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DENTAL ASPECTS OF MANIFESTATION OF ADVERSE DRUG REACTIONS

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Abstract

Background: Drug-induced oral adverse reactions (ADRs) are frequently encountered in dental practice but are often underrecognized or misdiagnosed due to their clinical resemblance to primary oral diseases. As systemic drug use increases, particularly in aging and polymerizate populations, awareness of these reactions becomes essential for timely diagnosis and effective management.

Objective: This review aims to synthesize current evidence on the range, frequency, causative agents, and clinical implications of drug-induced oral ADRs, with an emphasis on diagnostic relevance for dental professionals.

Methods: A structured literature search was conducted across PubMed, Scopus, Cochrane Library, and Google Scholar for articles published between January 2000 and March 2023. From an initial pool of 20 studies, 8 met the inclusion criteria and were analysed. Data were extracted on the type of oral ADRs, implicated drug classes, clinical presentation, and management strategies. A narrative synthesis was used due to heterogeneity in study design and outcome reporting.

Results: The most frequently reported ADR was **xerostomia**, commonly induced by antihypertensives, antidepressants, and diuretics. **Lichenoid reactions**, **oral ulcers**, and **mucositis** were frequently associated with NSAIDs, β-blockers, and methotrexate. **Gingival enlargement** was commonly observed in patients taking calcium channel blockers, phenytoin, or cyclosporine. **Medication-related osteonecrosis of the jaw (MRONJ)** was reported with bisphosphonates and antiangiogenic agents. **Tongue disorders**, including glossitis and burning tongue, were reported with nervous system and anti-infective medications. Several studies highlighted **underreporting and diagnostic challenges** due to lack of pharmacovigilance in dentistry.

Conclusion: A wide range of systemic medications can induce clinically significant oral ADRs. Dental professionals must be vigilant in recognizing these reactions, taking thorough drug histories, and collaborating with medical teams for appropriate interventions. Increased education, reporting practices, and awareness of pharmacogenomic variability are essential for improving oral healthcare outcomes related to medication use.

Keywords: Oral adverse drug reactions, xerostomia, gingival hyperplasia, lichenoid reaction, osteonecrosis of jaw, drug-induced oral lesions, pharmacovigilance, dental pharmacology.

Introduction:-The oral cavity, or buccal cavity, plays a vital role in systemic and local health. It is also a frequent site of adverse drug reactions (ADRs), which can significantly

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affect oral functionality, aesthetics, and patient quality of life. Despite this, oral ADRs are often underdiagnosed or misattributed, especially in polymerizate or systemically ill individuals. Oral ADRs commonly manifest as xerostomia (dry mouth), mucosal ulcerations, gingival overgrowth, pigmentation changes, and osteonecrosis. Prompt identification of drug-related oral presentations is critical for preventing long-term complications.

Xerostomia, one of the most common drug-induced oral conditions, arises from reduced salivary gland function and affects both comfort and oral microbiota. Drugs such as tricyclic antidepressants, opioids, anticholinergics, and illicit substances like methamphetamine, heroin, and cocaine are strongly linked to xerostomia and its sequelae—including rampant caries, oral candidiasis, and halitosis (1). A cross-sectional study by Sakai et al. (2025) found that 58.8% of cancer patients undergoing chemotherapy reported xerostomia, with significant negative impact on daily life activities (3).

Other medications, including angiotensin-converting enzyme (ACE) inhibitors like lisinopril and captopril, have been associated with oral ulcerations, angioedema, and dysgeusia. These symptoms can mimic autoimmune diseases, complicating diagnosis (2). Clarithromycin, terbinafine, and lansoprazole have also been reported to cause oral ulceration, mucosal irritation, and altered taste perception in various patient populations (4).

More severe adverse events include mucocutaneous syndromes such as Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN), linked to drugs such as phenytoin, methadone, and hormonal agents (3). These conditions are life-threatening and present with widespread oral and mucocutaneous erosions. Recent reviews have highlighted genetic susceptibility—particularly specific HLA haplotypes—as critical risk factors in drug-induced hypersensitivity syndromes (1).

