REVIEW ARTICLE · STRUCTURED REVIEW WITH QUANTITATIVE EVIDENCE SYNTHESIS

# From empirical to phenotype-guided pharmacotherapy of chronic orofacial pain: a structured review and quantitative synthesis of epidemiological, pharmacological, psychophysical and dental evidence

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## Abstract

**Background.** Chronic orofacial pain (OFP) comprises musculoskeletal, neuropathic and nociplastic disorders, yet first-line drug selection remains largely empirical and is frequently extrapolated from spinal and peripheral neuropathic pain.

**Objective.** To quantify the evidence underpinning pharmacotherapy of the four principal ICOP-2020 disorders and to appraise psychophysical, neurophysiological and dental markers as candidate predictors of treatment response.

**Methods.** Structured review of PubMed/MEDLINE and Cochrane sources to October 2026 (meta-analyses, randomised controlled trials [RCTs] and large observational cohorts). Estimates were extracted as reported; where only counts or confidence intervals were available, odds/risk ratios with 95% CI and exact two-sided *p* values were computed (Fisher's exact test; Altman–Bland method).

**Results.** Prevalence spanned three orders of magnitude, from 31.1% for temporomandibular joint disorders to 0.03% for persistent idiopathic facial pain. OFP-specific randomised evidence was small (burning mouth syndrome: 23 RCTs, 1,121 participants), whereas neuropathic-pain recommendations rest on 313 trials (48,789 participants) that excluded idiopathic OFP; first-line numbers needed to treat increased between 2015 and 2025 (tricyclics 3.6→4.6; SNRIs 6.4→7.4). Patients with TMD had lower remote pressure pain thresholds (SMD −1.92; $p<0.01$), and non-paroxysmal OFP showed enhanced temporal summation (SMD 0.30; $p=0.002$), whereas impaired conditioned pain modulation (CPM) did not reach significance ($p=0.066$; $I^2=98\%$). Mechanism-stratified studies outside the face showed phenotype-dependent efficacy (CPM–duloxetine r=0.628, $p<0.001$; oxcarbazepine phenotype interaction $p=0.047$). Bruxism was associated with TMD (OR 2.25; $p<0.001$), but self-reported sleep bruxism discriminated cases from controls (OR 6.89; $p<0.001$) whereas polysomnography did not (OR 0.88; $p=0.78$).

**Conclusions.** Current evidence supports, but has not yet tested, phenotype-guided first-line drug selection in chronic OFP. Prospective trials combining standardised psychophysics, trigeminal neurophysiology and instrumentally verified dental factors are required; a testable phenotype-to-drug framework is proposed.

**Keywords:** orofacial pain; temporomandibular disorders; burning mouth syndrome; trigeminal neuralgia; quantitative sensory testing; conditioned pain modulation; bruxism; personalised pharmacotherapy

## 1. Introduction

Chronic orofacial pain (OFP), defined as pain in the face, mouth or jaws lasting at least three months, encompasses aetiologically heterogeneous disorders: painful temporomandibular disorders (TMD), trigeminal neuralgia (TN), burning mouth syndrome (BMS) and persistent idiopathic facial pain (PIFP). The International Classification of Orofacial Pain (ICOP, 2020) was the first to separate these conditions on anatomical and mechanistic grounds [1]. TMD alone affect an estimated 6–9% of adults worldwide and are the second most common chronic musculoskeletal pain condition after low back pain [2]; across the spectrum, OFP is accompanied by high rates of somatisation, depression, anxiety and sleep disturbance [3,4].

Nociceptive processing in the trigeminal system differs from that in spinal segments. Convergence of cutaneous, mucosal, pulpal, muscular and articular input onto wide-dynamic-range neurones of the trigeminal subnucleus caudalis is denser, primary afferents are rich in calcitonin gene-related peptide, and the pharmacological response is distinctive: carbamazepine is highly effective in TN but of marginal value in most other neuropathic pains, whereas triptans and anti-CGRP agents act in migraine and nowhere else [5]. Nevertheless, drug recommendations for TMD, BMS and PIFP are largely borrowed from trials in diabetic polyneuropathy, post-herpetic neuralgia and low back pain [6–8].

The practical consequence is empirical prescribing. In a Swiss tertiary orofacial pain unit, more than half of 208 consecutive patients were already receiving drugs at the first specialist consultation, with non-steroidal anti-inflammatory drugs (NSAIDs) predominating and both over- and under-treatment documented [9]. Patients whose myofascial TMD resists conservative care differ from responders in somatosensory, psychosocial and genetic profile [10], suggesting that non-response is partly predictable.

A mechanism-based approach to pain therapy was proposed almost three decades ago [11] and operationalised through sensory profiling [12]. Quantitative sensory testing (QST), temporal summation of pain (TSP), conditioned pain modulation (CPM) and trigeminal brainstem reflexes index peripheral and central sensitisation, descending inhibition and brainstem conduction, respectively [13–15]. Whether such markers can guide first-line drug selection

in OFP is unknown. The contribution of dental factors (occlusion, bruxism) remains contested [16,17] and has rarely been examined together with neurophysiology; for Central Asia, epidemiological and normative data are lacking altogether.

