; Abraham, D.; Singh, A.; Jala, S.; Chauhan, N. Effect of intracanal cryotherapy on postendodontic pain: A systematic review and meta-analysis of randomized controlled trials. *J. Dent. Anesth. Pain Med.* **2021**, *21*, 15–27. [[CrossRef](#)]
37. Sadaf, D.; Ahmad, M.Z.; Onakpoya, I.J. Effectiveness of Intracanal Cryotherapy in Root Canal Therapy: A Systematic Review and Meta-analysis of Randomized Clinical Trials. *J. Endod.* **2020**, *46*, 1811–1823. [[CrossRef](#)]
38. Monteiro, L.P.B.; Guerreiro, M.Y.R.; de Castro Valino, R.; Magno, M.B.; Maia, L.C.; da Silva Brandão, J.M. Effect of intracanal cryotherapy application on postoperative endodontic pain: A systematic review and metaanalysis. *Clin. Oral Investig.* **2021**, *25*, 23–35. [[CrossRef](#)]
39. Alonaizan, F.A.; Alfawaz, Y.F. Is phototherapy effective in the management of post-operative endodontic pain? A systematic review of randomized controlled clinical trials. *Photodiagnosis Photodyn. Ther.* **2019**, *26*, 53–58. [[CrossRef](#)]
40. Nagendrababu, V.; Gutmann, J.L. Factors associated with postobturation pain following single-visit nonsurgical root canal treatment: A systematic review. *Quintessence Int.* **2017**, *48*, 193–208. [[CrossRef](#)]
41. AlRahabi, M.K. Predictors, prevention, and management of postoperative pain associated with nonsurgical root canal treatment: A systematic review. *J. Taibah. Univ. Med. Sci.* **2017**, *12*, 376–384. [[CrossRef](#)] [[PubMed](#)]
42. Moher, D.; Shamseer, L.; Clarke, M.; Ghersi, D.; Liberati, A.; Petticrew, M.; Shekelle, P.; Stewart, L.A.; PRISMA-P Group. Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015 statement. *Syst. Rev.* **2015**, *4*, 1. [[CrossRef](#)] [[PubMed](#)]
43. Shea, B.J.; Reeves, B.C.; Wells, G.; Thuku, M.; Hamel, C.; Moran, J.; Moher, D.; Tugwell, P.; Welch, V.; Kristjansson, E.; et al. AMSTAR 2: A critical appraisal tool for systematic reviews that include randomised or non-randomised studies of healthcare interventions, or both. *BMJ* **2017**, *358*, j4008. [[CrossRef](#)] [[PubMed](#)]
44. Richardson, W.S.; Wilson, M.C.; Nishikawa, J.; Hayward, R.S. The well-built clinical question: A key to evidence-based decisions. *ACP J. Club* **1995**, *123*, 12–13. [[CrossRef](#)]
45. Santini, M.; Da Rosa, R.A.; Ferreira, M.B.; Barletta, F.; Longo do Nascimento, A.; Weissheimer, T.; Estrela, C.; So, M.V. Medications Used for Prevention and Treatment of Postoperative Endodontic Pain: A Systematic Review. *Eur. Endod. J.* **2021**, *6*, 15–24. [[CrossRef](#)]
46. Shirvani, A.; Shamszadeh, S.; Eghbal, M.J.; Asgary, S. The efficacy of non-narcotic analgesics on post-operative endodontic pain: A systematic review and meta-analysis: The efficacy of non-steroidal anti-inflammatory drugs and/or paracetamol on post-operative endodontic pain. *J. Oral Rehabil.* **2017**, *44*, 709–721. [[CrossRef](#)]