Among the most debilitating oral ADRs is medication-related osteonecrosis of the jaw (MRONJ), primarily caused by bisphosphonates like zoledronic acid and pamidronate. These drugs, commonly used in oncology and osteoporosis treatment, compromise bone remodelling and increase the risk of necrosis following minor trauma or dental surgery. A 13-year review by Zhong et al. (2025) based on FAERS data identified bisphosphonates and RANKL inhibitors as the most common drug classes associated with MRONJ, with females and older adults showing the highest prevalence (2).

Gingival overgrowth, or gingival hyperplasia, is most frequently seen with calcium channel blockers (e.g., amlodipine), phenytoin, and cyclosporine. This condition can impair oral hygiene, promote periodontal disease, and require surgical correction. Lichenoid drug reactions—clinically similar to oral lichen planus—have also been associated with ACE inhibitors, NSAIDs, and some antiepileptics (6).

In addition to structural lesions, sensory disturbances such as dysgeusia (distorted taste) and burning mouth syndrome have been linked to drugs like metronidazole, lithium, and chemotherapy agents. Discoloration of oral tissues and teeth is another concern. Agents such as tetracycline, chlorhexidine, and iron salts can lead to pigmentation, while some antimalarials and antipsychotics induce bluish or brown-black mucosal changes (5).

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Pharmacogenetics is increasingly recognized as a determinant of oral ADR susceptibility. Genetic polymorphisms, particularly in the cytochrome P450 enzyme system (e.g., CYP2C9, CYP2D6), modulate drug metabolism and can influence the likelihood and severity of adverse reactions. Torpet et al. (2021) highlighted the importance of pharmacogenetic screening in identifying high-risk patients, especially when multiple high-risk drugs are co-administered (8).

To improve outcomes, clinical vigilance, early diagnosis, and interdisciplinary management—including dental consultations—are vital. Oral adverse events are not just cosmetic or minor; they can herald more serious systemic toxicity or serve as clues to underlying hypersensitivity. Differential diagnosis should always include potential iatrogenic aetiologies, particularly in patients with persistent or atypical oral lesions.

A recent innovation in managing drug-induced oral damage is the use of autologous platelet lysate gel, especially in patients with chronic graft-versus-host disease (cGvHD). A study by Rodríguez et al. (2025) showed significant symptom relief and improved healing in patients with cGvHD-associated oral ulcers, pointing to regenerative therapies as a potential adjunct in managing oral ADRs (4).

Ultimately, understanding drug-specific oral ADR profiles, along with patient-specific risk factors (genetic, systemic disease, and concurrent therapies), can guide clinicians toward safer prescribing practices and timely interventions.

Methodology:- This review paper adopts a systematic and integrative approach to the synthesis of current evidence on drug-induced oral adverse reactions or ADRs, specifically those of significance to dental and oral healthcare practice. The overall objective was to evaluate the nature of ADRs in the oral cavity, their corresponding drug classes, and the clinical issues they present for dental practitioners. The approach taken was a systematic search of the literature, selection and screening of studies, and narrative synthesis of findings.

Literature searching was conducted on four principal academic databases: PubMed, Scopus, Google Scholar, and the Cochrane Library. These websites were selected to give comprehensive coverage of clinical and pharmacological research on the topic. The literature review searched publications from January 2000 to March 2023, representing more than two decades of cumulative understanding of oral ADRs. To create the search string, a mix of Medical Subject Headings (MeSH) keywords and free-text words was utilized. These included: "oral adverse drug reactions," "drug-induced oral lesions," "oral mucosal disorders," "oral lichen planus," "xerostomia," "oral pigmentation," "gingival hyperplasia," "osteonecrosis of the jaw," "oral aphthous ulcers," "drug-induced tongue disorders," and "oral manifestations of systemic medications

The inclusion criteria for studies were determined a prior to these studies . The studies had to be written in the English language, involve human subjects, and describe definite documentation of adverse oral presentations resulting from systemic drug use. Research articles and review articles were included, as well as high-level case reports if they provided new or significant information on the clinical presentation or pathogenesis of oral ADRs. Trials were included if they described or investigated ADRs that occurred in the oral mucosa, gingiva, tongue, salivary glands, jawbones, or perioral tissues, either as single events or as

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part of a broader systemic reaction. Exclusion criteria were also applied: non-English publications, in vitro or animal research, editorials or commentaries without primary data, and reports without evident association between oral findings and drug use were excluded.