The aim of this review was therefore to quantify (i) the epidemiological burden of the four principal ICOP disorders; (ii) the size and certainty of OFP-specific pharmacological evidence relative to the extrapolated neuropathic-pain evidence; (iii) psychophysical and neurophysiological differences between patients and controls and the measurement properties of these tests; (iv) evidence that phenotype predicts drug response; and (v) the association of dental factors with OFP, and to derive a testable phenotype-to-drug framework.

## 2. Materials and Methods

### *2.1. Design and information sources*

A structured review with quantitative evidence synthesis was performed; reporting followed the applicable items of PRISMA 2020 [18]. PubMed/MEDLINE was searched without language restriction from inception to October 2026, supplemented by the Cochrane Database of Systematic Reviews, reference lists of guidelines and the 259-source literature review compiled for the authors' doctoral research programme on chronic OFP. Search strings combined disorder terms (“orofacial pain”, “temporomandibular disorders”, “burning mouth syndrome”, “trigeminal neuralgia”, “persistent idiopathic facial pain”) with domain terms (“prevalence”, “pharmacotherapy”, “randomized controlled trial”, “meta-analysis”, “quantitative sensory testing”, “temporal summation”, “conditioned pain modulation”, “blink reflex”, “bruxism”, “occlusion”).

### *2.2. Eligibility*

Eligible were systematic reviews and meta-analyses, RCTs, and prospective cohort or case–control studies reporting a quantitative estimate within one of five domains: prevalence or incidence; pharmacological efficacy or harm; patient–control differences in psychophysical or neurophysiological measures; prediction of treatment response or disease onset by such measures; and association of dental factors with pain. Meta-analyses of non-orofacial neuropathic pain were included as the reference body of extrapolated evidence. Case reports, narrative reviews without data, animal studies and surgical interventions were excluded.

### *2.3. Data extraction and derived statistics*

For each estimate, design, number of studies ($k$) and participants ($n$), effect measure, 95% confidence interval (CI) and exact $p$ value were extracted as reported, and all numbers were re-checked against the source. Derived statistics are flagged with a dagger (†). When 2×2 counts were available or could be reconstructed from reported percentages and denominators, odds or risk ratios with Woolf (logit) 95% CI and two-sided Fisher's exact $p$ (Pearson $\chi^2$ for $n$>1,000) were computed; proportions are given with Wilson 95% CI. When only an estimate and its CI were reported, $p$ was obtained by the Altman–Bland method on the log scale for ratio measures [19]; numbers needed to treat (NNT) were first converted to absolute risk differences (1/NNT). No new pooling across sources was undertaken because of clinical and methodological heterogeneity. Calculations were performed in Python 3 (SciPy 1.17); $\alpha$=0.05 (two-sided). Certainty of evidence is reported as rated by the source (GRADE or Cochrane risk-of-bias). The review used published aggregate data only and did not require ethical approval.

## 3. Results

### *3.1. Epidemiological burden*

Population estimates spanned more than three orders of magnitude (Figure 1). Temporomandibular joint disorders diagnosed with RDC/TMD or DC/TMD affected 31.1% of adults and elderly and 11.3% of children and adolescents, disc displacement with reduction being the most frequent diagnosis (25.9% in adults) [20]. The pooled prevalence of BMS was 1.73% in the general population ($n$=26,632) and 7.72% in clinical samples ($n$=86,591), higher in women than men (1.15% vs 0.38%) and above than below 50 years of age (3.31% vs 1.92%) [21]. In a German population sample, lifetime prevalence was 0.3% for TN (10/3,336; 95% CI 0.1–0.5%) and 0.03% for PIFP (1/3,336) [22].

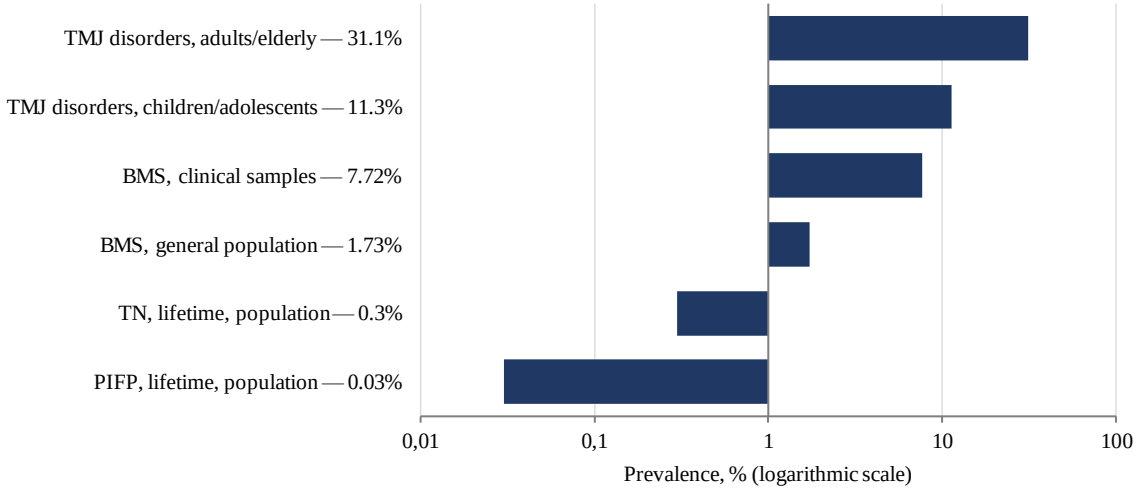



**Figure 1.** Prevalence of chronic orofacial pain disorders (logarithmic scale). Data from meta-analyses [20,21] and a population-based study [22]. TMJ, temporomandibular joint; BMS, burning mouth syndrome; TN, trigeminal neuralgia; PIFP, persistent idiopathic facial pain.

