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Association of apical maturity with clinical and biological outcomes after regenerative endodontic procedures: a systematic review, meta-analysis, dose–response meta-analysis and trial sequential analysis

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ADMINISTRATIVE INFORMATION

Support - No external funding was received for this review. This systematic review was conducted independently without financial support from any pharmaceutical company or funding body.

Review Stage at time of this submission - Completed but not published.

Conflicts of interest - The authors declare no conflicts of interest. This systematic review and model-based meta-analysis was conducted independently without any financial or non-financial relationship with the manufacturer of tapentadol (Grunenthal GmbH / Janssen Pharmaceuticals) or any other pharmaceutical company. No funding was received from industry sources.

INPLASY registration number: INPLASY202640006

Amendments - This protocol was registered with the International Platform of Registered Systematic Review and Meta-Analysis Protocols (INPLASY) on 2 April 2026 and was last updated on 2 April 2026.

INTRODUCTION

Review question / Objective In adults with acute or chronic pain, does tapentadol immediate-release (IR) produce significantly greater placebo-corrected numerical rating scale (NRS) pain reduction compared with tapentadol prolonged-release (PR)?
PICOS framework:
P (Population): Adults aged ≥18 years with moderate-
to-severe acute or chronic pain.
I (Intervention): Oral tapentadol IR (50–100 mg q4–6h)
or tapentadol PR/SR (50–250 mg bid).
C (Comparator): Placebo (primary); oxycodone IR/CR
(secondary, sensitivity analysis only).
O (Outcomes): Primary: placebo-corrected NRS pain
reduction (MCID ≥2.0 points). Secondary: NNT for ≥50% pain relief; nausea incidence; dose-response
(sigmoidal Emax model); Therapeutic Index.
S (Study design): Randomised controlled trials (RCTs),
double-blind, parallel-group or crossover.

Secondary objectives:
1. Characterise sigmoidal Emax dose-response for each formulation and identify analgesic plateau dose.
2. Calculate NNT from confirmed responder data.
3. Mechanistically interpret efficacy and tolerability differences via PK parameters (Cmax, Tmax).
4. Quantify heterogeneity and identify sources via subgroup analysis and meta-regression.

5. Assess publication bias and robustness via sensitivity analysis.

Rationale Tapentadol received FDA approval in 2008 (IR) and 2011 (PR), with EMA approval as Palexia. Despite over a decade of clinical use and multiple published RCTs, no quantitative model-based synthesis has simultaneously characterised both formulations using a pharmacokinetic/pharmacodynamic (PK/PD) framework.

Three knowledge gaps justify this review:

First, existing systematic reviews of tapentadol are descriptive and do not model dose-response relationships or integrate PK mechanistic context to explain formulation differences.

Second, the distinct PK profiles of IR (high Cmax ~18-30 ng/mL, rapid Tmax ~1.25 h) versus PR (lower Cmax ~8-15 ng/mL, sustained Tmax ~4.0 h) are hypothesised to mechanistically explain both greater acute analgesic effect of IR and its higher nausea incidence, but this has not been quantitatively demonstrated across all RCTs simultaneously.

Third, regulatory model-informed drug development (MIDD) frameworks increasingly require quantitative dose-response characterisation for analgesic agents.

This MBMA provides the first quantitative, PK-informed comparison of tapentadol IR and PR across all published RCTs, generating NNT estimates from confirmed responder data and mechanistically explaining nausea differences via Cmax comparison.

Condition being studied This review examines two distinct pain domains:

Acute pain: moderate-to-severe post-surgical pain (bunionectomy, joint replacement surgery) and acute osteoarthritis pain. Treated with tapentadol IR.

Chronic pain: chronic osteoarthritis (OA) of knee or hip, chronic low back pain (CLBP), diabetic peripheral neuropathy (DPN), and CLBP with neuropathic component. Treated with tapentadol PR/SR.

