REVIEW

Drug induced orofacial manifestations commonly encountered by dental practitioners- A Systematic review.

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Abstract

Background: Orofacial manifestations are often the earliest indicators of systemic drug reactions. With the increasing prevalence of polypharmacy, patients are more likely to encounter drug-induced oral adverse effects, which are frequently underdiagnosed or misattributed.

Objective: This systematic review aims to compile, categorize, and analyze reported cases of drug-induced orofacial manifestations, highlighting the commonly implicated drugs, clinical patterns, and management strategies to aid in patient care.

Methods: A literature search was conducted across PubMed, Scopus, and Google Scholar for English-language case reports from the past decade documenting drug-related orofacial effects. Out of 124 initially identified articles, 16 were selected, comprising 38 individual case reports. Inclusion criteria required clear documentation of oral symptoms linked to drug use.

Results: The most frequently implicated drugs included cyclosporine A, phenytoin, methotrexate, propranolol, and newer agents such as the BNT162b2 vaccine and pembrolizumab. Common orofacial manifestations included gingival hyperplasia, oral ulcers, mucositis, pigmentation, and xerostomia. In pediatric cases, in utero exposure to medications like warfarin led to delayed tooth eruption and dental anomalies. Treatment often involved drug withdrawal, corticosteroids, or supportive care.

Conclusion: Orofacial manifestations serve as vital clinical clues to underlying drug reactions. Increased awareness among dental professionals, thorough drug histories, and interdisciplinary collaboration are essential for timely diagnosis and improved patient outcomes. This review underscores the need for standardized diagnostic protocols and better pharmacovigilance, particularly in regions with high self-medication and irrational drug use.

Keywords: Drug-induced, Orofacial manifestations, Gingival hyperplasia, Oral ulceration, Adverse drug reactions, Systematic review

Introduction

Oro-facial manifestations are usually the first and foremost symptoms for most diseases. A drug-induced state or reaction is provoked using drugs. It is of paramount importance to detect the orofacial manifestations in clinical practice. "Drug-induced" orofacial manifestations are those which, on immediate or prolonged use of a specific drug, elicit a change in the morphological and functional nature of oral tissues. They tend to exacerbate their effects if the use of said drug is continued. These orofacial manifestations can be due to adverse reactions or site reactions.

WHO defines an adverse drug reaction as, "A response which is noxious and unintended, and which occurs at doses normally used in humans for the prophylaxis, diagnosis, or therapy of disease, or for the modification of physiological function." Oral manifestations are highly heterogeneous encompassing varied categories, each having its own distinct morphological, clinical, and pathological features. The clinical patterns of adverse drug reactions of the oral cavity include xerostomia, swelling, nonspecific ulceration, vesiculobullous or ulcerative mucositis that mimics other disease states, nonspecific vesiculoulcerative mucositis, pigmentation, gingival enlargement, and medication-related osteonecrosis of the jaws.

Chronic inflammation in the oral cavity has been increasingly recognized as a critical factor contributing to the pathogenesis of a wide range of oral diseases, including precancerous and cancerous lesions. Numerous studies have demonstrated that inflammatory processes play a pivotal role in the initiation, promotion, and progression of neoplas-

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tic changes by influencing cellular proliferation, angiogenesis, and genomic instability. Despite this growing body of evidence, there remains a significant gap in understanding the specific cellular and molecular mechanisms that link chronic inflammation to oral carcinogenesis.

This review aims to synthesize current findings on the histopathological and molecular correlations between chronic inflammation and oral cancer. By evaluating both well-established and emerging biomarkers involved in the inflammatory microenvironment, the study seeks to elucidate the pathways through which inflammation contributes to malignant transformation in oral tissues.

