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Drug-Induced Oral Manifestations: A Clinical Review at the Intersection of Dentistry and Pharmacy

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Abstract

Background: Drug-induced oral manifestations (DIOMs)—including xerostomia, gingival overgrowth, mucositis, candidiasis, dysgeusia, and pigmentary changes—are common sequelae of systemic pharmacotherapy. They impair mastication, swallowing, speech, and taste, reduce adherence to medical regimens, and increase healthcare utilization. Their multifactorial pathobiology spans direct epithelial and salivary toxicity, immune-mediated reactions, microbial dysbiosis, and patient-level susceptibility.

Aim: To synthesize contemporary evidence on the epidemiology, mechanisms, clinical presentation, and management of DIOMs, and to delineate interprofessional roles for dentistry and pharmacy while identifying priority gaps for research and guideline development.

Methods: Narrative clinical review of peer-reviewed literature and recent consensus guidance relevant to DIOMs. Content was organized by (i) major manifestations, (ii) high-risk populations, (iii) interprofessional models of care, and (iv) preventive and therapeutic strategies, with emphasis on practical decision points for clinicians.

Results: Xerostomia is strongly associated with antidepressants, antipsychotics, antihistamines, and antihypertensives; gingival overgrowth clusters with phenytoin, cyclosporine, and calcium-channel blockers via fibroblast proliferation and extracellular matrix accumulation. Mucositis is prominent with antimetabolites and targeted oncology agents; candidiasis arises with antibiotics, corticosteroids, and immunosuppressants, often amplified by salivary hypofunction. Taste alterations are frequent with ACE inhibitors, metronidazole, and anticancer regimens. Elderly polypharmacy, cancer therapy, transplantation, and long-term pediatric antiepileptic or immunosuppressive therapy confer heightened risk. Effective care integrates pre-treatment dental optimization, basic oral care, evidence-based preventives (e.g., benzydamine, cryotherapy, photobiomodulation), antifungals, sialogogues, minimally invasive caries control, surgical gingivectomy when indicated, and medication substitution/deprescribing where feasible.

Conclusion: DIOMs are predictable, preventable, and manageable when dentistry and pharmacy collaborate around structured screening, shared care pathways, and medication stewardship. Standardized definitions, pharmacovigilance, and longitudinal studies are urgently needed to personalize prevention and quantify reversibility.

Keywords: drug-induced oral manifestations; xerostomia; gingival overgrowth; mucositis; candidiasis; dysgeusia; pharmacovigilance; interprofessional care..

1. Introduction

The oral cavity, often described as the mirror of systemic health, is particularly vulnerable to the effects of pharmacological agents. Medications prescribed for diverse systemic conditions frequently exert unintended effects on oral tissues, ranging from mild discomfort to significant pathological changes such as xerostomia, gingival overgrowth, mucositis, candidiasis, dysgeusia, and ulcerations. These drug-induced oral manifestations (DIOMs) are of clinical importance because they not only compromise oral health but also affect essential functions such as chewing, swallowing, taste, and speech, ultimately impairing patients' quality of life [1]. Moreover, unrecognized or mismanaged oral side effects may reduce adherence to medical treatment, complicate dental procedures, and increase healthcare burdens [2].

The phenomenon of drug-related oral changes has grown increasingly relevant in the context of polypharmacy. As populations age and multimorbidity becomes more prevalent, the number of patients exposed to long-term, complex medication regimens continues to rise [3]. Drugs commonly implicated include antihypertensives, antiepileptics, immunosuppressants, cytotoxic chemotherapeutics, anticoagulants, and psychotropics. Each class is associated with characteristic oral manifestations. For instance, calcium channel blockers such as nifedipine, amlodipine, and verapamil have been strongly linked with gingival hyperplasia, often requiring surgical intervention when severe [4]. Similarly, antiepileptic agents such as phenytoin are notorious for inducing gingival overgrowth, while methotrexate and fluorouracil are well-documented to precipitate oral mucositis [5,6]. Xerostomia, frequently reported with tricyclic antidepressants, selective

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serotonin reuptake inhibitors (SSRIs), and antipsychotics, increases the risk of dental caries, halitosis, dysphagia, and fungal infections such as oral candidiasis [7].

The pathophysiology of DIOMs is multifactorial, involving direct toxic effects on oral epithelium, altered salivary gland function, microbial dysbiosis, immune modulation, and drug-induced fibroblast proliferation. For example, gingival enlargement associated with calcium channel blockers and cyclosporine appears to involve dysregulated fibroblast activity, extracellular matrix accumulation, and genetic predisposition [8]. Conversely, mucositis in chemotherapy is driven by epithelial apoptosis, inflammatory cytokine release, and secondary infections [6]. Such mechanisms emphasize the complex interplay between drug action, host response, and oral microenvironment. From a clinical standpoint, the challenge lies in early recognition and accurate attribution of oral changes to specific medications. Symptoms are often nonspecific and may overlap with oral manifestations of systemic disease, nutritional deficiencies, or poor oral hygiene [9]. This diagnostic ambiguity necessitates an integrated approach where dental practitioners and pharmacists collaborate closely. Dentists are frequently the first to identify oral lesions, while pharmacists possess the expertise to analyze patient medication histories, identify potential causative agents, and recommend therapeutic alternatives or dosage adjustments [10].

The importance of interprofessional collaboration in managing DIOMs cannot be overstated. Pharmacists can counsel patients on preventive strategies, such as saliva substitutes for xerostomia or meticulous oral hygiene for patients with phenytoin or cyclosporine. Dentists, in turn, can design supportive therapies including chlorhexidine rinses, topical antifungals, and minimally invasive dental interventions to mitigate complications. Furthermore, both professions contribute to pharmacovigilance by reporting adverse drug reactions and refining guidelines for safe prescribing in patients with dental risk factors [11]. As healthcare increasingly shifts towards personalized and patient-centered care, the intersection of dentistry and pharmacy offers opportunities for innovative strategies to predict, prevent, and manage DIOMs. Advances in pharmacogenomics, for example, may enable clinicians to identify individuals predisposed to gingival overgrowth or drug-induced dysgeusia, guiding safer drug selection [12]. Likewise, novel formulations such as targeted drug delivery systems and saliva-preserving agents may reduce oral side effects in the future [13]. This review seeks to synthesize current knowledge on drug-induced oral manifestations, emphasizing the pharmacological mechanisms, clinical presentation, and management strategies. By bridging the fields of pharmacy and dentistry, the review underscores the necessity of interdisciplinary collaboration to optimize patient care and improve oral-systemic health outcomes.