Incidence data are available only for TMD: in the OPPERA cohort, 260 of 2,737 initially pain-free adults developed first-onset TMD over a median of 2.8 years, an incidence of 3.9% per annum [23]. Baseline low back pain (adjusted HR 1.50; 95% CI 1.08–2.10; $p$=0.017†) and genital pain (adjusted HR 1.75; 1.04–2.93; $p$=0.034†) predicted onset [24], and global psychological and somatic symptoms were the most robust psychological predictor [25]. Among patients with established TMD, moderate-to-severe somatisation was reported in 28.5–76.6% and moderate-to-severe depression in 21.4–60.1% across 14 RDC/TMD studies [3]; anxiety and depression were the psychological factors most consistently implicated in BMS [4].

### *3.2. Size and certainty of the pharmacological evidence base*

Randomised evidence specific to OFP was small and predominantly of low or very low certainty (Table 1). For TN, carbamazepine and oxcarbazepine remain first-line [26], yet the Cochrane review identified only 10 RCTs (480 participants across TN, diabetic neuropathy and post-stroke pain), nine of cross-over design and none longer than four weeks, providing third-tier efficacy evidence only [27]. Harm, in contrast, was quantifiable: adverse events occurred in 65.3% of carbamazepine-treated and 27.2% of placebo-treated participants (RR 2.40; 95% CI 1.84–3.14; $p$<0.001†), corresponding to a number needed to harm of 2.6. For TMD, 40 RCTs were identified, but only 11 qualified for network meta-analysis [28]; the 2023 *BMJ* guideline issued conditional recommendations against gabapentin, benzodiazepines and botulinum toxin and a strong recommendation against NSAIDs combined with opioids [2]. For BMS, 23 RCTs (1,121 participants) yielded very-low-certainty evidence, with only one trial at low risk of bias [29]. No pooled randomised estimate exists for PIFP [8].

**Table 1.** Randomised evidence for pharmacotherapy of the four ICOP disorders compared with the neuropathic-pain evidence from which recommendations are extrapolated

| Condition | Source (design) | Evidence base | | Principal quantitative finding | | | Certainty / risk of bias |
|---|---|---|---|---|---|---|---|
| | | Studies | Participants | Outcome / comparison | Estimate (95% CI) | *p* | |
| *A. Direct evidence in ICOP disorders* | | | | | | | |
| Trigeminal neuralgia [a] | Wiffen et al., 2014, Cochrane SR (carbamazepine) [27] | 10 | 480 | Any adverse event: 113/173 vs 47/173 | RR 2.40 (1.84–3.14)† | <0.001† | Third-tier efficacy evidence only; 9/10 cross-over; all ≤4 weeks |
| | | | | Withdrawal for adverse events: 8/268 vs 0/255 | RD 3.0% (1.5–5.8)† | 0.008† | |
| TMD, arthrogenous | Häggman-Henrikson et al., 2017, HTA + NMA [30] | 15 | 790 | NSAIDs, corticosteroid and hyaluronate injections effective (narrative synthesis) | NR | NR | Limited (GRADE) |
| TMD, myogenous | Häggman-Henrikson et al., 2017 [30] | 9 | 375 | Cyclobenzaprine superior to comparators (NMA) | NR | NR | Limited (GRADE) |
| TMD, all | Christidis et al., 2024, SR + NMA [28] | 40 | NR | Only 11 RCTs eligible for NMA; >50% of patients use drugs regularly | — | — | Small trials; heterogeneous outcomes |
| Burning mouth syndrome | McMillan et al., 2016, Cochrane SR [29] | 23 | 1,121 | Any intervention vs placebo, short-term symptom relief | — | — | Very low; 1/23 trials at low risk of bias |
| | Gremeau-Richard et al., 2004, RCT [31] | 1 | 48 | Topical clonazepam 1 mg t.i.d., 14 days: NRS decrease 2.4 vs 0.6 | MD 1.8 points | 0.014 (ITT 0.027) | Single small RCT |
| PIFP | Benoliel & Gaul, 2017, review [8] | 0 | 0 | TCAs and gabapentinoids recommended by analogy | — | — | Expert opinion |
| *B. Extrapolation source: non-orofacial neuropathic pain* | | | | | | | |

| Condition | Source (design) | Evidence base | | Principal quantitative finding | | | Certainty / risk of bias |
|---|---|---|---|---|---|---|---|
| | | Studies | Participants | Outcome / comparison | Estimate (95% CI) | *p* | |
| Neuropathic pain | Finnerup et al., 2015, SR/MA [6] | 229 | NR | NNT for ≥50% relief, first-line classes (Figure 2) | NNT 3.6–7.7 | <0.001† [b] | Moderate–high (GRADE) |
| Neuropathic pain, idiopathic OFP excluded | Soliman et al., 2025, SR/MA [7] | 313 | 48,789 | NNT for responders, first-line classes (Figure 2) | NNT 4.6–8.9 | <0.001† [b] | Moderate (GRADE) |
| *C. Real-world prescribing* | | | | | | | |
| Mixed OFP | Mundackal et al., 2026, retrospective cohort [9] | 1 | 208 | Any pharmacotherapy before vs after specialist consultation: 51.4% vs 74.5% | +23.1 percentage points | <0.001 [c] | Single centre |