20 articles were identified at first using the combined search strategy. These records were screened independently by two reviewers in a two-stage process. During the first stage, the title and abstract were screened for relevance and duplicates eliminated. In the second stage, full-text articles were retrieved and screened in detail against inclusion and exclusion criteria. Following assessment, 8 articles were eventually considered suitable to be included within this review. These studies were chosen for their clinical relevance, scientific quality, clinical utility to dental practice, and richness of data on unique ADRs, associated drug classes, and to patient care relevance.

Relevant data points from each of these selected studies were extracted into a standardized table for comparison and consolidation. These included the article title, authors, publication year, journal, study design (e.g., review, case series, observational study), type of oral ADRs reported, involved drugs, postulated mechanisms of action, and suggested diagnostic or management strategies. The data were then tabulated to search for patterns of recurring drug classes, common oral presentations, and reporting trends. Special attention was given to drug classes that are high risk, such as cardiovascular medications, NSAIDs, immunosuppressants, chemotherapeutic drugs, and bisphosphonates, all of which were demonstrated to have an essential role to play in oral ADR causation.

Owing to study heterogeneity by study type, patient population, and reporting strategy, a meta-analysis was not feasible. Rather, a narrative synthesis approach was utilized to synthesize and put into context evidence across studies. This qualitative review of the evidence would highlight the gaps in the literature and make practical suggestions for improving the identification and reporting of ADRs among dental practitioners. It also illustrates how underreporting, pharmacovigilance among dentists, and misdiagnosis of ADRs as primary oral diseases like lichen planus or aphthous ulcers tend to cause issues.

Since the review was derived from secondary analysis of previously published data and entailed no data from direct contact with patients, ethical approval was not required. All information was derived from publicly available literature and the review accords with approved guidelines for narrative reviews.

Overall, this method provides a reproducible and systematic approach to evaluate drug-induced oral ADRs, increasingly significant in the context of the growing polypharmacy, especially in elderly populations. Based on the consolidation of evidence from appropriate literature, the present review aims to make ADRs better known, enhance diagnostic accuracy, and enhance clinical management of oral ADRs in dentistry.

Results

This review synthesized findings from eight peer-reviewed articles published between 2004 and 2023, each detailing various manifestations of drug-induced adverse effects in the oral cavity. The collected data revealed that a broad range of systemic medications are capable of inducing oral adverse drug reactions (ADRs), spanning from relatively minor and reversible

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effects such as xerostomia to severe mucocutaneous and osseous complications, including ulcerative lesions and osteonecrosis of the jaw.

Across nearly all studies, xerostomia, or dry mouth, emerged as the most commonly documented oral ADR. This condition was predominantly linked to systemic medications that impair salivary gland innervation or reduce glandular blood flow. Chief among these were antihypertensives, antidepressants, and diuretics. Yousefi et al. noted that cardiovascular drugs were also the most frequently implicated agents in the development of ulcerative and vesicular-bullous lesions, followed closely by methotrexate and nonsteroidal anti-inflammatory drugs (NSAIDs) [8]. Løkken and Skoglund further emphasized that virtually all drug classes have the potential to trigger oral manifestations, but particularly highlighted xerostomia, taste disturbances, and mucosal ulceration as recurring symptoms in users of anticholinergic and psychoactive drugs [9]. Complementing these findings, Aziz et al. analysed a Dutch drug database and reported that out of 1,645 systemically used drugs, 121 (7.4%) were associated with tongue-related ADRs, including glossitis, tongue burning, and discoloration [10].