Relevance of the Study:

Understanding the intricate relationship between chronic inflammation and oral cancer is crucial for the development of targeted diagnostic, preventive, and therapeutic strategies. Given the high incidence and morbidity associated with oral squamous cell carcinoma (OSCC), particularly in regions with high prevalence of tobacco use and poor oral hygiene, this review is especially pertinent. It holds relevance for clinicians, pathologists, and researchers by highlighting potential biomarkers for early detection and novel targets for intervention. Moreover, the findings could contribute to public health strategies aimed at reducing the burden of oral cancer through inflammation control and improved oral health practices.

The significance of this report shows that there is an estimated increase in the frequency of intake of drugs per patient in the recent years, with an estimated prevalence of 59% of the U.S. population taking at least one prescription medication and 15% taking five or more prescription drugs[1]. In India, a significant proportion of medications are prescribed by private practitioners, often without rigorous diagnostic protocols. Combination drug formulations—frequently containing 'hidden' pharmacological classes—are routinely administered without adequate disclosure or consideration of potential adverse effects. The indiscriminate use of anti-infectives, including antibiotics and antifungals, remains widespread and often inappropriate. Moreover, several high-risk or banned drugs in the West continue to be used as first-line therapies in India due to lack of regulatory enforcement and over-the-counter accessibility.[1]

This unregulated landscape contributes to a rising incidence of drug-induced orofacial manifestations, which are frequently misdiagnosed due to low clinical awareness. Studies have reported gingival enlargement linked with the prolonged use of phenytoin, cyclosporine A, and calcium channel blockers—many of which are prescribed without dental consultation.[2] Additionally, oral ulcerations, mucositis, pigmentation, and xerostomia are increasingly being reported with systemic drugs including methotrexate, minocycline, and biologics like adalimumab and nivolumab.[3,4]

Despite these trends, there is a critical lack of consolidated Indian data addressing orofacial adverse drug reactions. Most documentation remains limited to isolated case reports, with few large-scale, region-specific studies focusing on oral health implications. As a result, dental professionals often remain unaware of these drug-related risks, leading to diagnostic delays and suboptimal management.

This underscores the urgent need for interdisciplinary training, prescription audits, and inclusion of dental perspectives in pharmacovigilance programs to safeguard against preventable oral morbidity associated with common medications. Several factors contribute to the under recognition and mismanagement of drug-induced orofacial manifestations. These include limited awareness among dental practitioners, misinterpretation of symptoms due to overlap with other oral conditions, and the increasing prevalence of polypharmacy and over-the-counter medication use. This study aims to improve patient-cantered care by enhancing clinicians' understanding of these adverse effects and reducing diagnostic and therapeutic uncertainty in practice.

Adverse drug reactions (ADRs) can be systematically classified into six pharmacological categories[6]:

Type A (Augmented): Dose-related reactions
Type B (Bizarre): Non-dose-related reactions
Type C (Chronic): Dose- and time-related reactions
Type D (Delayed): Time-related reactions
Type E (End of use): Withdrawal-related reactions
Type F (Failure): Unexpected failure of therapy

Given the complexity and variability of these reactions, especially when they manifest in the oral cavity, a structured synthesis of the literature is essential. Systematic reviews are regarded as the highest level of evidence in the hierarchy of scientific research, as endorsed by the Indian Council of Medical Research (ICMR) in its 'Beginner's Guide to Systematic Reviews'. This review is registered with the international PROSPERO database (Registration No: CRD42024472510), ensuring methodological transparency and adherence to systematic review standards.

Identified Knowledge Gap:

Despite the increasing prevalence of drug-induced adverse effects, there is a significant lack of consolidated, evidence-based data specifically focused on orofacial manifestations encountered in routine dental practice. While individual case reports and pharmacological studies acknowledge such manifestations, they remain scattered across diverse medical and dental literature with inconsistent diagnostic criteria, incomplete documentation, and limited emphasis on oral implications.