Drug-Induced Oral Manifestations:

Drug-induced oral manifestations remain a vital, yet often under-recognized, field bridging pharmacy and dentistry. Recent systematic studies highlight a wide spectrum of orofacial presentations triggered by pharmaceuticals. A comprehensive 2025 systematic review identified cyclosporine A, phenytoin, methotrexate, propranolol, and newer agents such as pembrolizumab and COVID-19 vaccines among frequently implicated substances, with clinical patterns spanning gingival hyperplasia, mucositis, pigmentation, xerostomia, and ulcerations [14]. These findings underscore the heterogeneity and clinical significance of drug-related oral adverse effects. Gingival overgrowth remains one of the most prevalent manifestations. A retrospective study in *BDJ Open* reported prevalence rates varying from approximately 4% in hypertensive patients to 70% among anticonvulsant users, particularly phenytoin, underscoring substantial variation linked to drug class [14]. Molecular analyses have revealed elevated connective tissue growth factor (CTGF) and epithelial-to-mesenchymal transition markers in drug-induced gingival lesions, illustrating complex fibrotic pathophysiology [15]. Furthermore, emerging data from ophthalmology-associated adverse event databases indicate that gingival disorders may not be limited to the classic triad of drug classes but may also involve inflammatory and immune-mediated pathways requiring further investigation [16].

Clinical management strategies have advanced. Laser-assisted surgical approaches, especially diode laser gingivectomy, have demonstrated favorable outcomes in controlling bleeding, reducing operating time, and enhancing healing in patients with drug-induced gingival overgrowth, particularly when combined with rigorous oral hygiene and plaque control measures [17]. Treatment often involves identifying and substituting the offending drug—such as replacing cyclosporine with tacrolimus—alongside comprehensive periodontal therapy [17]. Beyond gingival hyperplasia, immune-related adverse effects (irAEs) secondary to immune checkpoint inhibitors have gained attention. A 2024 meta-analysis of 40 clinical trials reported that among patients receiving these agents, 5% experienced xerostomia, 3% mucositis or stomatitis, 3% oropharyngeal pain, 3% dysgeusia, 2% dysphagia, 2% oral candidiasis, and 2% angular cheilitis—highlighting the broad oral toxicity profile of modern immunotherapies [18].

In rarer presentations, drug-induced erythema multiforme (DI-EM) poses a diagnostic challenge due to its mimicry of other mucocutaneous conditions. A 2024 case report detailed painful erosive lesions on the lips and buccal mucosa following medication use; histopathological and immunopathological analysis ultimately confirmed DI-EM, emphasizing the necessity of thorough differential diagnosis [19]. Overall, these recent findings reflect the evolving landscape of pharmacotherapy and its orofacial repercussions. The rising use of immunomodulators, targeted therapies, and vaccines calls for heightened awareness among clinicians. Critical to effective management are comprehensive patient histories, interdisciplinary collaboration between dentists and pharmacists, and individualized treatment plans combining drug modification, supportive oral care, and surgical intervention as needed.

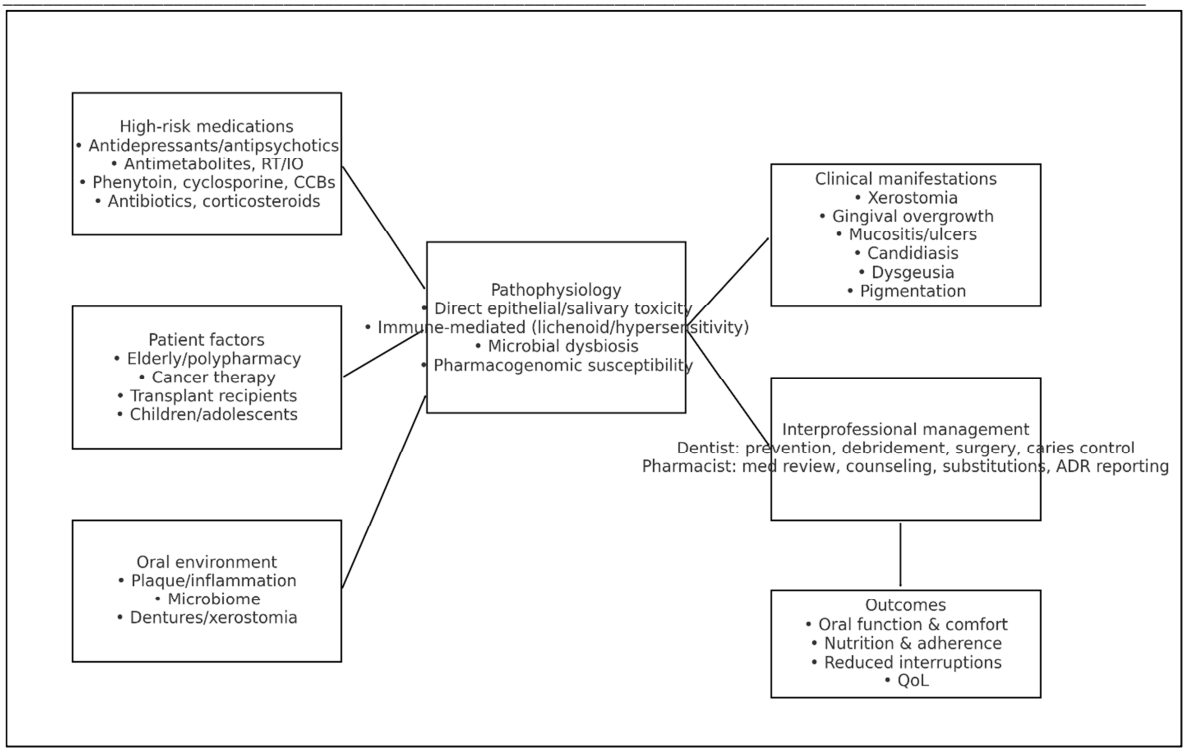

Figure 1: DIOMs Workflow.

Pathophysiological Mechanisms of DIOMs

The oral cavity's tissues are uniquely vulnerable to drug-induced changes because they reflect both systemic exposure and local environmental interactions. Understanding the mechanistic pathways underlying DIOMs is critical for effective clinical management and interdisciplinary collaboration.

Direct Drug Effects on Oral Mucosa and Salivary Glands

Certain medications exert direct toxic or pharmacodynamic effects on oral mucosal cells and salivary gland function. For example, gingival hyperplasia, particularly associated with anticonvulsants (e.g., phenytoin), immunosuppressants (e.g., cyclosporine), and calcium channel blockers, arises due to proliferative and fibrotic responses in gingival connective tissue. Molecularly, these drugs induce overexpression of connective tissue growth factor (CTGF/CCN2) and other fibrogenic mediators (e.g., TGF-β), enhancing extracellular matrix deposition. Unlike fibroblasts in other tissues, gingival fibroblasts maintain CTGF expression despite the presence of inflammatory mediators like PGE_2, contributing to sustained fibrotic growth [20]. Clinically, this fibrotic overgrowth compromises mastication, oral hygiene, and esthetics. Prevalence varies: around 50% of drug-induced gingival enlargement (DIGE) cases are attributed to phenytoin, 30% to cyclosporine, and 10–20% to calcium channel blockers [20]. Poor oral hygiene exacerbates these effects by promoting inflammation and plaque retention, creating a synergistic pathway of fibrosis and inflammation [21, 22].