[a] Carbamazepine trials included trigeminal neuralgia, diabetic neuropathy and post-stroke pain. [b] Derived for each first-line class separately (Altman–Bland, risk-difference scale). [c] McNemar test as reported. † Calculated by the present authors. HTA, health technology assessment; ITT, intention-to-treat; MD, mean difference; NMA, network meta-analysis; NNT, number needed to treat; NR, not reported; NRS, 0–10 numeric rating scale; RCT, randomised controlled trial; RD, risk difference; RR, risk ratio; SR/MA, systematic review/meta-analysis; TCAs, tricyclic antidepressants; TMD, temporomandibular disorders.

The extrapolated evidence was larger by two orders of magnitude: the 2015 NeuPSIG meta-analysis included 229 studies [6], and its 2025 update 313 trials with 48,789 participants, explicitly excluding idiopathic OFP [7]. Every first-line class retained a significant effect (derived $p<0.001$ for each), but NNTs were consistently higher in 2025 (Figure 2), i.e. one additional responder per 4.6 to 8.9 patients treated. In routine care, specialist consultation increased the proportion of patients receiving drugs from 51.4% to 74.5% ($p<0.001$), topical NSAIDs (64.0%) and magnesium (40.0%) being prescribed most often [9]—agents with little or no OFP-specific randomised support.

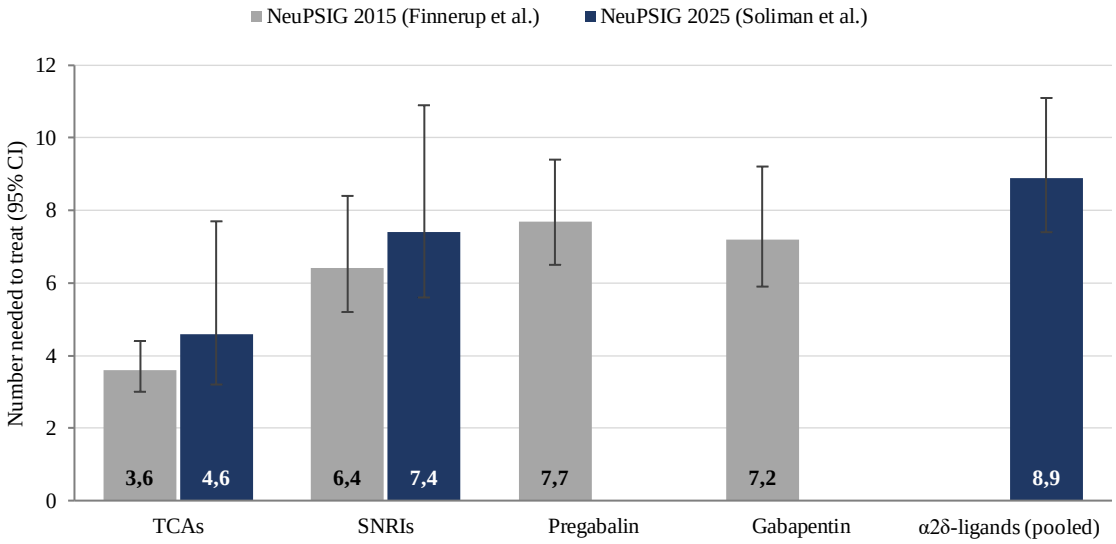



**Figure 2.** Number needed to treat (NNT, with 95% CI) for first-line drug classes in non-orofacial neuropathic pain, NeuPSIG 2015 [6] versus 2025 [7]. Lower values indicate greater efficacy; in 2025 pregabalin and gabapentin were pooled as α2δ-ligands. TCAs, tricyclic antidepressants; SNRIs, serotonin–noradrenaline reuptake inhibitors.

### *3.3. Psychophysical and neurophysiological markers*

Pressure hyperalgesia was the most robust psychophysical abnormality (Table 2). In TMD, pressure pain thresholds (PPT) were lower at trigeminal and at remote, extra-trigeminal sites (SMD −1.55 and −1.92; both $p<0.01$; five studies, $n$=1,985), whereas heat and cold pain thresholds did not differ [32]; remote involvement indicates widespread, centrally mediated sensitisation. In non-paroxysmal OFP, TSP was moderately but consistently enhanced (SMD 0.30; $p$=0.002), while impaired CPM, although large, was not significant and was distorted by extreme heterogeneity and publication bias ($p$=0.066; $I^2$=98.0%) [33].