Currently, no comprehensive review exists that systematically compiles and categorizes drug-induced orofacial manifestations across drug classes, correlates these with clinical presentations, and evaluates their impact on oral health outcomes. This leaves a critical gap in:

- Clinical awareness among dental practitioners who are often the first to observe these signs.
- Standardized protocols for diagnosis, documentation, and management of these drug-related conditions.
- Interdisciplinary communication between physicians and dentists in preventing, detecting, and managing adverse oral reactions.

Furthermore, in regions such as India, where irrational drug prescription and over-the-counter medication use are prevalent, the risk of undetected or misattributed orofacial re-

Table 1: Standardized Table of Drug-Induced Orofacial Manifestations:

S. No.	Author(s)	Year	Place	Age	Gender	Drug Used	Orofacial Manifestation (s)	Dosage	Duration	Systemic Manifestation (s)*	Reason for Drug Use	Treatment Given
1	Aradhana Sood et al.	2018	Pune, India	45	F	Imatinib Mesylate	Extensive red rash on face, oral ulcers	400 mg/day	6 weeks	Erythematous plaques with pustules on skin	Chronic Myeloid Leukemia	Prednisolone, dapsone, drug switch to hydroxyurea
2	Vinodh Gangadaran et al.	2023	Chennai, India	45	F	Phenytoin	Submucosal ecchymosis, spontaneous gingival bleeding	100 mg TID	Not reported	Cutaneous purpuric spots	Seizures post-accident	Drug switch to sodium valproate
3	Serena Cocca et al.	2016	Siena, Italy	41	M	Anabolic Androgenic Steroids	Burning sensation of mouth, oral erythematous maculopapular and vesicular lesions	Not reported	Not reported	Conjunctival edema, photophobia	Athletic enhancement	Systemic glucocorticoids, antithrombotics, enteral nutrition
4	Fanny Zulay Acero Brand et al.	2018	Montreal, Canada	69	M	Pembrolizumab	Painful oral cavity and oropharyngeal ulcers	200 mg IV q3w	Not reported	Dysphagia, weight loss	Squamous cell carcinoma	IV methylprednisolone, oral prednisone, analgesics
5	Syed Ahamed Raheel et al.	2016	Riyadh, Saudi Arabia	32	F	Propranolol Hydrochloride	Marked gingival hyperplasia	40 mg tablet	6 years	Craniofacial anomalies	Congenital heart disease	Multidisciplinary management
6	Luciana Rosa Grando et al.	2014	Brazil	16	M	Oral Isotretinoin	Papulous-pustular acne on face and trunk	Not reported	Not reported	Not reported	Acne	Prednisone (0.5-1.0 mg/kg/day) tapered
7	Rahul Moranar et al.	2021	New Delhi, India	8	M	Warfarin (via mother)	Fibrous gingiva, delayed eruption	5 mg daily (maternal)	1st trimester	Dyspnea, facial anomalies	Post-surgical anticoagulation in pregnancy	Oral prophylaxis, restorative treatments, extractions
8	Jinhan Zhou et al.	2021	Hangzhou, China	60s	M	SHR-1210 (anti-PD-1 antibody)	Gingival hyperplasia with large pedunculated lesions	Not reported	Not reported	Capillary hemangiomatous lesions	Non-small cell lung cancer	Surgical removal of lesions
9	Meera Gandhi et al.	2020	Vellore, India	12	F	Cyclosporine A	Grade III gingival hyperplasia, bleeding gums	Not reported	5 months	Thalassemia major with autoimmune cytopenia	Post-HSCT immunosuppression	Antibiotics, gingivectomy, immunosuppressant switch, oral hygiene program
10	Malak J. Alzahrani et al.	2020	Dammam, SAU	34	M	Hydroxychloroquine, Lopinavir/Ritonavir	Pustular rash in oral cavity and tongue	Not reported	4 days	Erythematous rash on face and trunk	COVID-19	Topical corticosteroids, antihistamines, supportive care
11	Massimo Petruzzi et al.	2022	Bari, Italy	55	F	BNT162b2 Vaccine (Pfizer-BioNTech)	Painful lesions on lips, oral mucosa	Single dose	24 hours post-vaccination	Lesions on hands, knees, feet	COVID-19 vaccination	Prednisone, clobetasol ointment
12	Aniruddha Soni et al.	2023	Wardha, India	78	M	Moxifloxacin, Amikacin, Atropine, others	Bleeding gums, redness and discharge from eyes	Not reported	Few months	Peripheral ulcerative keratitis	Eye infection and glaucoma	Prednisolone drops, acetazolamide, supportive care