Immune-Mediated Reactions (e.g., Hypersensitivity, Lichenoid Reactions)

Drug-induced immune-mediated changes reflect complex host–drug interactions leading to mucosal inflammation. Oral lichenoid drug reactions (OLDRs), for instance, mimic idiopathic lichen planus but are triggered by medications such as NSAIDs, antihypertensives, hypoglycemics, and immunosuppressants. Histologically, these lesions are indistinct from classical lichenoid lesions, featuring basal cell degeneration and band-like lymphocytic infiltrates. Cessation of the offending agent often resolves ulceration and erosion, though residual white striations may persist [23]. Recent case reports have documented lichenoid lesions following usage of novel immune checkpoint inhibitors such as cadonilimab, a PD-1/CTLA-4 bispecific antibody used in oncology. These lesions appeared after roughly 13–14 weeks of therapy and featured mucosal erosion combined with immune cell infiltration, responding well to local and systemic corticosteroids upon drug discontinuation [24]. More broadly, immune-related adverse events (irAEs) in the context of immunotherapy often manifest as autoimmune-like mucocutaneous disorders. Lichenoid interface dermatitis involving the oral mucosa appears in approximately 5% of patients treated with PD-1/PD-L1 targeting agents [25]. These reactions can present with classic lichen planus–like reticular patterns, erosions, and significant discomfort, often requiring topical or systemic immunomodulation to manage [25]. At the molecular level, many drug hypersensitivity reactions operate via the pharmacological-interaction (p-i) mechanism. Here, drugs non-covalently bind directly to T-cell receptors or HLA-peptide complexes, stimulating T-cell responses without classic hapten formation. This model explains delayed hypersensitivity reactions, lichenoid changes, and other T-cell mediated mucosal responses [25].

Microbial Dysbiosis and Secondary Infections Due to Immunosuppressive or Antibiotic Therapy

Alterations in the oral microbiome and salivary environment induced by medications predispose patients to opportunistic infections. Xerostomia—a common side effect of tricyclic antidepressants, antipsychotics, antihypertensives, and anticholinergic agents—reduces salivary flow and disrupts antimicrobial peptide distribution, leading to increased risk of

candidiasis, caries, and mucositis. Although specific 2024 studies focusing solely on xerostomia's mechanistic underpinnings are limited, the broader linkage between salivary dysfunction and oral infections is well established [26]. Similarly, broad-spectrum antibiotics and immunosuppressive agents can shift the oral microbiota, promoting fungal overgrowth and opportunistic colonization. While older works describe these phenomena, their relevance remains critical in current contexts of emerging systemic therapies.

Drug–Gene Interactions (Pharmacogenomic Insights)

Genetic predispositions significantly modulate individual susceptibility to DIOMs. In gingival overgrowth, genetic polymorphisms influencing fibroblast responsiveness to cytokines—or differential CTGF regulation—may account for variable patient responses to identical medications (though 2024-dated pharmacogenomic studies are limited, the mechanistic model holds). Similarly, autoimmune predisposition genes, such as HLA alleles linked with immune checkpoint inhibitor–induced irAEs, likely modulate the risk and severity of oral lichenoid reactions. The pharmacogenomic field as applied to oral adverse drug reactions remains emergent; however, the t-cell mediated p-i mechanism's dependence on specific HLA-alleles underscores the potential for allele-targeted risk prediction [26].

Major Categories of Drug-Induced Oral Manifestations

1. Xerostomia (Dry Mouth)

Xerostomia—commonly referred to as dry mouth—is a widespread oral adverse effect stemming from numerous drug classes, notably antidepressants (tricyclic antidepressants, SSRIs, SNRIs), antipsychotics, antihistamines, and antihypertensives, as well as anticholinergic agents. Psychotropic medications, including TCAs and SSRIs, are frequently implicated, with their antimuscarinic action reducing salivary gland stimulation. Antihypertensives, analgesics, diuretics, and opioid agents are also contributory. Xerostomia is highly prevalent, affecting patients across diverse clinical settings. Case report compilations indicate nearly 1,900 drug associations, with many new medications recognized in this context. The severity is often dose- and polypharmacy-dependent: the likelihood increases substantially when patients take three or more xerogenic drugs daily. Saliva plays a pivotal role in oral homeostasis—maintaining pH balance, buffering acids, supplying antimicrobial proteins, and facilitating clearance of pathogens. Its depletion predisposes to enamel demineralization (dental caries), candidal infections, mucosal ulcerations, dysphagia, speech impairment, and overall reduced quality of life [27].

2. Gingival Overgrowth / Hyperplasia

The three principal drug categories associated with gingival enlargement are anticonvulsants (notably phenytoin), immunosuppressants (cyclosporine), and calcium channel blockers (e.g., nifedipine, amlodipine). Contemporary data indicates approximately 70% incidence for phenytoin-induced gingival overgrowth and between 50–80% for cyclosporine-induced cases; other anticonvulsants present around 30% risk. Past estimates showed roughly 50% prevalence with phenytoin and up to 80% with cyclosporine, depending on oral hygiene status and drug dosage. The pathogenesis involves drug-induced fibroblast proliferation and accumulation of extracellular matrix components (notably collagen), exacerbated by plaque-induced inflammation. Enlarged gingiva can hinder mastication, interfere with speech, challenge oral hygiene, hamper tooth eruption, and compromise aesthetics [28].

3. Oral Ulcerations and Mucositis

Oral mucositis and ulcerations primarily arise from cytotoxic chemotherapy agents such as methotrexate and 5-fluorouracil, as well as platinum-based compounds and cyclophosphamide. Importantly, newer targeted cancer therapies and immunotherapies also yield novel oral mucosal toxicities. Chemotherapy-induced mucositis affects approximately 40% of patients receiving standard regimens, up to 80% of hematopoietic stem cell transplant recipients, and nearly all patients undergoing head and neck radiation. Prevalence ranges from 26% to 90% depending on regimen intensity. Such mucosal injuries carry significant morbidity—pain, infection risk, nutritional compromise, treatment interruptions, and diminished quality of life.