A consistent finding across the reviewed studies was the occurrence of lichenoid drug reactions (LDRs), a form of delayed hypersensitivity reaction that closely resembles idiopathic oral lichen planus. Teoh et al. extensively discussed these reactions, identifying β-blockers, NSAIDs, and antihypertensives as the most frequent triggers [11]. Clinically, LDRs present as bilateral white striations on the buccal mucosa and require detailed patient history and diagnostic exclusion of autoimmune aetiologies. Additionally, Yousefi et al. described the potential for methotrexate and NSAIDs to induce vesicular-bullous disorders such as Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN) [8]. Teoh et al. corroborated these observations, warning that in rare cases, LDRs can escalate to severe immune-mediated conditions such as pemphigus vulgaris or mucous membrane pemphigoid, necessitating histopathological and immunofluorescence investigations to confirm diagnosis [11].

Gingival enlargement, or drug-induced gingival hyperplasia, was also a recurring ADR, most commonly associated with calcium channel blockers (e.g., nifedipine), the anticonvulsant phenytoin, and the immunosuppressant cyclosporine. Glick et al. reported that this fibrovascular overgrowth is generally dose-dependent and often exacerbated by inadequate oral hygiene [12]. The affected gingiva typically becomes firm, lobulated, and asymptomatic, although it can severely affect aesthetics, mastication, and hygiene practices. Torpet et al. delved into the pathophysiology of this ADR, suggesting that these drugs stimulate excessive fibroblast proliferation and extracellular matrix accumulation, especially in genetically predisposed individuals [13].

The most severe oral ADR discussed in the included studies was medication-related osteonecrosis of the jaw (MRONJ), primarily associated with long-term use of bisphosphonates and, more recently, antiangiogenic agents. According to studies by Yuan et al. and Glick et al., MRONJ typically presents as areas of exposed necrotic bone in the maxillofacial region persisting for over eight weeks in patients with no history of radiation therapy to the head or neck [14,12]. Patients who had undergone dental extractions or other invasive procedures while on these medications were particularly vulnerable. Both studies stressed the importance of preventive strategies such as pre-treatment dental evaluations,

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conservative surgical techniques, and prophylactic antibiotics to reduce the risk of MRONJ development.

Aziz et al. dedicated their investigation to drug-induced tongue disorders, identifying a wide range of symptoms including glossitis, burning tongue syndrome, macroglossia, and discoloration [10]. The drugs most often responsible were from the nervous system, anti-infective, and metabolic categories. For instance, antibiotics like tetracyclines were linked to black hairy tongue, while central nervous system stimulants frequently resulted in burning sensations and taste disturbances. These findings emphasize the need for clinicians to evaluate tongue morphology and function during routine oral assessments, especially in patients undergoing long-term pharmacotherapy.

In addition to structural and sensory disruptions, pigmentary and taste changes were also frequently reported ADRs. These included bluish-black oral mucosal pigmentation associated with drugs such as minocycline and chloroquine, as well as dysgeusia or metallic taste induced by metronidazole [9,12]. While often benign and reversible, these manifestations can cause psychological distress in patients and thus require appropriate counselling and clinical explanation.

An important trend observed across the studies was the frequent association of specific drug classes with distinct oral ADRs. Cardiovascular drugs were consistently linked to xerostomia, lichenoid lesions, and taste alterations [8,13]. NSAIDs were responsible for lichenoid lesions, oral ulcers, and mucositis [8,11], while antidepressants and antipsychotics were associated with xerostomia and dysgeusia [9]. Immunosuppressants such as cyclosporine were often implicated in gingival overgrowth [12], and bisphosphonates were the leading cause of MRONJ [12,14]. Notably, mTOR inhibitors emerged as a newer class linked to deep oral ulcerations that can mimic autoimmune lesions [14].

Finally, a critical issue highlighted in several studies was the underreporting of oral ADRs. Authors such as Padayachee and Teoh et al. emphasized that many dental practitioners may fail to recognize or report drug-induced lesions due to inadequate training in pharmacovigilance and diagnostic uncertainty [11,15]. This often results in misdiagnosis—treating drug-induced lesions as idiopathic conditions such as aphthous ulcers, candidiasis, or lichen planus—and can delay appropriate management. These findings underscore the urgent need for improved education, better drug history documentation, and interdisciplinary collaboration in identifying and managing ADRs in the oral cavity.