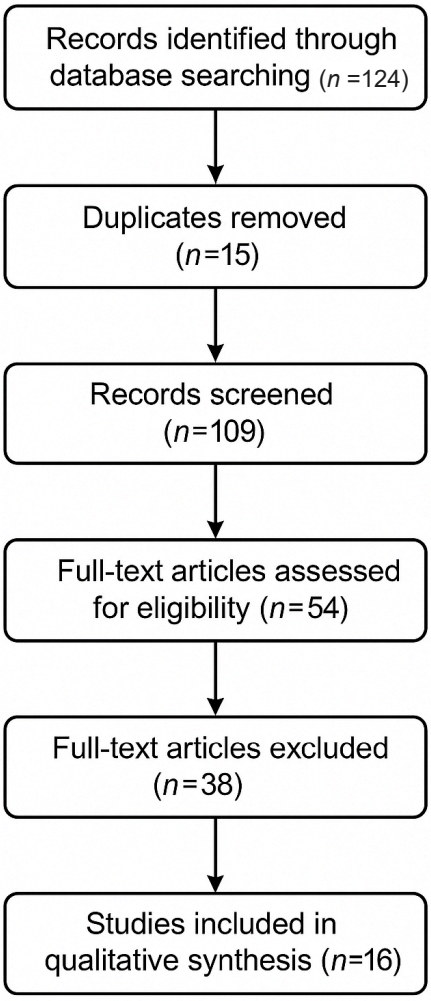
*Systemic manifestations are included only if directly relevant to orofacial presentation

actions is particularly high. This review aims to bridge this gap by offering a structured, evidence-based synthesis of reported cases, thereby enhancing diagnostic accuracy, treatment strategies, and preventive measures in dental and broader clinical practice.

Review of Literature

The literature reveals a wide spectrum of drug-induced orofacial manifestations, most associated with anticonvulsants (e.g., phenytoin), immunosuppressants (e.g., cyclosporine A), and biologics (e.g., pembrolizumab). Frequently reported manifestations include gingival hyperplasia, oral ulcerations, mucositis, pigmentation, and xerostomia. Despite numerous case reports, existing research is fragmented, with limited data on prevalence, severity grading, and clinical management protocols. This review consolidates these findings to provide a clearer understanding for dental practitioners and highlight the need for standardized recognition and reporting of such adverse effects.

PRISMA Flow Diagram:



Aims and Objectives

Aim: To systematically review published case reports on drug-induced orofacial manifestations to identify commonly implicated drugs, characterize clinical presentations, and summarize management strategies relevant to dental and medical practice.

Objectives: To compile and categorize case reports that document orofacial manifestations resulting from drug therapy, with a focus on mucosal, gingival, and dental tissue involvement.

To identify the most frequently reported drugs and drug classes associated with orofacial adverse effects.

To analyze the clinical spectrum of orofacial manifestations, including signs, symptoms, and patterns of presentation.

To evaluate the therapeutic approaches used to manage these manifestations, including drug withdrawal, symptomatic treatments, and multidisciplinary care.

To highlight existing gaps in documentation, diagnosis, and management that can inform future research and clinical guidelines.

Material and Methods

Search Strategy:

A comprehensive literature search was conducted using PubMed, Google Scholar, and Scopus to identify case reports and studies published in English that documented drug-induced orofacial manifestations. The keywords included combinations of "drug-induced," "orofacial manifestations," "oral adverse drug reactions," "gingival hyperplasia," "oral ulcers," and "mucositis." The search was limited to publications from the last 10 years.