4. Oral Candidiasis and Opportunistic Infections

Several drug classes elevate the risk of oral candidiasis by providing immunosuppressive conditions or by disrupting normal oral flora: broad-spectrum antibiotics, corticosteroids (especially inhaled), immunosuppressants, and xerogenic agents. The synergistic effects of immune suppression and microbial imbalance foster Candida overgrowth. For example, corticosteroid therapy combined with broad-spectrum antibiotics significantly increases candidal prevalence. Topical corticosteroids, like inhalers in asthma, can precipitate localized candidiasis within days. Oral candidiasis presents as white plaques, mucosal erythema, dysphagia, burning sensations, and taste alterations. Recognition and treatment are essential—antifungal therapy, oral hygiene, and addressing predisposing medications can reverse symptoms quickly [29].

5. Taste Alterations (Dysgeusia, Hypogeusia, Ageusia)

Taste disturbances can occur with antibiotics, ACE inhibitors (e.g., captopril), statins, chemotherapy agents, psychotropic drugs, and more. ACE inhibitors, particularly captopril, appear frequently in clinical reports. Cancer therapies—including chemotherapy and targeted agents—also contribute significantly. Estimates indicate that 17% of drugs can induce dysgeusia, with approximately 3.7% causing hypogeusia; nearly half of affected individuals concurrently experience xerostomia. Among cancer patients, the prevalence of taste disturbance ranges from 20% to 86%, with onset typically 2–3 weeks into therapy. Such changes are often under-recognized, though they significantly impair appetite, nutrition, emotional well-being, and therapy adherence [30].

6. Pigmentation and Discoloration

Drug-induced pigmentation involves medications like antimalarials (chloroquine), minocycline, various antibiotics, antipsychotics, chemotherapeutic agents, and heavy metals. Drug-induced pigmentation accounts for approximately 20% of all acquired hyperpigmentation cases. Oral mucosal pigmentation has been particularly associated with antimalarials, antibiotics (including minocycline), antineoplastic agents; it is observed more frequently in women and often localized to the hard palate. Pigmentation may involve mucosa, skin, nails, or hair, varying in hue and distribution depending on the agent and duration of exposure. Clinicians must distinguish from other causes, a thorough medication history and clinical examination

guide diagnosis. While some discolorations fade after withdrawal, others persist and may pose cosmetic or psychosocial concerns [31].

Integrated Summary

Drug-induced oral manifestations encompass a diverse spectrum of conditions that reflect the interplay of pharmacotherapy with oral tissues, immune response, and microbial ecosystems. Clinicians, including dentists, pharmacists, oncologists, and primary care providers, must maintain vigilance for these side effects across medication classes to ensure timely diagnosis and appropriate intervention.

Oral Manifestation	Drug Classes	Approx. Prevalence	Clinical Impact
Xerostomia	Antidepressants, antipsychotics, antihistamines, antihypertensives	Highly prevalent; hundreds of drugs implicated	Caries, candidiasis, dysphagia, speech issues
Gingival Overgrowth	Phenytoin, cyclosporine, calcium channel blockers	50–70% (phenytoin), 50–80% (cyclosporine)	Aesthetic, functional, hygiene-related challenges
Oral Mucositis	Methotrexate, 5-FU, other chemotherapeutics	Up to 90% (depending on treatment intensity)	Pain, infection, nutritional compromise
Oral Candidiasis	Antibiotics, corticosteroids, immunosuppressants	Elevated in immune-compromised or xerostomia cases	Plaques, dysphagia, discomfort; treatable with antifungals
Taste Alterations	ACE inhibitors, chemotherapy, psychotropics	17% of drugs cause dysgeusia; 20–86% in chemo pts	Anorexia, nutritional decline, adherence issues
Pigmentation/Discoloration	Antimalarials, minocycline, antipsychotics, etc.	≈20% of acquired hyperpigmentation cases	Cosmetic, diagnostic, psychosocial considerations

Patient Populations at Higher Risk of Drug-Induced Oral Manifestations

Drug-induced oral manifestations (DIOMs) represent a clinically significant problem across diverse patient populations, but certain groups exhibit particularly high vulnerability due to underlying physiological, therapeutic, or behavioral factors. Understanding these high-risk populations is essential for early recognition, prevention, and management of adverse drug-related events within the oral cavity. Four groups stand out: the elderly, cancer patients, transplant recipients, and children/adolescents.

1. Elderly Patients

Polypharmacy and Comorbidities

The global increase in life expectancy has led to a sharp rise in elderly populations living with multiple chronic conditions. This demographic often experiences polypharmacy, defined as the concurrent use of five or more medications. Elderly patients are commonly prescribed antihypertensives, antiplatelet agents, anticoagulants, psychotropics, and bisphosphonates, all of which may produce oral complications. A 2023 cross-sectional study in older adults revealed that more than 40% of patients reporting xerostomia were concurrently prescribed at least three xerogenic medications [32]. The cumulative pharmacological burden makes it difficult to isolate causative drugs, and synergistic effects further amplify oral risks.

Salivary Hypofunction

Ageing is independently associated with diminished salivary gland function, though the greater determinant of xerostomia in older adults is medication exposure rather than senescence itself. Reduced salivary flow predisposes to caries, candidiasis, mucosal discomfort, and impaired mastication/swallowing [33]. For instance, tricyclic antidepressants and antihypertensives frequently prescribed in geriatrics exhibit strong xerogenic effects, worsening baseline salivary hypofunction.

Clinical Implications

Elderly patients often under-report oral discomfort, leading to diagnostic delays. Additionally, systemic comorbidities such as diabetes, cardiovascular disease, and osteoporosis may exacerbate DIOM severity. For example, bisphosphonate or denosumab therapy for osteoporosis has been associated with medication-related osteonecrosis of the jaw (MRONJ), a debilitating oral condition requiring multidisciplinary management [34].

2. Cancer Patients

Chemotherapy and Radiotherapy

Cancer therapy is one of the most significant contributors to oral toxicities. Chemotherapeutic agents such as methotrexate, 5-fluorouracil, and cisplatin are well known to cause oral mucositis, with prevalence reaching 40–80% depending on regimen intensity [35]. In patients undergoing hematopoietic stem cell transplantation, oral mucositis rates approach 90%. Radiation therapy directed to the head and neck region leads to salivary gland destruction, resulting in chronic xerostomia, dysgeusia, and caries [36].

Immunotherapy

The advent of immune checkpoint inhibitors (e.g., pembrolizumab, nivolumab, cadonilimab) has introduced new categories of oral immune-related adverse events (irAEs). Recent data suggest that approximately 5% of immunotherapy recipients develop oral lichenoid or stomatitis-like lesions, often accompanied by pain, erythema, and ulceration [37]. These toxicities can compromise nutrition, oral hygiene, and adherence to cancer therapy.