47. Smith, E.A.; Marshall, J.G.; Selph, S.S.; Barker, D.R.; Sedgley, C.M. Nonsteroidal Anti-inflammatory Drugs for Managing Postoperative Endodontic Pain in Patients Who Present with Preoperative Pain: A Systematic Review and Meta-analysis. *J. Endod.* **2017**, *43*, 7–15. [[CrossRef](#)]
48. Zanjir, M.; Sgro, A.; Lighvan, N.L.; Yarascavitch, C.; Shah, P.S.; da Costa, B.R.; Azarpazhooh, A. Efficacy and Safety of Postoperative Medications in Reducing Pain after Nonsurgical Endodontic Treatment: A Systematic Review and Network Meta-analysis. *J. Endod.* **2020**, *46*, 1387–1402.e4. [[CrossRef](#)]
49. Wong, A.W.; Zhang, C.; Chu, C.H. A systematic review of nonsurgical single-visit versus multiple-visit endodontic treatment. *Clin. Cosmet. Investig. Dent.* **2014**, *6*, 45–56. [[CrossRef](#)]
50. Law, A.S.; Nixdorf, D.R.; Aguirre, A.M.; Reams, G.J.; Tortomasi, A.J.; Manne, B.D.; Harris, D. Predicting severe pain after root canal therapy in the National Dental PBRN. *J. Dent. Res.* **2015**, *94*, 37–43. [[CrossRef](#)]
51. Nixdorf, D.R.; Law, A.S.; Lindquist, K.; Reams, G.J.; Cole, E.; Kanter, K.; Nguyen, R.H.; Harris, D.R. Frequency, impact, and predictors of persistent pain after root canal treatment: A national dental PBRN study. *Pain* **2016**, *157*, 159–165. [[CrossRef](#)] [[PubMed](#)]
52. Law, A.S.; Nixdorf, D.R.; Rabinowitz, I.; Reams, G.J.; Smith, J.A., Jr.; Torres, A.V.; Harris, D.R. Root canal therapy reduces multiple dimensions of pain: A national dental practice-based research network study. *J. Endod.* **2014**, *40*, 1738–1745. [[CrossRef](#)] [[PubMed](#)]
53. Pak, J.G.; White, S.N. Pain prevalence and severity before, during, and after root canal treatment: A systematic review. *J. Endod.* **2011**, *37*, 429–438. [[CrossRef](#)] [[PubMed](#)]
54. Uzunoglu-Özyürek, E.; KüçükayaEren, S.; Karahan, S. Effect of root canal sealers on the fracture resistance of endodontically treated teeth: A systematic review of in vitro studies. *Clin. Oral Investig.* **2018**, *22*, 2475–2485. [[CrossRef](#)] [[PubMed](#)]
55. Iandolo, A.; Iandolo, G.; Malvano, M.; Pantaleo, G.; Simeone, M. Modern Technologies in Endodontics. *G. Ital. Endod.* **2016**, *30*, 2–9. [[CrossRef](#)]
56. Silva, E.J.; Carapiá, M.F.; Lopes, R.M.; Belladonna, F.G.; Senna, P.M.; Souza, E.M.; De-Deus, G. Comparison of apically extruded debris after large apical preparations by full-sequence rotary and single-file reciprocating systems. *Int. Endod. J.* **2016**, *49*, 700–705. [[CrossRef](#)]
57. Wong, A.W.; Zhang, S.; Zhang, C.F.; Chu, C.H. Perceptions of single-visit and multiple-visit endodontic treatment: A survey of endodontic specialists and general dentists in Hong Kong. *J. Investig. Clin. Dent.* **2016**, *7*, 263–271. [[CrossRef](#)]