Inclusion Criteria:

1. Case reports or series documenting orofacial manifestations clearly linked to drug use.
2. Articles published in English.
3. Studies involving human subjects.

Exclusion Criteria:

1. Studies that reported only systemic manifestations without oral findings.
2. Articles lacking clear drug attribution to orofacial symptoms.
3. Non-English language articles.
4. Reviews and editorials without primary data.

Study Selection Process:

1. Records identified: 124
2. Duplicates removed: 15
3. Records screened: 109
4. Records excluded based on title/abstract: 55
5. Full-text articles assessed for eligibility: 54
6. Full-text articles excluded (due to lack of clear orofacial focus): 38
7. Studies included in the qualitative synthesis: 16 (including 38 individual case reports)

Quality Assessment:

All included articles were assessed for relevance, completeness of clinical description, and clarity of drug-event linkage.

Only reports with sufficiently detailed clinical and therapeutic data were included in the synthesis.

Results

The most frequently reported drugs associated with orofacial manifestations were cyclosporine A, methimazole, phenytoin sodium, propranolol, BNT162b2 (Pfizer-BioNTech COVID-19 vaccine), and methotrexate. The most common orofacial manifestations included gingival hyperplasia, painful oral ulcers, crusting and erosions of the lips, submucosal ecchymosis, and erythematous or bullous mucosal lesions. Notably, BNT162b2, immunomodulators (e.g., azathioprine, adalimumab), and immune checkpoint inhibitors (e.g., pembrolizumab, nivolumab) were linked with multifocal oral ulcerations and mucositis. In hard tissue, delayed tooth eruption and dental caries were observed in cases of in utero exposure to warfarin.

Treatment approaches varied, with drug withdrawal or substitution, use of systemic or topical corticosteroids, and supportive oral care being the most commonly adopted strategies. These findings underscore the importance of recognizing early oral signs as indicators of systemic drug reactions and highlight the need for routine drug history screening in dental settings to facilitate timely diagnosis and interdisciplinary management.

OROFACIAL MANIFESTATIONS observed in this study are: -

1. Itching /pruritis was reported with the use of imatinib mesylate, tamoxifen, bupropion HCl.
2. Extensive erythematous raised skin rash over the entire body with surface annular erythematous plaques studded with micro pustules was reported with the use of imatinib mesylate.
3. Facial red rash was reported with the use of ivermectin, phenytoin sodium, levetiracetam.
4. Burning sensation of mouth and eyes was reported with the use of –anabolic androgenic steroids.
5. Painful erythematous maculopapular and vesicular lesions all over the body was reported with the use of -anabolic androgenic steroids.
6. Conjunctival edema –anabolic androgenic steroids
7. Photophobia was reported with the use of -indapamide, anabolic androgenic steroids.
8. Papulous-pustular acne with nodular and keloid lesions on face and trunk was reported with the use of - oral isotretinoin.
9. Pustular rash on erythematous base was reported with the use of- hydroxychloroquine, lopinavir, ritonavir.
10. Hypertelorism, depressed nasal bridge with stippling of cartilage in femur and calcaneum was reported in a young child with the use of - warfarin therapy in pregnant mother.
11. Bright reddish-purple dome shaped papules were reported with the use of –SHR-1210
12. Multiple hyperpigmented reddish-purple target macules/papules were reported with the use of -cefixime.
13. Blisters on forearm/swelling on nose was reported with the use of -methimazole.
14. Discoloration of bilateral sclera/nail beds was reported with the use of minocycline.
15. Dry eyes were reported with the use of indapamide.
16. Eye pain was reported with the use of indapamide.
17. Redness and discharge/tearing from both the eyes was reported with the use of amikacin/atropine/moxifloxacin, ivermectin.
18. Black eschars on lips were reported with the use of ivermectin.
19. Erythematous bullous eruptions on entire body were reported with the use of vildagliptin, sitagliptin, linagliptin.
20. Diminished vision was reported with the use of indapamide, as the drug has the potential to concentrate in the retina after long lasting treatment, thereby increasing the chances of light induced retinal damages during and after cataract surgery50.
21. Mid-sized pupils were reported with the use of- diazinon
22. Diaphoresis was reported with the use of- diazinon.
23. Bluish spots on lower limbs and labial edema were reported with the use of- allopurinol.
24. Erosive cheilitis was reported with the use of-allopurinol.
25. Crusty lesions on lips/vermilion were reported with the use of -BNT 162b2, salbutamol.
26. Hemorrhagic crusts on lips were reported with the use of- azithromycin, diclofenac sodium.
27. Facial erythema was reported with the use of- tamoxifen.
28. Painful ulcers on lips were reported with the use of -salbutamol.
29. Painful lesions on lips/hands/knees/feet were reported with the use of -BNT162b2.
30. Painful open sores with purulent discharge on face was reported with the use of -adalimumab.
31. Painful erosions on lips were reported with the use of -azathioprine.
32. Bilateral conjunctival infection was reported with the use of n-azathioprine.
33. Facial edema was reported with the use of -sulfasalazine.