**Table 2.** Psychophysical and neurophysiological markers in chronic orofacial pain: differences from controls, predictive value and measurement properties

| Marker (mechanism indexed) | Population; source | Patients vs controls (or prospective prediction) | | | | Heterogeneity / measurement properties |
|---|---|---|---|---|---|---|
| | | *k* | *n* | Effect (95% CI) | *p* | |
| *A. Static quantitative sensory testing* | | | | | | |
| PPT, trigeminal sites (segmental sensitisation) | TMD; La Touche et al., 2018 [32] | 5 | 1,985 | SMD −1.55 (−2.23 to −0.77) | <0.01 | NR |
| PPT, remote sites (widespread / central sensitisation) | | 5 | 1,985 | SMD −1.92 (−2.95 to −0.89) | <0.01 | NR |
| Heat and cold pain thresholds | | NR | NR | No difference | NS | Trigeminal and remote areas |
| *B. Dynamic psychophysics* | | | | | | |
| Temporal summation of pain (central facilitation) | Non-paroxysmal OFP; Moana-Filho et al., 2018 [33] | 18 [a] | NR | SMD 0.30 (0.11–0.49) | 0.002 | $I^2$=70.2%; 406 studies used 63 different calculation methods [34] |

| Marker (mechanism indexed) | Population; source | Patients vs controls (or prospective prediction) | | | | Heterogeneity / measurement properties |
|---|---|---|---|---|---|---|
| | | *k* | *n* | Effect (95% CI) | *p* | |
| Conditioned pain modulation (descending inhibition) [b] | | 9 [a] | NR | SMD 1.36 (−0.09 to 2.81) | 0.066 | $I^2$=98.0%; publication bias; ICC intra-session 0.77 (0.70–0.82), inter-session 0.44 (0.11–0.69) [35] |
| *C. Neurophysiology and autonomic function* | | | | | | |
| Trigeminal reflexes R1/R2 (brainstem conduction) | TN, symptomatic vs classic; Cruccu et al., 2006 [36] | 1 | 120 | Sensitivity 95.8% (79.8–99.3)† Specificity 92.7% (85.7–96.4)† | <0.001† [c] | Prospective consecutive series |
| HRV, high-frequency power (parasympathetic tone) | Chronic pain, mixed; Tracy et al., 2016 [37] | 26 [d] | NR | Moderate-to-large reduction | NR | High heterogeneity; effect driven by fibromyalgia |
| 39 experimental pain measures; resting heart rate | TMD-free adults, OPPERA; Greenspan et al., 2013 [38] | 1 | 2,737 | 14/39 pain measures and resting HR predicted first-onset TMD | <0.05 | Prospective cohort; 260 incident cases |

[a] Number of effect estimates. [b] Positive SMD denotes less efficient inhibition in patients. [c] Fisher's exact test on counts reconstructed from reported sensitivity and specificity (23/24 symptomatic vs 7/96 classic TN with abnormal reflexes). [d] Moderate-to-high-quality studies entering meta-analysis. † Calculated by the present authors. HRV, heart rate variability; ICC, intraclass correlation coefficient; NR, not reported; NS, not significant; PPT, pressure pain threshold; SMD, standardised mean difference.

The measurement properties of dynamic tests limit their direct clinical use. With a pressure test stimulus and cold-pressor conditioning, CPM showed good intra-session (ICC 0.77) but only fair inter-session reliability in patients (ICC 0.44) [35], and TSP protocols varied in stimulation frequency (31 frequencies) and calculation (63 methods) [34]. Among neurophysiological tests, trigeminal reflexes distinguished symptomatic from classic TN with a sensitivity of 96% and specificity of 93% [36]. Reduced high-frequency heart rate variability is a consistent finding in chronic pain [37], but in OPPERA only resting heart rate among autonomic measures, together with 14 of 39 experimental pain measures, predicted first-onset TMD [38].

### *3.4. Phenotype-defined subgroups and treatment response*

No randomised trial in OFP was identified in which the first-line drug was allocated according to psychophysical or neurophysiological phenotype. Outside the face, two studies demonstrated phenotype-dependent efficacy (Table 3). In painful diabetic neuropathy, baseline CPM correlated with duloxetine efficacy (r=0.628; $p$<0.001) and was the only independent predictor ($p$=0.001), whereas TSP had no predictive role [39]. In a phenotype-stratified RCT, the NNT of oxcarbazepine was 3.9 in patients with the irritable-nociceptor phenotype and 13 in those without it (interaction $p$=0.047) [40]. A systematic review found that all 11 pharmacological studies reported at least one predictive QST parameter, TSP and CPM being predictive most often [41].