58. Fleming, C.H.; Litaker, M.S.; Alley, L.W.; Eleazer, P.D. Comparison of classic endodontic techniques versus contemporary techniques on endodontic treatment success. *J. Endod.* **2010**, *36*, 414–418. [[CrossRef](#)]
59. Siqueira, J.F., Jr.; Rôças, I.N.; Souto, R.; Uzeda, M.; Colombo, A.P. Microbiological evaluation of acute periradicular abscesses by DNA-DNA hybridization. *Oral Surg. Oral Med. Oral Pathol. Oral Radiol. Endod.* **2001**, *92*, 451–457. [[CrossRef](#)]
60. Rôças, I.N.; Siqueira, J.F., Jr.; Andrade, A.F.; Uzeda, M. Oral treponemes in primary root canal infections as detected by nested PCR. *Int. Endod. J.* **2003**, *36*, 20–26. [[CrossRef](#)]
61. Jacinto, R.C.; Gomes, B.P.; Ferraz, C.C.; Zaia, A.A.; Filho, F.J. Microbiological analysis of infected root canals from symptomatic and asymptomatic teeth with periapical periodontitis and the antimicrobial susceptibility of some isolated anaerobic bacteria. *Oral Microbiol. Immunol.* **2003**, *18*, 285–292. [[CrossRef](#)]
62. Jayakodi, H.; Kailasam, S.; Kumaravadivel, K.; Thangavelu, B.; Mathew, S. Clinical and pharmacological management of endodontic flare-up. *J. Pharm. Bioallied. Sci.* **2012**, *4*, 294–298. [[CrossRef](#)] [[PubMed](#)]
63. Lockhart, P.B.; Tampi, M.P.; Abt, E.; Aminoshariae, A.; Durkin, M.J.; Fouad, A.F.; Gopal, P.; Hatten, B.W.; Kennedy, E.; Lang, M.S.; et al. Evidence-based clinical practice guideline on antibiotic use for the urgent management of pulpal- and periapical-related dental pain and intraoral swelling: A report from the American Dental Association. *J. Am. Dent. Assoc.* **2019**, *150*, 906–921. [[CrossRef](#)] [[PubMed](#)]
64. Fouad, A.F.; Byrne, B.E.; Diogenes, A.R.; Sedgley, C.M.; Cha, B.Y. AAE Guidance on the Use of Systemic Antibiotics in Endodontics, AAE Position Statement. 2017. Available online: [www.aae.org/specialty/wp-content/uploads/sites/2/2017/06/aae\\_systemic-antibiotics.pdf](http://www.aae.org/specialty/wp-content/uploads/sites/2/2017/06/aae_systemic-antibiotics.pdf) (accessed on 29 September 2021).
65. Varghese, D.; Ishida, C.; HaseerKoya, H. Polypharmacy. In *StatPearls [Internet]*; StatPearls Publishing: Treasure Island, FL, USA, 2021.
66. Huang, Y.F.; Muo, C.H.; Tsai, C.H.; Liu, S.P.; Chang, C.T. The association with xerostomia from sialadenitis and the jaw osteonecrosis in head and neck cancer population: A nationwide cohort study. *Clin. Oral Investig.* **2019**, *23*, 585–593. [[CrossRef](#)] [[PubMed](#)]
67. Lungu, A.E.; Lazar, M.A.; Tonea, A.; Rotaru, H.; Roman, R.C.; Badea, M.E. Observational study of the bisphosphonate-related osteonecrosis of jaws. *Chujul. Med.* **2018**, *91*, 209–215. [[CrossRef](#)] [[PubMed](#)]
68. Di Spirito, F.; Argentino, S.; Martuscelli, R.; Sbordone, L. MRONJ incidence after multiple teeth extractions in patients taking oral bisphosphonates without “drug holiday”: A retrospective chart review. *Oral Implantol.* **2019**, *12*, 105–110.