INTRAORAL (SOFT TISSUE) MANIFESTATIONS observed in this study are:

34. Bleeding from gums was reported with the use of -phenytoin, cyclosporine A
35. Submucosal ecchymosis in upper and lower lip, anterior floor of the mouth, right lateral border of posterior 1/3rd of the tongue was reported with the use of –phenytoin.
36. Painful erythematous maculopapular and vesicular lesions on oral mucosa was reported with the use of -anabolic androgenic steroids.
37. Small ulcers of the oral cavity were reported with the use of -pembrolizumab.
38. Growth in upper and lower gums- Inderal (proprano-

lol hydrochloride).

39. Gingival hyperplasia was reported with the use of -propranolol hydrochloride, SHR-1210, cyclosporine A.
40. Fibrous gingiva was reported in a young child with the use of warfarin therapy in pregnant mother.
41. Eruption bulge was reported in a young child with the use of warfarin therapy in pregnant mother.
42. Ulcerative lesions on left labial and anterior mucosa with yellowish and dark brown pigmentation with central necrosis was reported with the use of -immunosuppressive drugs.
43. Confluent ulcerative lesions across labial mucosa were reported with the use of -allopurinol.
44. Gingival necrosis with pain was reported with the use of -methimazole.
45. Painful oral ulceration was reported with the use of -azithromycin, diclofenac sodium, amoxicillin, salbutamol.
46. Pustular rash on erythematous base on tongue and in oral cavity was reported with the use of – hydroxychloroquine, ritonavir, lopinavir.
47. Painful oral sores were reported with the use of –ivermectin.
48. Bilateral ulcers on oral mucosa of both cheeks covered with pseudo membrane and surrounded with erythematous border was reported with the use of - everolimus, sirolimus, omeprazole.
49. Generalized gingival pain was reported with the use of methimazole.
50. Whitish deposits on gums were reported with the use of methimazole.
51. Bullous lesions were reported with the use of -methotrexate, BNT162b2
52. ulcerative lesions in oral mucosa were reported with the use of – methotrexate.
53. Discoloration of gingival was reported with the use of –minocycline.
54. Hypersalivation was reported with the use of -diazinon.
55. Small punctuate white lesions superimposed on erythematous mucosa of hard palate was reported with the use of -nivolumab.
56. Painful oral mucosal lesions were reported with the use of -BNT162b2.
57. Painful oral erosions, oral erythema and pseudomembranous spread throughout the oral mucosa was reported with the use of - BNT162b2.
58. Intra oral burning sensation was reported with the use of –BNT162b2, salbutamol.
59. Erythematous lesions were reported with the use of -BNT162b2.
60. Pain and bleeding from mouth was reported with the use of -BNT162b2.
61. Gingival erosions were reported with the use of -BNT162b2.
62. Grade 3 gingival hyperplasia and severe episodes of bleeding gums were reported with the use of cyclosporin A.

a INTRAORAL (HARD TISSUE) MANIFESTATIONS observed in this study are :-

63. Multiple carious teeth were reported in a young child with the use of warfarin therapy in pregnant mother.
64. Delayed eruption of maxillary right permanent first molar was reported in a young child with the use of warfarin in the pregnant mother.