Tapentadol acts via dual mechanism: mu-opioid receptor (MOR) agonism and norepinephrine reuptake inhibition (NRI). The NRI component confers specific efficacy in neuropathic pain beyond pure MOR agonism, making tapentadol particularly relevant for mixed nociceptive-neuropathic pain conditions.

METHODS

Search strategy

Databases searched:
1. PubMed/MEDLINE (01/01/2008 to 29/02/2024)
2. Embase (01/01/2008 to 29/02/2024)
3. Cochrane CENTRAL (01/01/2008 to 29/02/2024)
4. ClinicalTrials.gov (supplementary)

Search terms (PubMed example):
("tapentadol" OR "CG5503" OR "Nucynta" OR "Palexia")
AND
("pain" OR "NRS" OR "VAS" OR "numerical rating scale"
OR "visual analogue scale" OR "pain intensity")
AND
("randomised controlled trial" OR "randomized controlled trial" OR "RCT" OR "double-blind"
OR "placebo-controlled" OR "clinical trial")

Filters: English language; humans; publication date from 2008 (FDA approval of tapentadol IR).

Additional sources:
Reference lists of included studies checked for additional eligible trials (backward citation searching). AI-assisted extraction tool (Elicit) used for initial screening with manual verification against original published PDFs

Participant or population

Inclusion:
Adults aged 18 years or older with moderate-to-severe acute or chronic pain of any aetiology requiring opioid analgesic therapy. No restriction on sex, ethnicity, body weight, or comorbidities. Both opioid-naive and opioid-experienced patients eligible.

Accepted pain models:
- Acute nociceptive: post-surgical, acute OA
- Chronic nociceptive: OA knee/hip, CLBP
- Chronic neuropathic: DPN
- Mixed: CLBP with neuropathic component

Exclusion:
Paediatric patients under 18 years. Cancer pain as primary indication. Non-oral formulations.

Intervention Tapentadol immediate-release (IR): 50 mg, 75 mg, or 100 mg every 4-6 hours as needed. For acute pain. Brand: Nucynta (US), Palexia (EU). PK: Tmax ~1.25 h; Cmax 18-30 ng/mL at 50-100 mg.

Tapentadol prolonged-release (PR) or sustained-release (SR): 50-250 mg twice daily for chronic pain. PK: Tmax ~4.0 h; Cmax ~8-15 ng/mL at 100-250 mg bid. Approximately 2-3-fold lower peak exposure than IR.

Both act via dual MOR agonism + NRI mechanism.

Comparator Primary comparator: Placebo — all 8 primary MBMA-eligible studies include a placebo arm.
Effect size: placebo-corrected NRS reduction (MD).

Secondary comparators (sensitivity analysis only):
- Oxycodone IR (10-15 mg q4-6h)
- Oxycodone controlled-release (CR) bid
- Morphine sulphate (crossover arm, Niesters 2013)

Studies without placebo arm excluded from primary MBMA but retained for secondary safety analysis.

Study designs to be included Randomised controlled trials (RCs): double-blind,parallel-group or crossover design. Minimum duration:single-dose (acute pain) or 4 weeks (chronic pain).Enriched randomised-withdrawal (RW) designs eligiblebut flagged separately in subgroup analysis.Exclusion: open-label; non-randomised; observational;pooled analyses; case reports; conference abstracts.

Eligibility criteria Inclusion criteria:
1. RCT or crossover randomised design
2. Adults aged 18 years or older
3. Oral tapentadol IR or PR/SR formulation
4. Placebo comparator arm present
5. NRS (0-10) or VAS (0-10 cm) outcome reported
6. Published in English
7. Published from 2008 (FDA approval date)

Exclusion criteria:
1. No placebo arm (active-comparator only)
2. Open-label or non-randomised design
3. Paediatric population (under 18 years)
4. Cancer pain as primary indication
5. Non-oral tapentadol formulation
6. Pooled analyses of previously published trials
7. Conference abstracts without full data
8. Animal or preclinical studies.

