Review Article

Precision Dental Pharmacotherapy: Role of Pharmacogenomics and the Oral Microbiome in Personalized Drug Therapy

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ABSTRACT

Dental pharmacotherapy is largely based on population-level evidence, although patients differ in analgesic response, adverse effects, drug exposure and susceptibility to treatment failure. Pharmacogenomics provides a biologically plausible and, for selected drug–gene pairs, clinically useful method for addressing part of this variability. CYP2D6 is particularly relevant to codeine and tramadol because genetic differences alter formation of active metabolites and can contribute to inadequate analgesia or toxicity. CYP2C9 variants can modify the pharmacokinetics of several non-steroidal anti-inflammatory drugs, although routine genotype-guided prescribing in dentistry has not yet been established. OPRM1, COMT, SCN9A and SCN10A have been investigated in relation to opioid response, pain perception and local anaesthetic efficacy, but their clinical utility remains limited. The oral microbiome represents another potential determinant of treatment response through microbial metabolism, nitrate reduction, biofilm ecology and interactions with host inflammation. However, direct evidence that oral microbial profiles can guide selection or dosing of dental medicines remains insufficient. This mini-review summarizes the most clinically relevant pharmacogenomic evidence, examines the emerging contribution of the oral microbiome, and discusses their potential application to analgesics, local anaesthetics and antimicrobial therapy. Particular emphasis is placed on evidence strength and the distinction between established pharmacogenomic guidance and exploratory biomarkers. Precision dental pharmacotherapy is most appropriately viewed as selective, evidence-based prescribing supported by validated biomarkers rather than routine broad genetic or microbiome testing.

Key words: Pharmacogenomics, Oral microbiome, Dental pharmacotherapy, Personalized medicine, CYP2D6, CYP2C9, Analgesics

Dental treatment frequently requires short courses of analgesics, anti-inflammatory drugs, local anaesthetics and, in selected clinical situations, antimicrobial agents. Although these medicines are prescribed according to established guidelines, the response of individual patients is not uniform. Differences in pain intensity, drug absorption and metabolism, receptor sensitivity, comorbidities, concomitant medicines and adherence can result in variable efficacy and adverse effects. Pharmacogenomics examines inherited genetic variation that influences drug pharmacokinetics and pharmacodynamics and therefore provides a potential explanation for a proportion of interindividual variability [1,2].

The clinical relevance of pharmacogenomics in dentistry is strongest when a genetic variant has a reproducible effect on a medicine and a prescribing recommendation is available.

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CYP2D6-mediated metabolism of codeine and tramadol represents the clearest example. In contrast, several candidate genes associated with opioid sensitivity or local anaesthetic response have generated promising mechanistic findings but have not yet reached the same level of clinical utility [1,3]. A second biological factor of interest is the oral microbiome. Oral microorganisms exist as structured communities on mucosal and dental surfaces and participate in acid production, nutrient metabolism, nitrate reduction and host inflammatory interactions. Periodontal disease and antiseptic exposure can alter microbial composition and function [4-7]. The microbiome may therefore influence the biological environment in which dental drugs act, but evidence for direct microbiome-guided prescribing remains substantially less developed than host pharmacogenomics. This review focuses on the clinically relevant interface between pharmacogenomics, oral microbial ecology and dental drug therapy.

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2. PHARMACOGENOMICS RELEVANT TO DENTAL ANALGESICS

Codeine is metabolized by several pathways, but conversion to morphine through CYP2D6 contributes importantly to its analgesic activity. CYP2D6 genetic variation produces phenotypes ranging from poor to ultrarapid metabolism. Poor metabolizers generate less morphine and may experience inadequate analgesia, whereas ultrarapid metabolizers may produce morphine rapidly and have increased risk of opioid toxicity. CPIC guidance consequently recommends avoiding codeine in CYP2D6 poor and ultrarapid metabolizers and provides phenotype-based recommendations for other metabolizer groups [2,8].This relationship has direct relevance to postoperative dental pain, but it should not be interpreted as a requirement for universal CYP2D6 testing. The clinical question is whether the test result will change the choice of analgesic. When codeine is being considered, a known CYP2D6 phenotype can help identify patients for whom another analgesic would be preferable. Medication review is also essential because CYP2D6 inhibitors can reduce enzyme activity and produce a phenotype that differs from the genetically predicted phenotype, a phenomenon termed phenoconversion [1,9]. Tramadol has a more complex pharmacology than codeine. Its parent compound has monoaminergic activity, while O-desmethyltramadol, formed partly through CYP2D6, has greater μ-opioid receptor activity. CYP2D6 poor metabolizers may therefore obtain reduced opioid-mediated analgesia, whereas ultrarapid metabolism can increase exposure to the active metabolite and potentially increase toxicity [3,10]. Current CPIC recommendations support avoidance of tramadol in CYP2D6 poor and ultrarapid metabolizers. These recommendations are particularly relevant when an opioid is being considered after dental surgery and a non-opioid regimen is insufficient [3].