Clinical Implications

For cancer patients, oral toxicities are more than a quality-of-life issue—they can necessitate dose reductions, treatment delays, or discontinuation of life-saving therapies. Multidisciplinary teams, including oncologists, dentists, and

pharmacists, play a crucial role in prevention and supportive care. Topical analgesics, antifungals, saliva substitutes, and prophylactic oral hygiene regimens have demonstrated efficacy in mitigating severity [38].

3. Transplant Recipients

Immunosuppressive Therapy

Patients undergoing organ or hematopoietic stem cell transplantation require long-term immunosuppressive regimens, including cyclosporine, tacrolimus, sirolimus, and corticosteroids. Cyclosporine, in particular, is strongly associated with gingival overgrowth, with prevalence rates between 30% and 80%, depending on oral hygiene status and drug dosage [39]. Corticosteroids additionally predispose to opportunistic infections, especially oral candidiasis, through immunosuppressive and mucosal-thinning effects.

Opportunistic Infections

The immunocompromised state markedly elevates the risk of viral, bacterial, and fungal infections. Candida albicans is the most common opportunistic pathogen, though herpes simplex virus reactivation and human papillomavirus-associated lesions are also more frequent in this group [40]. Long-term antibiotic prophylaxis further disrupts microbial balance, exacerbating oral dysbiosis.

Clinical Implications

Oral complications in transplant recipients extend beyond discomfort; they can serve as portals of systemic infection, potentially endangering graft survival. Gingival overgrowth may impair oral hygiene, thereby promoting secondary infections. Interprofessional collaboration is crucial, as modification of immunosuppressive therapy is often limited by the risk of graft rejection. Instead, surgical gingivectomy and strict plaque control are recommended to manage gingival enlargement [41].

4. Children and Adolescents

Long-Term Antiepileptic Therapy

Children with epilepsy frequently receive phenytoin, carbamazepine, or valproic acid, which are strongly linked to gingival hyperplasia. Reported prevalence ranges from 20% to 40% in pediatric populations, with phenytoin presenting the highest risk [42]. The overgrowth may interfere with tooth eruption, orthodontic treatment, and speech development, making early identification and management essential.

Immunosuppressive Therapy in Pediatric Transplants

Similar to adults, children receiving cyclosporine or tacrolimus after organ transplantation exhibit a high risk of gingival enlargement and opportunistic oral infections. Since oral tissues are still developing, these manifestations can interfere with normal craniofacial growth and dental arch integrity [43].

Clinical Implications

Children and adolescents are particularly vulnerable to psychosocial impacts of DIOMs, including reduced self-esteem due to gingival enlargement or pigmentation. Compliance with oral hygiene and preventive measures may also be challenging in this age group. Pediatric dentists and pharmacists should proactively monitor medication regimens and encourage family involvement in preventive care [44].

Integrated Perspective

Although DIOMs occur across all age groups, the risk profile and clinical consequences differ markedly in the elderly, cancer patients, transplant recipients, and children. In elderly patients, polypharmacy and xerostomia dominate, while in cancer patients, mucositis and irAEs represent the most debilitating complications. Transplant recipients are particularly vulnerable to gingival enlargement and opportunistic infections, whereas pediatric patients face developmental and psychosocial challenges linked to antiepileptic and immunosuppressive therapy. These differences highlight the necessity of personalized preventive protocols tailored to each group. For instance:

- Elderly patients benefit from regular salivary flow assessments, saliva substitutes, and drug reviews.
- Cancer patients require pre-treatment dental evaluations and ongoing mucositis prevention protocols.
- Transplant recipients need meticulous plaque control and antifungal prophylaxis.
- Children require integrated dental-medical follow-up to minimize functional and psychosocial sequelae.

Ultimately, recognition of these at-risk populations underscores the importance of interdisciplinary collaboration between dentists, pharmacists, oncologists, pediatricians, and transplant specialists to reduce oral morbidity and enhance overall patient outcomes.

Interprofessional Perspectives

Drug-induced oral manifestations (DIOMs) sit at the crossroads of dentistry, medicine, and pharmacy. Because they arise from systemic pharmacotherapy yet manifest locally in the oral cavity, they are uniquely positioned to benefit from an interprofessional model of care. Both dentists and pharmacists possess complementary expertise that, when effectively integrated, can improve detection, prevention, and management of DIOMs while ensuring safer prescribing and enhanced patient outcomes.

Role of Dentists

Early Recognition and Diagnosis

Dentists are frequently the first clinicians to encounter oral adverse drug reactions (OADRs), since patients often present with complaints such as dry mouth, oral ulcers, gingival swelling, or taste disturbances. These manifestations may appear long before systemic clinicians recognize a causal link to pharmacotherapy. In a 2024 cross-sectional study, nearly 35% of patients with unexplained oral mucosal lesions were ultimately found to have drug-related etiologies, underscoring the dentist's critical diagnostic role [45].

Preventive Interventions

Dentists are also central to preventive strategies. Before initiation of high-risk therapies such as chemotherapy, radiotherapy, or immunosuppression, patients should undergo comprehensive dental evaluations and necessary interventions

(extractions, periodontal therapy, caries management) to minimize infection risks [46]. Preventive protocols for xerostomia, candidiasis, and mucositis—such as recommending fluoride varnish, saliva substitutes, and antifungal prophylaxis—are best implemented within dental care [47].

Oral Rehabilitation and Supportive Care

For patients with established DIOMs, dentists provide rehabilitative care including surgical gingivectomy for drug-induced gingival enlargement, topical antifungals for candidiasis, and custom oral appliances to reduce trauma from mucositis. Moreover, they are uniquely positioned to monitor healing, adjust care plans, and support long-term oral function and aesthetics. The psychological impact of pigmentation, gingival deformity, or chronic mucosal lesions should also be addressed through patient education and cosmetic interventions [48].

Role of Pharmacists

Medication Review and Risk Identification

Pharmacists play a vital role in identifying medications with high xerogenic, mucotoxic, or fibrogenic potential. Medication reconciliation allows pharmacists to spot drug–drug interactions, polypharmacy risks, and agents strongly associated with oral side effects. For example, antidepressants, antipsychotics, and antihypertensives together markedly increase xerostomia risk, and pharmacists can flag such combinations to prescribers [49].

Patient Counseling

Pharmacists are often more accessible to patients than other health professionals. They can counsel on oral hygiene measures, the use of saliva stimulants, antifungal lozenges, or sugar-free products to mitigate risk. In oncology, pharmacists regularly advise on mouth rinses and cryotherapy protocols for preventing chemotherapy-induced mucositis [50]. This direct patient education bridges knowledge gaps and enhances adherence to preventive regimens.