**Table 3.** Phenotype-defined subgroups, treatment response and risk of chronic orofacial pain

| Study (design) | Population, *n* | Phenotyping tool | Intervention / outcome | Phenotype-defined subgroups | | Test of difference | |
|---|---|---|---|---|---|---|---|
| | | | | Favourable phenotype | Unfavourable phenotype | Statistic (95% CI) | *p* |
| *A. Mechanism-stratified drug response (non-orofacial neuropathic pain)* | | | | | | | |
| Yarnitsky et al., 2012 (prospective, placebo run-in) [39] | Painful diabetic neuropathy, 30 | CPM | Duloxetine 60 mg/day, 4 weeks / patient-rated efficacy | Less efficient CPM: greater efficacy | Efficient CPM: lesser efficacy | r=0.628; model $R^2$=0.673 | <0.001 |
| | | TSP | | — | — | No predictive role | NS |
| Demant et al., 2014 (RCT, cross-over, phenotype-stratified) [40] | Peripheral neuropathic pain, 83 (ITT) | Detailed QST (DFNS) | Oxcarbazepine 1,800–2,400 mg vs placebo / ≥50% relief | Irritable nociceptor (*n*=31): NNT 3.9 (2.3–12) | Non-irritable (*n*=52): NNT 13 (5.3–∞) | Interaction 0.7 NRS (0.01–1.4) | 0.047 |
| Petersen et al., 2021 (SR) [41] | Chronic pain, 11 drug studies | QST, TSP, CPM | Various analgesics / analgesic effect | 11/11 studies: ≥1 predictive QST parameter | — | TSP 50%, CPM 44% of studies predictive | NA |
| *B. Orofacial pain (observational)* | | | | | | | |
| De la Torre Canales et al., 2025 (case–control) [10] | Myofascial TMD, 72 (24/24/24) | QST (PPT, WUR), psychosocial, HTR1A | Conservative care, 3 months / resistance | Responders | Resistant: ↓PPT, ↑WUR, ↑distress, rs6295 | ANOVA with post hoc tests | 0.01; <0.01; 0.02 |
| Bair et al., 2016 (OPPERA) [42] | 1,031 TMD cases vs 3,247 controls | Supervised clustering of QST and psychosocial measures | Cluster membership / chronic TMD | Adaptive cluster: 8.5% of cases | Pain-sensitive + global symptoms: 91.5% of cases vs 58.8% of controls | OR 7.51 (5.97–9.45)† [a] | <0.001† |
| | TMD-free cohort | | Cluster / first-onset TMD | Other clusters | Global symptoms cluster | HR 2.8 | NR |

[a] Pearson $\chi^2$ on counts reconstructed from reported percentages (943/1,031 cases vs 1,909/3,247 controls in non-adaptive clusters). † Calculated by the present authors. CPM, conditioned pain modulation; DFNS, German Research Network on Neuropathic Pain protocol; HR, hazard ratio; NA, not applicable; PPT, pressure pain threshold; QST, quantitative sensory testing; TSP, temporal summation of pain; WUR, wind-up ratio.

Within OFP the evidence is observational. Women with treatment-resistant myofascial TMD had lower PPT and higher wind-up ratios at trigeminal and spinal sites ($p$=0.01), greater psychosocial burden ($p$<0.01) and a higher frequency of the HTR1A rs6295 polymorphism ($p$=0.02) than responders [10]. In OPPERA, 91.5% of chronic TMD cases but 58.8% of controls belonged to the pain-sensitive or global-symptoms clusters (OR 7.51; 95% CI 5.97–9.45; $p$<0.001†), and the global-symptoms cluster carried a 2.8-fold hazard of first-onset TMD [42].

### *3.5. Dental factors*

Bruxism was associated with TMD in a meta-analysis of 20 studies (OR 2.25; awake bruxism 2.51; sleep bruxism 2.06; derived $p<0.001$ for each) [43]; however, the association depended on how bruxism was ascertained (Table 4, Figure 3). In a laboratory study of women with myofascial TMD, self-reported sleep bruxism was 3.6 times more frequent in cases than in controls (OR 6.89; $p<0.001$†), whereas two-night polysomnography showed similar rates (9.7% vs 10.9%; OR 0.88; $p=0.78$†) [44]. Of 11 occlusal features, only anterior open bite, unilateral crossbite, overjet >6–7 mm, loss of ≥5–6 posterior teeth and RCP–ICP slides >2 mm increased risk, and most variance in each TMD group remained unexplained [45]; occlusal adjustment lacks evidence of benefit [46]. In OPPERA, self-reported oral parafunctions predicted first-onset TMD, whereas examiner-assessed tooth-wear facets did not [47]. No study evaluated dental factors as predictors of pharmacological response.

**Table 4.** Dental factors and temporomandibular disorders: dependence of the association on the method of ascertainment

| Factor | Source (design) | Ascertainment | Prevalence, n/N (%) | | Association | |
|---|---|---|---|---|---|---|
| | | | TMD cases | Controls | OR (95% CI) | *p* |
| *A. Bruxism* | | | | | | |
| Bruxism, any type | Mortazavi et al., 2023 (SR/MA, *k*=20) [43] | Predominantly self-report and clinical signs | NR | NR | 2.25 (1.94–2.56) | <0.001† |
| Awake bruxism | | | NR | NR | 2.51 (2.02–2.99) | <0.001† |
| Sleep bruxism | | | NR | NR | 2.06 (1.82–2.30) | <0.001† |
| Sleep bruxism, myofascial TMD (women) | Raphael et al., 2012 (case–control) [44] | Structured interview (self-report) | 68/123 (55.3) | 7/46 (15.2) | 6.89 (2.86–16.60)† | <0.001† |
| | | Polysomnography, two nights | 12/124 (9.7) | 5/46 (10.9) | 0.88 (0.29–2.65)† | 0.78† |
| Oral parafunctions; tooth-wear facets | Ohrbach et al., 2013 (OPPERA cohort, *n*=2,737) [47] | Self-report; examiner | — | — | Parafunctions predictive; facets not predictive [a] | NR |
| *B. Occlusion* | | | | | | |
| Anterior open bite | Pullinger et al., 1993 (case–control; 413 TMD vs 147 controls) [45] | Clinical occlusal analysis; multiple logistic regression | NR | NR | Increased risk [b] | <0.01 |
| Unilateral maxillary lingual crossbite | | | | | Increased risk [b] | <0.05 to <0.01 |
| Overjet >6–7 mm | | | | | Increased risk [b] | <0.05 to <0.01 |
| ≥5–6 missing posterior teeth | | | | | Increased risk [b] | <0.05 to <0.01 |
| RCP–ICP slide >2 mm | | | | | Increased risk [b] | <0.05 to <0.01 |
| Occlusal adjustment (therapy) | Koh & Robinson, 2003 (Cochrane SR) [46] | RCTs | — | — | No evidence of benefit | — |