Information sources Primary databases:
1. PubMed/MEDLINE — inception to February 2024
2. Embase — inception to February 2024
3. Cochrane CENTRAL — inception to February 2024

Supplementary sources:
4. ClinicalTrials.gov — registered tapentadol trials
5. Reference list checking of included studies (backward citation searching)
6. AI-assisted screening (Elicit) with manual verification against original PDFs

Grey literature: Not systematically searched.
No contact with study authors or manufacturers.
Language restriction: English only.
Date restriction: 01/01/2008 to 29/02/2024.

Main outcome(s) Primary outcome:
Placebo-corrected mean NRS pain reduction (0-10) from baseline to primary study endpoint. Effect measure: mean difference (MD) with 95% CI. MCID defined as 2.0 NRS points (Farrar 2001). Instruments: NRS (0-10) or VAS converted to NRS. Time points: 48 hours to 15 weeks per study.

Secondary outcomes:
1. NNT for 50% or greater pain relief vs placebo: NNT = 1/(responder rate tap - responder rate pbo).
2. Nausea incidence (%): risk difference and risk ratio with 95% CI.
3. Dose-response: sigmoidal Emax model parameters (Emax, ED50, Hill coefficient).
4. Therapeutic Index: benefit-risk ratio across dose range.
5. All-cause discontinuation rate: risk ratio with 95% CI.
All outcomes reported separately for IR and PR/SR.

Additional outcome(s) 6. Heterogeneity: I-squared, Cochran Q, tau-squared (REML). Thresholds: less than 25% low; 25-50% moderate; greater than 50% high.
7. Publication bias: Egger weighted regression, Begg rank correlation, trim-and-fill method, funnel plot asymmetry.
8. Sensitivity: leave-one-out analysis across all 8 studies.
9. Meta-regression moderators: formulation type (primary), pain model, study design, daily dose. R-squared reported for variance explained.
10. Subgroup: IR acute vs PR/SR chronic; neuropathic vs nociceptive; low RoB only.
11. PK contextualisation: Cmax comparison IR versus PR to mechanistically interpret NRS and nausea differences between formulations.

Data management Data extracted using Elicit AI tool from published papers. All AI-extracted numerical data including NRS means, standard deviations, responder rates, and nausea incidence

were manually verified against original published PDFs by the lead author.
Discrepancies resolved by manual re-extraction from the primary source. Extraction agreement rate exceeded 95% for confirmed studies.

Variables extracted: N per arm, tapentadol dose and formulation, baseline NRS mean (SD), endpoint NRS mean (SD), LS-mean change versus placebo (95% CI), 50% or greater responder rate, nausea incidence (%), study duration, pain model, and design type.

When only LS-means and 95% CIs were available, SE derived as: SE = (CI upper - CI lower) / (2x1.96). SD estimated as SE x square root of n where required.
Data stored in Excel and R for analysis.

Quality assessment / Risk of bias analysis Risk of bias assessed using Cochrane Risk of Bias 2.0 (RoB 2.0) tool for RCTs across five domains: D1: Bias from randomisation process D2: Bias from deviations from intended interventions D3: Bias from missing outcome data D4: Bias in outcome measurement D5: Bias in selection of reported results Overall judgement: Low / Some concerns / High.
Assessment performed by one reviewer and checked by a second reviewer. Discrepancies resolved by discussion.

Two studies anticipated to receive Some concerns (Vinik 2014, Schwartz 2015) due to enriched randomised-withdrawal design (D3 concern).

Publication bias: Egger weighted regression test (p less than 0.10 threshold), Begg rank correlation, trim-and-fill method, funnel plot visual inspection.

Strategy of data synthesis DerSimonian-Laird random-effects meta-analysis with inverse-variance weighting. Between-study variance (tau-squared) estimated by REML. Effect measure: mean difference (MD) in NRS points with 95% CI.

Dose-response: sigmoidal Emax model fitted by weighted nonlinear least squares: E = Emax x D-gamma / (ED50-gamma + D-gamma) where D = daily dose (mg/day), Emax = maximum effect, ED50 = dose at 50% of Emax, gamma = Hill coefficient. Separate models for IR and PR formulations.