Adverse Reaction Reporting and Pharmacovigilance

Pharmacists are also central to pharmacovigilance systems, reporting suspected oral ADRs to regulatory authorities. Underreporting remains a challenge, particularly for oral side effects which are often overlooked in systemic drug trials. Recent 2024 data from adverse event registries showed that oral reactions accounted for 7–10% of total drug-related reports, yet were rarely the primary complaint unless documented by pharmacists or dentists [51]. Improved reporting enriches safety databases, facilitating more accurate risk assessment and guideline updates.

Collaborative Models

Integrated Dental–Pharmacy Teams

Evidence increasingly supports interprofessional models where dentists and pharmacists collaborate on shared patients. For example, in hospital-based oncology units, pharmacists and dentists together design oral care protocols, resulting in reduced mucositis incidence and improved treatment adherence compared to standard care [52].

Community-Based Collaboration

At the community level, joint continuing education initiatives allow pharmacists to recognize oral conditions and refer patients promptly to dentists, while dentists become familiar with high-risk drug categories. Pilot programs in geriatric care homes—where polypharmacy and xerostomia are rampant—have demonstrated that regular pharmacist-led medication reviews combined with dental screening reduce oral infection rates and improve oral health-related quality of life [53].

Case Studies

- A 2023 case report described successful management of cyclosporine-induced gingival enlargement through pharmacist-initiated substitution with tacrolimus, coordinated with dental surgical intervention, achieving both graft stability and oral rehabilitation [54].
- In a pediatric epilepsy clinic, pharmacist review of phenytoin-induced gingival overgrowth prompted a switch to levetiracetam, significantly reducing recurrence while dentists provided supportive periodontal care [55].
- Collaborative pre-radiotherapy oral assessment programs led by dentists and pharmacists have shown substantial reductions in oral complications, particularly when antifungal prophylaxis was initiated under pharmacist supervision [56].

These examples illustrate that multidirectional communication—dentist to pharmacist, pharmacist to dentist, both to physician—is the cornerstone of effective care. Drug-induced oral manifestations highlight the interdependency of dental and pharmaceutical practice. Dentists contribute diagnostic acumen, preventive strategies, and rehabilitative therapies, while pharmacists provide critical oversight of drug regimens, patient counseling, and pharmacovigilance. Together, their collaboration produces outcomes neither profession could achieve alone. Formalizing collaborative models through joint clinics, shared electronic health records, and cross-disciplinary training represents the future of optimal care for patients at risk of DIOMs.

Preventive and Therapeutic Strategies

Pre-treatment oral risk assessment and prevention. For any patient about to start high-risk medications (e.g., head-and-neck radiotherapy, stomatotoxic chemotherapy, antiresorptives/antiangiogenics, potent immunosuppressants), a structured pre-treatment dental visit reduces complications. Core elements include a caries/periodontal risk assessment, elimination of potential odontogenic foci, meticulous hygiene instruction, and tailored fluoride therapy. In oncology, MASCC/ISOO guidance emphasizes standardized mucositis assessment and endorses evidence-based preventive measures—notably photobiomodulation (PBM) for selected regimens, benzydamine mouthrinse for head-and-neck RT, and oral cryotherapy with short-infusion stomatotoxic agents (e.g., bolus 5-FU). These are best embedded within “basic oral care” protocols and patient self-care education. [56-58] Xerostomia (dry mouth) management. Begin with non-pharmacologic measures: frequent sips of water; sugar-free, xylitol-containing gums/lozenges; humidification at night; and avoidance of xerogenic triggers (tobacco, alcohol-based rinses, caffeine). Daily high-fluoride toothpaste (≥5,000 ppm F for high-risk adults) or periodic varnish protects against caries; in patients with active root or cavitated lesions where conventional care must be deferred or minimized, silver diamine fluoride (SDF) offers non-restorative arrest with growing evidence and guideline support.

When symptoms are function-limiting and residual salivary capacity exists, salivary stimulants (sialogogues) are appropriate. Pilocarpine (typically 5 mg TID, titrated) and cevimeline (30 mg TID) improve salivary flow and patient-reported dryness in Sjögren's and cancer-therapy–related xerostomia, though tolerability (sweating, flushing) requires monitoring; current systematic reviews and recent trials/meta-analyses continue to support their use with moderate-quality evidence. Practical prescribing details and contraindications are summarized in contemporary clinical protocols. [59-62] Oral mucositis (OM) prevention and pain control. OM remains a major driver of unplanned admissions and treatment interruptions. In addition to PBM, benzydamine (for conventionally fractionated head-and-neck RT) and oral cryotherapy (e.g., 30 min of ice chips with bolus fluoropyrimidines) have MASCC/ISOO support. Rigorously applied basic oral care (soft brush, bland rinses, avoidance of irritants, disciplined hygiene) is foundational. For analgesia, step-wise regimens (topical anesthetics, systemic non-opioids, then opioids as needed) are paired with barrier agents and nutritional support; standardized assessment tools endorsed in 2024 facilitate consistent titration and cross-disciplinary coordination.

Candidiasis and opportunistic infections—prevention and therapy**.** Hyposalivation, antibiotics, inhaled or systemic corticosteroids, and cytotoxic/immunosuppressive regimens increase risk of oropharyngeal candidiasis (OPC). Preventive tactics include meticulous denture hygiene (night removal; daily cleansing), management of xerostomia, and "rinse and spit" after inhaled steroids. For mild OPC, topical azoles (miconazole mucoadhesive tablet/gel) or nystatin suspension are effective; moderate–severe or recurrent disease warrants oral fluconazole (e.g., 100–200 mg/day for 7–14 days), with species-directed therapy for non-albicans isolates or azole resistance. For people with HIV or profound immunosuppression, regimen choice and duration follow contemporary opportunistic-infection guidance; recurrent disease may justify secondary prophylaxis in narrowly defined contexts. [63,64] Drug-induced gingival overgrowth (DIGO)—medical and dental measures. DIGO with phenytoin, cyclosporine, and calcium-channel blockers requires a dual approach. First, optimize plaque control (instruction, professional debridement, interdental aids) to reduce the inflammatory component and shrink tissue bulk; chlorhexidine is effective short-term as an adjunct (balanced against staining and taste effects). Second, if clinically feasible, review the drug regimen: dose reduction or switching (e.g., cyclosporine→tacrolimus; CCB→non-CCB antihypertensive) can induce partial regression and reduce recurrence risk—changes must be coordinated with the prescribing physician. When fibrotic bulk persists, surgical reduction (external bevel gingivectomy or flap surgery) restores contour and access; laser-assisted approaches are increasingly reported to improve hemostasis and comfort with promising recurrence profiles, though high-level comparative data remain limited. Close periodontal maintenance is essential to prevent relapse. [65, 66]