[a] Multivariable Cox regression; hazard ratios not reported in the abstract. [b] Odds ratios differ across five TMD subgroups and are not reproduced here; anterior open bite in osteoarthrosis was considered a consequence rather than a cause. † Calculated by the present authors (Woolf CI, Fisher's exact test; Altman–Bland method for meta-analytic ORs). ICP, intercuspal position; RCP, retruded contact position.

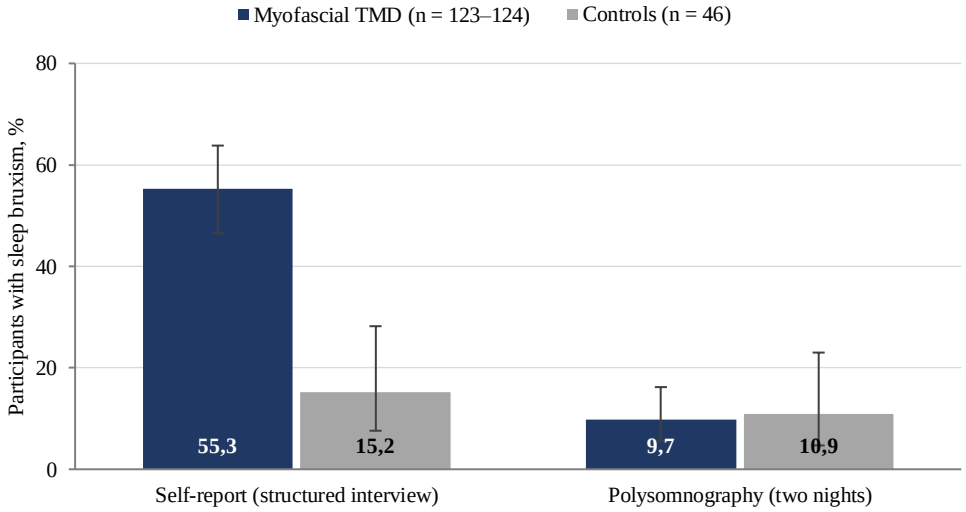



**Figure 3.** Prevalence of sleep bruxism in women with myofascial TMD and in controls according to the method of ascertainment (Wilson 95% CI). Self-report: OR 6.89, $p<0.001$†; polysomnography: OR 0.88, $p=0.78$† (Fisher's exact test). Data from Raphael et al. [44].

## 4. Discussion

### *4.1. Principal findings*

This synthesis identifies three asymmetries that define the current state of OFP pharmacotherapy. First, burden and evidence are inversely matched: the most prevalent disorders, TMD and BMS, are supported by small, low-certainty trial bases, while the drug classes used for them are validated in neuropathic-pain populations from which

idiopathic OFP is explicitly excluded [7]. Second, patients with OFP differ measurably from controls in pressure hyperalgesia, temporal summation and, less certainly, descending inhibition [32,33], and outside the face these differences already predict drug response [39,40], yet no OFP trial has used them for allocation. Third, the apparent role of bruxism depends on how it is measured, with the self-report association disappearing under polysomnography [44].

### *4.2. The extrapolation gap and trigeminal specificity*

Extrapolation would be defensible if trigeminal and spinal nociception responded alike. They do not: the efficacy of carbamazepine in TN is not reproduced in most other neuropathic pains, and anti-CGRP therapy is effective only in migraine [5]. The rise in first-line NNTs between 2015 and 2025 (Figure 2) further indicates that the effect sizes being extrapolated are modest and probably overestimated in older literature [6,7]. Meanwhile, real-world prescribing is dominated by NSAIDs and supplements [9], and guideline panels recommend against several drugs commonly used for TMD [2]. Unselected populations dilute treatment effects; phenotype-stratified designs are the logical response, as the oxcarbazepine trial illustrates, in which the NNT more than tripled when the irritable-nociceptor phenotype was absent [40].

### *4.3. A testable phenotype-to-drug framework*

Combining the mechanistic rationale of each drug class with the markers reviewed above yields an operational framework (Table 5) in which baseline phenotype, defined against reference limits obtained from local healthy controls, determines the first-line agent. The hierarchy places the paroxysmal neuropathic phenotype first because sodium-channel blockers have the strongest trigeminal-specific evidence [26]; deficient descending inhibition is matched to duloxetine on the basis of the CPM–duloxetine coupling [39]; central sensitisation with preserved CPM is matched to α2δ-ligands [48]; and a purely peripheral nociceptive profile to short-course NSAIDs or, in BMS, topical clonazepam [30,31].