Discussion:-

The findings of this systematic review reaffirm the fact that drug-induced oral ADRs are an undoubtedly significant, but often overlooked, subset of clinical dental and general practice systemic drug side effects. Oral cavity, being part of the gastrointestinal and immune system, is routinely left out of systemic pharmacovigilance. However, as demonstrated in this review, most pharmaceutical drugs in routine practice have the potential to cause oral manifestations mimicking or obscuring primary oral pathology.

The spectrum of ADRs varies from harmless xerostomia to potentially life-threatening lichenoid mucositis, mucosal ulceration, pigmentation, burning mouth syndrome, and

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medication-related osteonecrosis of the jaw (MRONJ), as well as from initial, sometimes asymptomatic changes to irreversible damage. ADRs may imitate idiopathic or autoimmune mucosal illnesses and, therefore, may cause misdiagnosis, overtreatment, and unwarranted surgery. ADRs may significantly worsen the quality of life, oral function, and overall health of the patient

The most frequently occurring ADR to be regularly reported in the studies under consideration was Xerostomia due to antihypertensives, antidepressants, and anticholinergic agents.

1–2,6. Xerostomia is relatively harmless in nature but significantly compromises oral homeostasis through reduced salivary secretion and increased risk of dental caries, oral infections (particularly candidiasis), halitosis, dysphagia, and intolerance to prosthesis. Xerostomia is also responsible for interfering with speech and taste and social discomfort and reduced nutritional intake. Treatment involves saliva substitutes, sugar-free gum, systemic sialagogues, and fluoride rinses to prevent long-term oral morbidity.

More complex is NSAID, β-blocker, and methotrexate-induced lichenoid reactions and mucosal ulcerations, which have been reported due to clinical similarity to lichen planus and pemphigus. 1,4. Inevitably, misdiagnosis of these lesions will lead to unnecessary biopsies and prolonged corticosteroid treatment. Bilaterality, temporal association with onset of drug, resolution on withdrawal of drug, and supportive histopathology are emphasized in the literature as requirements. Recognition of such characteristics will allow misdiagnosis to be avoided and early conservative treatment to take place. Lesions typically resolve weeks after withdrawal of the causative drug, stressing the importance of meticulous drug history in dental clinical examination.

The most serious ADR in this report is Medication-Related Osteonecrosis of the Jaw (MRONJ), which is typically caused by bisphosphonates and antiangiogenic agents

5,7. MRONJ is uncovered necrotic bone within the maxillofacial area unhealed after eight weeks. It is most commonly caused by invasive dental treatment or spontaneous development in patients undergoing high-dose intravenous antiresorptive or antiangiogenic treatment. MRONJ requires complicated multidisciplinary treatment by specialists from dentistry, medicine, and pharmacy. Pre-treatment dental assessment, risk classification, patient education, and elective extractions during treatment aversion are critical to preventing irreversible complications.

Gingival hyperplasia resulting from phenytoin, cyclosporine, and calcium channel antagonists is one of those adverse drug reactions that are penned in black and white pages however very little is spoken on the subject, either in professional literature or in clinical practice. It impacts dental aesthetics, makes practicing oral hygiene more challenging, and causes inflammation in the area of the gums. Usually, the patient does not feel pain, but the disease can become so extensive or resistant to treatment that surgical intervention will be required. Non-surgical therapy, elimination of the etiology, and a strict patient-centred approach are among the conservative treatment options. It is a case in point of the significance of regular oral checks in patients on chronic systemic medications.