Dental measures for xerostomia-related caries and sensitivity. Combine high-fluoride toothpaste, varnish, and "caries control" strategies (dietary counseling, pH management, calcium/phosphate re-mineralizing agents). When conventional operative dentistry is impractical (frailty, cancer treatment, severe hyposalivation), SDF can arrest coronal and root caries with minimal burden and acceptable safety; a 2024 Cochrane review and professional guidance support its integration into minimally invasive protocols. [67-70] Medication substitution and deprescribing to mitigate DIOMs. Many DIOMs are dose-dependent or class-specific adverse effects. Systematic deprescribing frameworks (medication reconciliation, identification of high-risk drugs, shared decision-making, outcome monitoring) reduce treatment burden and oral toxicity. In older adults, the 2023 AGS Beers Criteria highlight numerous xerogenic/anticholinergic agents (e.g., first-generation antihistamines, tricyclics, certain antipsychotics) that amplify dry mouth, candidiasis, and caries risk; safer alternatives or dose reductions should be considered. A 2024 BMJ practice review outlines stepwise deprescribing (prioritizing symptomatic harms, tapering where needed, and monitoring for withdrawal/relapse), which fits neatly into a dental-pharmacy co-management model. [71, 72]

MRONJ risk mitigation when antiresorptives/antiangiogenics are planned. For patients starting bisphosphonates or denosumab (cancer or osteoporosis dosing) or antiangiogenic agents, provide pre-treatment dental optimization, emphasize atraumatic techniques, and avoid elective extractions during periods of highest risk when feasible. Contemporary national guidance (e.g., SDCEP 2024 update) affirms practical chairside protocols and reinforces patient education regarding signs/symptoms and the need for regular review [73-75].

Table 2. Preventive & Therapeutic Strategies with Interprofessional Roles

Condition	Preventive measures	First-line management	Escalation/Procedural	Medication adjustments / deprescribing	Dentist role	Pharmacist role
Before high-risk therapy (chemo/RT, antiresorptives, strong immunosuppression)	Comprehensive dental exam; treat infection foci; hygiene instruction; tailored fluoride; denture fit check; baseline salivary assessment	Basic oral care protocol; patient self-care education; schedule close follow-up	Atraumatic extractions before therapy as indicated; defer elective invasive care during peak risk windows	Review xerogenic/bleeding-risk meds; coordinate timing with oncology/medicine	Risk triage, definitive dental stabilization, preventive plan, recall cadence	Medication reconciliation, flag high-risk drugs, counseling on rinses/cryotherapy/benzydamine where appropriate
Xerostomia	Hydration; sugar-free/ xylitol	High-fluoride toothpaste/v	Non-restorative caries control (e.g., SDF) if	Consider sialogogues (pilocarpine/cevi	Caries control strategy;	Assess anticholinergic load; advise sialogogue

	gum/lozenges; avoid alcohol-based rinses/tobacco; humidify sleeping area	arnish; saliva substitutes; frequent sips	needed; custom trays for high-fluoride gel	meline) if residual function; review anticholinergic burden	apply varnish/ SDF; monitor salivary flow and lesions	candidacy/monitoring; counsel on product selection and interactions
Oral mucositis / ulcerations	Basic oral care; benzydamine for selected head-and-neck RT; oral cryotherapy for short-infusion 5-FU	Topical anesthetics; bland rinses; barrier agents; nutrition support	Photobiomodulation in eligible settings; systemic analgesics per stepwise ladder	Oncology-led dose/timing modifications when necessary	Assess severity; hygiene optimization; topical regimens; coordinate with oncology	Protocolize analgesia and mucositis prophylaxis; screen for interactions; patient education
Candidiasis / opportunistic infections	Rinse/spit after inhaled steroids; denture hygiene; manage xerostomia	Topical azoles or nystatin for mild disease	Oral fluconazole for moderate–severe or recurrent; culture/speciation if refractory	Review antibiotics/corticosteroids; consider dose/formulation changes	Diagnosis and lesion monitoring; denture care; reinforce hygiene	Select antifungal, check interactions (e.g., azoles), counsel on adherence and adverse effects
Gingival overgrowth / hyperplasia	Plaque control and frequent professional debridement	Hygiene reinforcement; chlorhexidine short term if indicated	Gingivectomy/periodontal surgery; consider laser-assisted approaches	Discuss substitution (e.g., cyclosporine→tacrolimus; CCB→alternative antihypertensive) with prescriber	Periodontal therapy; surgical management; maintenance program	Advise on feasible substitutions and monitoring; coordinate with medical team
Taste alterations (dysgeusia/hypogeusia)	Anticipatory counseling; oral hygiene optimization; manage xerostomia	Dietary/taste training strategies; flavor trials; treat oral infections	Nutritionist referral for weight loss or poor intake	Review candidate culprit drugs (e.g., ACE inhibitors, metronidazole, chemo); consider alternatives when safe	Rule out local causes; support hygiene and infection control	Identify offending agents; counsel on expected course; suggest alternatives in collaboration with prescribers
Pigmentation / discoloration	Baseline documentation; medication history	Reassurance; monitor after withdrawal if feasible	Cosmetic options (camouflage); consider laser on a case-by-case basis	Assess risk–benefit of substitution/cessation	Differentiate from melanocytic pathology; biopsy if indicated; patient education	Weigh cosmetic burden vs. therapeutic need; discuss substitution feasibility

Gaps in Current Literature

Limited pharmacogenomic data on susceptibility to DIOMs

Although clinical observations and mechanistic studies implicate host factors in drug-induced oral manifestations (DIOMs)—for example, inter-individual variation in gingival fibroblast responses to cyclosporine or phenytoin—robust, oral-specific pharmacogenomic (PGx) evidence remains sparse. Recent umbrella and systematic reviews in PGx emphasize that, despite expanding genomic technologies, the field still lacks comprehensive, phenotype-anchored catalogs of variants that

reproducibly predict adverse drug effects across care settings, and most published PGx associations pertain to systemic toxicities rather than orofacial outcomes. Even large real-world PGx analyses and trials continue to evaluate composite "ADR reduction" endpoints without capturing DIOMs as adjudicated outcomes, limiting transferability to dental risk stratification and counseling. In parallel, contemporary basic and translational work continues to revisit cellular mechanisms of drug-induced gingival overgrowth, underscoring the multifactorial and incompletely resolved biology (cell-cycle regulation, fibroblast proliferation, matrix turnover), but without linking these pathways to validated genetic predictors suitable for chairside screening. Collectively, the literature points to a need for adequately powered, multi-omic cohorts with standardized oral endpoints (e.g., gingival overgrowth indices, xerostomia scales, mucositis grades), genome-wide rather than candidate-gene discovery, and external validation across populations—work that has begun for systemic ADRs but is largely unrealized for DIOMs.