CYP2C9 contributes to the metabolism of several NSAIDs, including ibuprofen and other commonly used agents. Reduced-function CYP2C9 phenotypes can decrease clearance and increase systemic exposure. CPIC guidance recognizes genotype-dependent differences in NSAID pharmacokinetics and provides recommendations for selected agents [11]. In dentistry, however, the incremental value of routine CYP2C9 testing remains uncertain because NSAID safety is also strongly influenced by renal function, gastrointestinal history, cardiovascular risk, age, treatment duration, and concomitant medicines. Genotype should therefore be regarded as one component of risk assessment rather than an independent measure of NSAID safety (Table 1).

3. PHARMACODYNAMIC GENETIC FACTORS IN PAIN AND LOCAL ANAESTHESIA

OPRM1 encodes the μ-opioid receptor, the principal receptor mediating many opioid effects. COMT influences catecholamine metabolism and has been investigated in relation to pain sensitivity and opioid requirements. Associations between variants in these genes and analgesic response have been reported, but results have not been sufficiently consistent to support routine genotype-based selection or dosing of dental opioids [3,12].

Their current value is therefore primarily research-oriented. A biologically plausible association should not be equated with clinical utility unless it improves prediction beyond conventional clinical variables.Local anaesthetic response is also influenced by biological variability. Voltage-gated sodium channels, including Nav1.7 and Nav1.8 encoded by SCN9A and SCN10A, are involved in peripheral nociceptive signaling. Genetic studies have consequently examined whether sodium-channel variants contribute to differences in pain phenotypes or local anaesthetic response [13]. Evidence remains insufficient to recommend genetic testing for routine local anaesthetic selection or prediction of inferior alveolar nerve block failure.The multifactorial nature of local anaesthetic failure is important in interpreting genetic studies. Inflammation can reduce tissue pH and affect the proportion of unionized anaesthetic available for membrane penetration. Anatomical variation, accessory innervation, injection technique, needle position, drug concentration, volume, and patient-related factors can also contribute [14]. Future studies should therefore determine whether genetic markers add predictive value beyond these established factors rather than simply demonstrating an association with anaesthetic response.

Table 1. Current evidence and potential clinical relevance of major biomarkers in dental pharmacotherapy

Biomarker	Principal therapeutic relevance	Evidence status	Current clinical position
CYP2D6	Codeine; tramadol	Strongest dental pharmacogenomic evidence	Targeted use when these medicines are considered
CYP2C9	Selected NSAIDs	Validated effect on pharmacokinetics; dental utility conditional	Consider in selected patients; not universal screening
OPRM1 / COMT	Opioid response and pain sensitivity	Inconsistent/investigational	Research use; no routine prescribing recommendation
SCN9A / SCN10A	Nociception and local anaesthetic response	Early/investigational	Not recommended for routine anaesthetic selection

4. ORAL MICROBIOME AS A POTENTIAL MODIFIER OF DENTAL PHARMACOTHERAPY

The oral microbiome is a complex ecosystem distributed across saliva, tongue, teeth, gingival tissues and subgingival sites. Its composition and activity are influenced by diet, oral hygiene, periodontal status, host immunity, and antimicrobial exposure. Microbial metabolism contributes to local pH, carbohydrate fermentation, proteolysis, and production of biologically active metabolites. These functions provide a mechanistic basis for considering the microbiome as a potential modifier of treatment response, although most proposed pharmacotherapeutic applications remain experimental [4,5].