69. He, X.; Tian, Y.; Guo, L.; Ano, T.; Lux, R.; Zusman, D.R.; Shi, W. In vitro communities derived from oral and gut microbial floras inhibit the growth of bacteria of foreign origins. *Microb. Ecol.* **2010**, *60*, 665–676. [[CrossRef](#)]
70. Guerrini, L.; Monaco, A.; Pietropaoli, D.; Ortu, E.; Giannoni, M.; Marci, M.C. Antibiotics in Dentistry: A Narrative Review of Literature and Guidelines Considering Antibiotic Resistance. *Open Dent. J.* **2019**, *13*, 383–398. [[CrossRef](#)]
71. Barone, A.; Chatelain, S.; Derchi, G.; Di Spirito, F.; Martuscelli, R.; Porzio, M.; Sbordone, L. Effectiveness of antibiotics in preventing alveolitis after erupted tooth extraction: A retrospective study. *Oral Dis.* **2020**, *26*, 967–973. [[CrossRef](#)]



72. Iannelli, A.; Favre, G.; Frey, S.; Esnault, V.; Gugenheim, J.; Bouam, S.; Schiavo, L.; Tran, A.; Alifano, M. Obesity and COVID-19: ACE 2, the Missing Tile. *Obes. Surg.* **2020**, *30*, 4615–4617. [[CrossRef](#)]
73. Kim, K.; Choi, S.; Chang, J.; Kim, S.M.; Kim, S.J.; Kim, R.J.; Cho, H.-J.; Park, S.M. Severity of dental caries and risk of coronary heart disease in middle-aged men and women: A population-based cohort study of Korean adults, 2002–2013. *Sci. Rep.* **2019**, *9*, 10491. [[CrossRef](#)] [[PubMed](#)]
74. Zannella, C.; Shinde, S.; Vitiello, M.; Falanga, A.; Galdiero, E.; Fahmi, A. Antibacterial activity of indolicidin-coated silver nanoparticles in oral disease. *Appl. Sci.* **2020**, *10*, 1837. [[CrossRef](#)]
75. Azim, A.A.; Shabbir, J.; Khurshid, Z.; Zafar, M.S.; Ghabbani, H.M.; Dummer, P.M.H. Clinical endodontic management during the COVID-19 pandemic: A literature review and clinical recommendations. *Int. Endod. J.* **2020**, *53*, 1461–1471. [[CrossRef](#)] [[PubMed](#)]
76. Nosrat, A.; Dianat, O.; Verma, P.; Yu, P.; Wu, D.; Fouad, A.F. Endodontics specialists' practice during the initial outbreak of COVID-19. *J. Endod.* **2021**, *48*, 102–108. [[CrossRef](#)]
77. Martina, S.; Amato, A.; Rongo, R.; Caggiano, M.; Amato, M. The Perception of COVID-19 among Italian Dentists: An Orthodontic Point of View. *Int. J. Environ. Res. Public Health* **2020**, *17*, 4384. [[CrossRef](#)]
78. Marinaci, T.; Carpinelli, L.; Venuleo, C.; Savarese, G.; Cavallo, P. Emotional distress, psychosomatic symptoms and their relationship with institutional responses: A survey of Italian frontline medical staff during the COVID-19 pandemic. *Heliyon* **2020**, *6*, e05766. [[CrossRef](#)]
79. Gasparro, R.; Scandurra, C.; Maldonato, N.M.; Dolce, P.; Bochicchio, V.; Valletta, A. Perceived job insecurity and depressive symptoms among Italian dentists: The moderating role of fear of COVID-19. *Int. J. Environ. Res. Public Health* **2020**, *17*, 1–12. [[CrossRef](#)]
80. Al-Sabbagh, M.; Okeson, J.P.; Bertoli, E.; Medynski, D.C.; Khalaf, M.W. Persistent pain and neurosensory disturbance after dental implant surgery: Prevention and treatment. *Dent. Clin. N. Am.* **2015**, *59*, 143–156. [[CrossRef](#)]
81. Ehsani, M.; Moghadamnia, A.A.; Zahedpasha, S.; Maliji, G.; Haghani, S.; Mir, S.M.; Kani, N.M. The role of prophylactic ibuprofen and N-acetylcysteine on the level of cytokines in periapical exudates and the post-treatment pain. *Daru* **2012**, *20*, 30. [[CrossRef](#)]
82. Dalewski, B.; Kamińska, A.; Szydłowski, M.; Kozak, M.; Sobolewska, E. Comparison of Early Effectiveness of Three Different Intervention Methods in Patients with Chronic Orofacial Pain: A Randomized, Controlled Clinical Trial. *Pain Res. Manag.* **2019**, *2019*, 7954291. [[CrossRef](#)]
83. Pigg, M.; Nixdorf, D.R.; Law, A.S.; Renton, T.; Sharav, Y.; Baad-Hansen, L.; List, T. New International Classification of Orofacial Pain: What Is in It for Endodontists? *J. Endod.* **2021**, *47*, 345–357. [[CrossRef](#)] [[PubMed](#)]