Underreporting and weak pharmacovigilance for oral adverse drug reactions

Underreporting of adverse drug reactions (ADRs) is a recurrent limitation in drug safety science; recent syntheses highlight knowledge gaps (what/when/to whom to report), workload, and diagnostic uncertainty as major barriers among clinicians. These deficits are magnified for oral ADRs, where attribution is confounded by common comorbidities (e.g., periodontal inflammation), polypharmacy, and overlapping nosology (e.g., distinguishing oral lichenoid drug reactions from idiopathic oral lichen planus). Real-world signal detection studies relying on spontaneous reports (e.g., FAERS) can identify xerostomia-linked drugs via disproportionality analysis, but such databases are inherently vulnerable to reporting bias and sparse clinical detail, limiting causal inference and phenotype precision for DIOMs. Early work focused specifically on oropharyngeal ADRs also suggests that dental professionals under-report, reflecting both awareness and system-design issues (e.g., lack of oral-specific fields in reporting portals). Strengthening pharmacovigilance for DIOMs will require targeted education for dentists and pharmacists, harmonized case definitions for oral phenotypes, and integrated, low-friction reporting workflows embedded in dental and pharmacy information systems.

Lack of standardized, cross-disciplinary guidance for DIOMs

Guidance exists for discrete conditions (e.g., mucositis prevention in oncology, candidiasis therapy, acute dental pain), yet there is no unified, interprofessional framework that spans the breadth of DIOMs (xerostomia, gingival overgrowth, lichenoid reactions, dysgeusia, pigmentation) and operationalizes shared responsibilities among dentists, pharmacists, and physicians. Even in mucositis—a comparatively well-studied domain—an international 2024 assessment documented substantial variability in how clinicians measure severity and respond to symptoms, including limited uptake of validated patient-reported outcome measures, which undermines comparability across centers and trials. In oral mucosal disease more broadly, expert reviews continue to note the absence of universally agreed clinicopathologic criteria for lichenoid disorders, complicating diagnosis, triage, and research endpoint selection. Meanwhile, mainstream guidelines (e.g., ADA acute pain guidance; CDC opioid prescribing guidance) address narrow therapeutic questions and do not function as comprehensive, DIOM-focused care pathways that combine medication review, dental interventions, patient counseling, and pharmacovigilance. Recent epidemiologic analyses of drug-associated gingival disorders also conclude with calls for interdisciplinary protocols, reinforcing that current practice remains fragmented across specialties.

Insufficient longitudinal data on progression and reversibility

Much of the DIOM evidence base derives from cross-sectional studies, case series, or short-term trials, leaving key questions about natural history and reversibility unanswered. For cancer therapy–related oral toxicities, new prospective studies are beginning to track trajectories and quality-of-life impact during treatment, but long-term follow-up after therapy cessation remains limited and heterogeneous in methods. Longitudinal work linking oral microbiome dynamics to mucositis severity is emerging yet often restricted to single-center cohorts or early endpoints, with few studies extending into survivorship to determine whether microbial or inflammatory perturbations persist and how they relate to late oral effects (e.g., chronic ulceration, dysgeusia, caries risk from xerostomia). Similarly, for medication-induced xerostomia, observational analyses document symptom improvement after drug modification in subsets of patients, but controlled, long-horizon studies quantifying salivary gland recovery, caries incidence, and candidiasis recurrence are scarce. For drug-induced gingival overgrowth, recurrence after surgical or nonsurgical management is well recognized, yet comparative effectiveness and relapse kinetics across drug substitutions (e.g., cyclosporine→tacrolimus) lack standardized, long-term evaluation with uniform periodontal endpoints. Expanding multicenter, prospective cohorts with harmonized definitions and repeated measures (clinical indices, salivary flow, PROMs, microbial and genomic profiles) is a critical next step to move beyond episodic snapshots toward causal understanding and durable risk-reduction strategies.

Conclusion:

Drug-induced oral manifestations occupy a crucial intersection between systemic therapeutics and oral health, with consequences that extend far beyond local discomfort. Across medication classes, recurring pathophysiologic themes emerge direct effects on epithelium and salivary glands; immune-mediated injury including lichenoid reactions; and therapy-driven ecological shifts that enable opportunistic infection. These mechanisms do not act in isolation; rather, they intersect with behavioral and host factors—plaque-induced inflammation, nutritional status, and genetic susceptibility—to determine phenotype, severity, and persistence. As the prevalence of multimorbidity and polypharmacy grows, clinicians should anticipate DIOMs as part of routine risk–benefit deliberations for common regimens. Clinically, several manifestations are both frequent and impactful. Xerostomia undermines caries control and oral comfort; gingival overgrowth impedes hygiene and function; mucositis compromises nutrition and can interrupt life-saving oncology treatment; candidiasis and other opportunists flourish under xerogenic and immunosuppressive pressures; and taste disorders degrade appetite and adherence. The burden is concentrated in identifiable groups—the elderly, patients receiving chemotherapy, radiotherapy, or immunotherapy, transplant recipients on long-term immunosuppression, and children on chronic antiepileptic or immunomodulatory therapy—making targeted prevention feasible.

The management message is fundamentally optimistic: many DIOMs are predictable and modifiable. Pre-treatment dental optimization standardized basic oral care, and evidence-based preventives (benzydamine, cryotherapy,

photobiomodulation in selected settings) reduce incidence and severity. Symptom-directed pharmacotherapy—topical and systemic antifungals, sialogogues where residual function exists, tiered analgesia for mucositis—improves comfort and function. Dental interventions ranging from minimally invasive caries control (high-fluoride protocols, silver diamine fluoride) to surgical gingivectomy restore access for hygiene and sustain long-term stability. When clinically permissible, medication substitution or deprescribing attenuates risk at its source and should be pursued through pharmacist-guided stewardship. Yet, three system-level deficits persist: underreporting of oral adverse drug reactions; fragmented, condition-siloed guidance rather than unified interprofessional pathways; and a paucity of longitudinal data defining natural history and reversibility. Addressing these will require harmonized diagnostic criteria, embedding oral endpoints and patient-reported outcomes into drug trials, strengthening dental-pharmacy pharmacovigilance, and funding multicenter cohorts integrating salivary metrics, microbiome and genomic profiling, and standardized periodontal and mucosal indices. In sum, DIOMs should be reframed from rare curiosities to routine, preventable complications of modern pharmacotherapy. When dentists and pharmacists co-manage screening, prevention, and medication stewardship, patient-centered outcomes—oral function, comfort, and adherence—measurably improve.

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