One of the best characterized oral microbial functions is nitrate reduction. Commensal bacteria, including members of the genera Neisseria and Rothia, reduce nitrate to nitrite, contributing to the oral–systemic nitric oxide pathway. Recent evidence indicates that nitrate exposure can modify oral microbial communities, while nitrate-reduction capacity is impaired in periodontitis [6,7]. These observations demonstrate a functional relationship between microbial ecology and host physiology. They do not, however, establish that nitrate metabolism can currently be used to select a dental drug or individualize antimicrobial treatment. Microbial drug metabolism is well established in the gastrointestinal tract, where bacteria can chemically modify medicines and alter their activity or exposure. The oral cavity may possess analogous biochemical capabilities, but direct evidence for clinically important transformation of commonly prescribed dental drugs is limited. The amount of drug reaching oral biofilms, local residence time, salivary dilution, pH, and microbial enzyme expression differ from the gastrointestinal environment. Therefore, findings from gut pharmacomicrobiomics should not be directly extrapolated to oral pharmacotherapy [15].

Dental therapeutics can also change the oral microbial ecosystem. Chlorhexidine is a well-studied example; repeated exposure can alter microbial composition, diversity, and nitrate-reducing activity [16,17]. This bidirectional relationship is relevant to antimicrobial stewardship because an intervention designed to suppress pathogenic organisms may also affect health-associated communities. At present, however, there is insufficient evidence to use an individual's microbiome profile to determine the choice or duration of chlorhexidine or antibiotic therapy.

5. PERSONALIZED PHARMACOTHERAPY IN DENTISTRY

Precision dental pharmacotherapy should be organized around a specific clinical decision rather than broad biological profiling. The most established application is selective use of validated pharmacogenomic information for medicines such as codeine and tramadol. If a CYP2D6 phenotype is known and an opioid is being considered, the result can inform selection of an alternative therapy when the predicted phenotype indicates poor efficacy or increased toxicity risk [2,3].

This approach uses pharmacogenomics as an adjunct to clinical assessment rather than as a replacement for it. For NSAIDs, pharmacogenomic information may have greater relevance in patients with substantial exposure risk or complex medication profiles. Nevertheless, genotype does not replace evaluation of renal function, gastrointestinal risk, cardiovascular disease, anticoagulant use, or other interacting medicines [11]. The benefit of testing depends on whether it produces a clinically meaningful change in treatment and whether that change improves outcomes compared with standard care.Microbiome-guided prescribing currently occupies a more exploratory position. Salivary or plaque microbial profiling may be useful for research into disease susceptibility, treatment response and host–microbe interactions, but taxonomic differences alone do not establish a causal mechanism or predict drug efficacy. Functional measurements, longitudinal sampling and intervention studies are required before microbiome data can be incorporated into routine therapeutic algorithms. In medically complex or older dental patients, precision pharmacotherapy may eventually become part of structured medication review. Polypharmacy increases the probability of drug–drug interactions, while organ dysfunction can modify drug exposure. A validated pharmacogenomic result may provide additional information in such cases, but it should be interpreted together with the current medication list, organ function, and clinical indication. This targeted model is more clinically defensible than routine testing of every dental patient.

5.1 Clinical Interpretation of Pharmacogenomic Results

A pharmacogenomic result should be interpreted as a probability modifier rather than a direct measurement of treatment success. Genotype-derived phenotype categories describe expected metabolic activity, but the observed response can also be modified by drug interactions, organ function, age, and disease state. CYP2D6 is a useful example because a patient with a genotype predicting normal metabolism may functionally behave as a poor metabolizer when exposed to a strong CYP2D6 inhibitor. Conversely, genotype alone cannot identify all factors responsible for inadequate postoperative analgesia. Clinical assessment and follow-up remain essential even when a pharmacogenomic result is available [1,9,18].

5.2 Analgesic Selection and Antimicrobial Stewardship

Precision prescribing should also be considered within the broader principle of minimizing unnecessary exposure. Dental pain can often be managed with non-opioid analgesic strategies, and the decision to use an opioid should be based on the severity and expected duration of pain and the patient's risk profile.

Pharmacogenomics is most useful when it changes a specific decision rather than encouraging additional medication use. The same principle applies to antibiotics. A microbiome profile should not be used as a substitute for establishing whether an antibiotic is indicated. Unnecessary antimicrobial exposure can alter microbial ecosystems and may contribute to selection of resistant organisms; therefore, microbiome-aware dentistry should strengthen rather than weaken antimicrobial stewardship [6,16,17].

5.3 Host Factors That Remain Essential

Genetic and microbial information should be integrated with established determinants of dental drug response. Renal and hepatic function influence systemic exposure; inflammation can alter local drug activity; age affects pharmacokinetics and pharmacodynamic sensitivity; and concomitant medicines can produce pharmacokinetic or pharmacodynamic interactions. In patients with substantial comorbidity, these conventional factors may have a larger immediate effect on prescribing than an exploratory genetic or microbiome marker. Precision dentistry should therefore add validated information to clinical assessment rather than replace established medication-safety practices [1,3,11].