**Table 5.** Operational phenotype-to-drug framework for first-line pharmacotherapy of chronic orofacial pain (hypothesis for prospective testing)

| Phenotype (priority order) | Operational criterion at baseline | First-line agent and titration | Mechanistic rationale | Supporting evidence |
|---|---|---|---|---|
| 1. Paroxysmal neuropathic | Paroxysmal shooting pain with trigger zones fulfilling ICOP criteria for TN, or paroxysmal component with DN4 ≥4 | Carbamazepine 100–200 mg b.i.d., +100–200 mg every 3 days, ≤1,200 mg/day; oxcarbazepine 600–1,800 mg/day if intolerant | Use-dependent $Na^+$-channel blockade of high-frequency ectopic discharge | EAN guideline [26]; phenotype-dependent oxcarbazepine effect [40] |
| 2. Deficient descending inhibition | CPM effect below the lower reference limit of healthy controls | Duloxetine 30 mg/day for 7 days, then 60 mg/day | Augmentation of descending monoaminergic inhibition | CPM predicts duloxetine efficacy [39] |
| 3. Central sensitisation | Enhanced TSP and/or extracephalic PPT below reference range with preserved CPM | Pregabalin 75 mg b.i.d., then 150 mg b.i.d., ≤600 mg/day; gabapentin 900–1,800 mg/day as alternative | α2δ-mediated reduction of central transmitter release | Remote hyperalgesia [32]; TSP facilitation [33] |
| 4. Peripheral nociceptive | Local mechanical hyperalgesia with TSP, CPM and extracephalic thresholds within reference range | Short-course NSAID (≤14 days); in BMS, topical clonazepam 0.5–1 mg t.i.d. (suck and spit) | Inhibition of peripheral prostanoid sensitisation; peripheral GABAergic modulation | TMD-joint NSAIDs [30]; topical clonazepam RCT [31] |

When criteria of more than one phenotype are met, the phenotype listed first takes priority. Reference limits are derived from 40 age- and sex-matched healthy controls. If pain intensity decreases by <30% at week 4 at the target dose, or the drug is not tolerated, the next class is selected by the same algorithm. Only agents registered in the Republic of Uzbekistan are used. DN4, Douleur Neuropathique 4 questionnaire; EAN, European Academy of Neurology.

Two measurement caveats follow from Table 2. Because CPM reliability between sessions is only fair [35], phenotype assignment should rely on protocols that follow consensus recommendations [15], with duplicate measurements and site-specific reference values, which cannot be transferred between populations or body regions [13,14]. Because TSP protocols are highly variable [34], the stimulation frequency, train length and calculation must be prespecified.

### *4.4. Dental factors: from association to verification*

The contrast between self-reported and polysomnographic bruxism (Figure 3) implies that self-report captures, at least in part, the symptom burden and hypervigilance of patients rather than motor activity. Bruxism should therefore be graded as possible, probable or definite according to international consensus [17], and dental variables entered into prognostic models only in instrumentally verified form. The hypothesis that a persistent peripheral input from occlusal, periodontal or parafunctional sources sustains central sensitisation [48], and thereby resistance to centrally acting drugs, is biologically plausible but has never been tested against drug response.

### *4.5. Implications for trial design*

These findings informed the design of an ongoing open, prospective, parallel-group study in the Republic of Uzbekistan, in which 248 patients with ICOP-verified TMD (*n*=68), TN (*n*=61), BMS (*n*=57) or PIFP (*n*=62) are allocated 1:1 within each disorder to phenotype-guided (Table 5) or empirical first-line therapy, and 40 healthy controls provide local reference values [1,49]. The primary endpoint is the proportion of patients with ≥30%

reduction in pain intensity at week 12 [50]. Assuming response rates of 62.5% and 45.0%, 124 patients per arm provide 80% power at two-sided $\alpha=0.05$; the targeted absolute difference of 17.5 percentage points corresponds to an NNT of 5.7, which lies between the NNTs observed in favourable and unfavourable phenotypes in stratified trials [40]. Secondary endpoints include ≥50% response, disability, oral-health-related quality of life, sleep, changes in CPM, R2 and ES2, and durability at 12 months; a prognostic index integrating clinical, neurophysiological, dental and laboratory variables will be internally validated by bootstrap.

### *4.6. Limitations*

This is a structured rather than a full systematic review: PubMed/MEDLINE was the principal database, extraction was performed by one reviewer with re-checking, the protocol was not registered, and risk of bias was not reassessed beyond the source ratings. Some derived *p* values and odds ratios rest on counts reconstructed from rounded percentages and are approximate. The phenotype–response evidence comes from neuropathic pain outside the face, and most cohorts were from Western Europe and North America. Publication bias affected the CPM literature [33]. No new pooled estimates were generated, so the review describes rather than resolves heterogeneity.

## 5. Conclusions

Pharmacotherapy of chronic OFP rests on a small direct evidence base and on extrapolation from neuropathic-pain trials that exclude idiopathic OFP and show modest, declining effect sizes. Pressure hyperalgesia, enhanced temporal summation and, less consistently, impaired CPM distinguish patients from controls and, outside the face, predict response to specific drug classes. The association of bruxism with TMD depends on self-report and is not confirmed by polysomnography. Phenotype-guided selection of the first-line drug is therefore a justified but untested hypothesis; prospective trials with locally standardised psychophysics, trigeminal neurophysiology and instrumentally verified dental factors are needed before it can enter practice.

## Declarations

Conflict of interest. The authors declare no conflict of interest.

**Data availability.** All data are derived from the published sources cited; the calculations underlying derived statistics are available from the corresponding author on request.

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