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A group of drug-induced tongue disorders can also cause a patient discomfort, yet that section is not dwelled upon, if at all. The disorders can range from glossitis to taste aberration and to burning tongue syndrome, and a relevant example is the report listed in Aziz et al. 3. Most of these symptoms are not specific to drug toxicity and are thus mixed up with other conditions particularly in the elderly and the timing of the coincident use of multiple drugs. Broader pharmacovigilance studies continue to document the side-by-side occurrence of such incidents. Early detection of the tongue pathology will decrease the likelihood of unnecessary exams and allow the discontinuation of treatment or dose modification of the incriminated drug.

One of the more concerning issues found in this research is the significant under declaration of symptoms resulting from oral drug consumption in every case, but in dental care settings, in particular

4,8. A majority of practitioners either do not recognize or just ignore the fact that oral dysfunctions are a medium for the side effects of systemic drugs. Moreover, lack of awareness of the symptoms leads to misdiagnosis, which is attributed to systemic causes, and psychiatric aetiology. Multiple overlapping factors like the popularity of conservative management, having a good doctor-patient relationship, and the lack of doctor's experience may lead to such underreporting. Thus, efforts to establish a compulsory teaching of ADR detection, reporting and also interprofessional relation in would be most enlightening into dental curricula, that even cross-professional cooperation within the field of oral care can prove effective.

Before undergoing dental treatment, the continuous checking whether the medication is consistent or not should be an act.

The future role of pharmacogenomics in oral ADR prevention is one of the advanced topics discussed in this review. The interindividual variability in cytochrome P450 enzymes, especially in the genes like CYP2D6 and CYP3A4, is the main factor causing the differences in drug metabolism 666. Thus, it is possible that one group of patients can develop severe reactions despite the standard therapeutic dose, while others may not be affected. Genetic screening technologies, when available, might facilitate the identification of individuals' risks for ADRs before they even initiate drug therapy, bringing precision medicine into dental practice.

Among the things I can also mention is the power of interprofessional collaboration. Dental practitioners who are treating patients that are on immunosuppressants, antineoplastic drugs, or antiepileptics must be in constant contact with doctors, pharmacists, and nurses. Such a partnership enables better treatment protocols, especially when it comes to dental interventions that might cause extra systemic problems.

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Limitations: In spite of the clinical applicability of these findings, some methodological weaknesses exist. The synthesis is founded mainly on narrative reviews, as well as case reports, without the statistical power and generalizability of randomized controlled trials. The lack of meta-analysis further prevents the determination of quantitative risk estimates or prevalence. Inconsistent reporting practices, differences in diagnostic criteria, and geographical bias (e.g., overrepresentation of Turkish and Iranian studies) could also influence the external validity of the findings. In addition, rare but serious ADRs could be overreported and mild ADRs could be underreported because of reporting bias. However, qualitative synthesis of these patterns across different studies provides valuable information on oral ADRs that deserve heightened clinical awareness and systematic study. Future research must be aimed at prospective cohort studies with the use of standardized diagnostic criteria for confirming findings and more accurately estimating the prevalence and risk factors for particular oral ADRs.

Conclusion: Harmful oral manifestations of drugs are among the most neglected yet significant areas of systemic pharmacotherapy and dental diagnosis. Here in this article, in comprehensive detail, we cover how commonly prescribed medications such as cardiovascular medications, NSAIDs, bisphosphonates, antidepressants, immunosuppressants, and anticonvulsants induce a vast range of oral pathologies from xerostomia and lichenoid lesions to osteonecrosis, pigmentation, gingival overgrowth, and tongue lesions. Identification of these patterns is the key to correct diagnosis, proper treatment planning, and the prevention of unwarranted procedures. Dental professionals need to be active participants in pharmacovigilance, obtaining thorough medication histories as a matter of course and being ever vigilant for the occurrence of oral ADRs, particularly when standard therapies fail. Incorporating ADR monitoring into daily dental practice and training in pharmacogenomics will significantly contribute to patient safety and quality of care. Finally, the results of this review emphasize the importance of increased clinical vigilance, ongoing education, and interprofessional dialogue to optimally manage and attenuate the burden of drug-induced oral ADRs. Through this, dentists can aid in decreasing avoidable complications, reduce patient morbidity, and help achieve a safer, more informed pharmacologic treatment.

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