6. INTEGRATION OF PHARMACOGENOMICS AND ORAL MICROBIOME EVIDENCE

Drug response in dental patients is determined by interacting host and environmental factors. Genetic variation may influence drug metabolism or receptor activity, while inflammation, tissue characteristics and microbial metabolism can modify the local therapeutic environment. Consequently, an integrated model that combines host genotype, clinical variables and microbial function is biologically attractive. However, integration should be driven by demonstrated incremental clinical value rather than by the availability of multiple data types [19,20]. The main scientific requirement is validation. A candidate biomarker should demonstrate analytical validity, reproducible clinical association, and clinical utility. For pharmacogenomics, this means showing that the variant predicts drug exposure or response and that genotype-guided prescribing improves outcomes. For microbiome research, sampling site, collection method, sequencing platform, and analytical pipeline need standardization. Taxonomic abundance should also be distinguished from functional activity because two communities with different bacterial composition may have similar metabolic capacity [4,5].

Computational methods, including machine learning, may eventually assist in integrating genomic, microbial, and clinical variables, but they should remain secondary to biological and clinical validation. A complex predictive model cannot compensate for poorly characterized biomarkers or inconsistent sampling. If computational decision-support is introduced, it should be externally validated, transparent about uncertainty, and evaluated against clinically meaningful outcomes. The primary objective remains better drug selection and safer treatment, not increased model complexity.

7. CLINICAL APPLICATIONS AND FUTURE DIRECTIONS

The most immediate clinical application is targeted pharmacogenomic support for analgesic selection. CYP2D6 information is particularly relevant when codeine or tramadol is being considered. Future dental services could incorporate pharmacogenomic results into electronic medication records so that validated recommendations are available when an appropriate medicine is prescribed. This would avoid repeated testing and reduce reliance on clinicians remembering genotype-specific recommendations [1,3].

For local anaesthesia, research should move beyond simple candidate-gene association studies. Future investigations should use adequately powered dental cohorts and assess whether genetic markers improve prediction after accounting for inflammation, anatomical factors, injection technique, and clinical characteristics. The outcome should be clinically meaningful anaesthetic success rather than a surrogate laboratory phenotype [13,14]. Oral microbiome research should similarly prioritize longitudinal and functional studies. Important questions include whether microbial metabolic activity predicts response to local antiseptics, whether treatment-induced microbial changes persist after therapy, and whether microbiome-directed interventions improve periodontal or caries outcomes. Studies should distinguish correlation from causation and include clinically relevant endpoints rather than relying only on sequencing-based measures [6,7,16,17].

Implementation also requires attention to cost, turnaround time, laboratory quality, informed consent, genetic privacy, and equitable access. Pharmacogenomic testing is unlikely to be useful when results are unavailable until after a short dental treatment course has ended. Conversely, pre-emptive testing may be more useful in patients who undergo repeated procedures or receive multiple medications. Clinical guidelines, standardized reporting and appropriate education will be necessary for responsible adoption [1,18].

CONCLUSION

Precision dental pharmacotherapy is best understood as an evidence-based extension of individualized prescribing rather than as routine genomic or microbiome screening. CYP2D6 provides the clearest clinically actionable example because variation affects codeine and tramadol response and established recommendations are available. CYP2C9 variation influences NSAID pharmacokinetics, but the value of routine testing in

dental practice remains conditional. OPRM1, COMT, SCN9A and SCN10A remain primarily investigational in this setting.The oral microbiome provides an additional biological layer through microbial metabolism, nitrate reduction, inflammation and ecological responses to antiseptics. Nevertheless, microbiome-guided drug selection has not yet achieved sufficient clinical validation. Future progress should therefore emphasize prospective dental studies, standardized biomarker methods, clinically meaningful outcomes and demonstration that biomarker-guided treatment improves care beyond conventional clinical assessment. Selective implementation of validated pharmacogenomic information, combined with continued investigation of the oral microbiome, represents the most scientifically defensible path toward personalized dental pharmacotherapy. The practical endpoint should be improved pain control, reduced adverse effects, appropriate antimicrobial use and efficient treatment, with testing reserved for situations in which the result can meaningfully alter management.

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