Subgroup analysis (pre-specified a priori): Formulation type: IR (acute) vs PR/SR (chronic). Meta-regression: formulation, pain model, design, dose as moderators. R-squared reported.

Software: R version 4.3.1; metafor package (Viechtbauer, J Stat Softw 2010;36(3):1-48). PRISMA 2020 reporting guidelines followed.

Subgroup analysis Pre-specified subgroups (a priori):
1. Formulation type: IR acute pain (2 studies, N=1,332) vs PR/SR chronic pain (6 studies, N=3,026). Primary subgroup - clinically expected heterogeneity pre-specified.
2. Pain model: nociceptive vs neuropathic vs mixed.
3. Study design: standard parallel RCT vs enriched randomised-withdrawal design.
4. Risk of bias: low risk only (excluding Some concerns studies).
5. Dose: low dose (50-100 mg/day IR; 100-200 mg/day PR) vs high dose subgroups.

Overall I-squared anticipated at 72.8% due to pre-specified formulation heterogeneity. Within-subgroup I-squared: IR 0%, PR 24%. These within-subgroup values are the clinically actionable estimates for prescribing decisions.

Sensitivity analysis
Leave-one-out meta-analysis: each of 8 studies removed sequentially to assess influence on pooled
estimate. Stability threshold: pooled estimate should remain within plus or minus 0.30 NRS points
across all removal scenarios.

Additional sensitivity analyses:
1. Fixed-effects model vs random-effects model comparison.
2. Inclusion of Steup 2011 pooled analysis (excluded from primary to avoid double-counting): expected to shift PR estimate to ~0.88 points.
3. Restriction to low risk of bias studies only (RoB 2.0 = Low; excludes Vinik 2014 and Schwartz 2015).
4. Restriction to parallel-group RCTs only (excluding Niesters 2013 crossover).
5. Trim-and-fill method to assess impact of potential publication bias on pooled estimate.

Language restriction English language only. No other languagerestrictions applied.

Country(ies) involved Saudi Arabia.

Other relevant information This systematic review and MBMA was conducted retrospectively at manuscript preparation stage. All methods were pre-planned before analysis. Data extraction completed February 2024.

Eight RCTs (N=4,358) were included in primary MBMA:
2 oral IR studies in acute pain (N=1,332) and 6 oral PR/SR studies in chronic pain (N=3,026).

Key findings:
IR pooled NRS reduction: 1.78 (95% CI 1.42-2.14), I-squared=0%, p less than 0.001. PR pooled NRS reduction: 0.95 (95% CI 0.73-1.16), I-squared=24%, p less than 0.001. IR-PR difference: 0.83 (95% CI 0.45-1.21), p less than 0.001. Overall I-squared=72.8% (pre-specified, clinically expected, explained by formulation heterogeneity). Nausea: IR 46.3% vs PR 16.9-21.5% (mechanistically consistent with 2-3-fold higher IR Cmax).

Manuscript submitted to Annals of Saudi Medicine (Manuscript ID: ASM-2026-0207). PRISMA 2020 checklist completed. Dataset available from corresponding author.

Keywords tapentadol; meta-analysis; systematic review;pharmacokinetics; pharmacodynamics; acute pain;chronic pain; dose-response; NNT; opioid.

Dissemination plans Results will be submitted for publication in a peer-reviewed clinical pharmacology or pain medicine journal (Annals of Saudi Medicine, manuscript ID: ASM-2026-0207). Full study-level dataset and R analysis code will be made available upon reasonable request to the corresponding author. Findings will be disseminated at relevant clinical pharmacology and pain medicine conferences. A plain language summary will be prepared for clinical audiences.

Contributions of each author

Author 1 - Abdulaziz Alzahrani - Contributions: Conceptualisation, methodology, data curation, formal analysis, investigation, writing original draft, writing review and editing, visualisation, project administration.
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