Discussion

This systematic review consolidates evidence from 38 case reports documenting a wide range of drug-induced orofacial manifestations, underscoring the oral cavity's role as a site of early and visible signs of systemic drug reactions. The findings reveal that anticonvulsants, immunosuppressants, beta-blockers, biologics, and newer therapeutic agents like mRNA vaccines and checkpoint inhibitors are frequently associated with significant orofacial changes.

Among the most prevalent manifestations observed were gingival hyperplasia (e.g., phenytoin, cyclosporine A, propranolol), oral ulcerations (e.g., methotrexate, azathioprine), mucositis (e.g., BNT162b2, isotretinoin), and xerostomia and pigmentation (e.g., minocycline, tamoxifen). These findings align with those of Glick et al. (2020), who emphasized the oral implications of commonly prescribed drugs, but our review expands this knowledge by integrating newer agents like BNT162b2 (COVID-19 vaccine) and PD-1 inhibitors (e.g., pembrolizumab)—therapies that were not yet prominent in earlier reviews.

For instance, the BNT162b2 vaccine was associated with erythematous and bullous oral lesions, a presentation possibly mediated by type IV hypersensitivity and immune system dysregulation. Similarly, immune checkpoint inhibitors such as pembrolizumab induced painful oral ulcers and dysphagia, likely due to enhanced T-cell-mediated cytotoxicity targeting epithelial tissues—a phenomenon previously underreported in oral medicine literature .

Importantly, many of these adverse effects were reversible upon withdrawal or substitution of the offending drug, and responded well to corticosteroids, immunosuppressants, or supportive oral care. However, a recurring issue was the delay in identifying these as drug-induced, due to either lack of awareness among dental professionals or the overlap of symptoms with other mucosal diseases like lichen planus or autoimmune disorders.

Clinical Implications for Dental Practitioners

The implications of this review are particularly significant for dental professionals, who are often the first to observe orofacial changes. Key takeaways include:

- Routine review of patient medication history should be standard in all dental evaluations, especially when patients present with unexplained or persistent oral lesions.
- Differential diagnosis should consider drug-induced

etiology alongside common inflammatory or infectious causes.
- Dental practitioners should establish collaborative communication with prescribing physicians to consider drug modifications or systemic treatment when necessary.
- Implementation of preventive oral health programs can mitigate severity in at-risk patients, particularly those on long-term immunosuppressants or polypharmacy.

The review also reaffirms the heterogeneous presentation of drug-related oral reactions, necessitating heightened diagnostic vigilance.

Comparisons with Existing Literature

While Glick et al. (2020) provided a valuable overview of common drug-related oral manifestations, their scope was primarily limited to established medications used in primary care and dentistry. In contrast, this review includes newer pharmaceutical agents and biotechnological therapies, reflecting current prescribing trends and the growing use of targeted immunotherapies and vaccines.

Additionally, while earlier studies lacked regional context, this review includes data from India, Saudi Arabia, Italy, Canada, and China, providing geographically diverse evidence and spotlighting variability in drug availability, prescription practices, and patient outcomes.

Gaps in Current Knowledge and Future Directions:

Despite the comprehensive synthesis, several critical knowledge gaps remain:
- Lack of standardized diagnostic criteria and severity grading for orofacial drug reactions impedes cross-study comparability.
- Underreporting and misdiagnosis persist due to limited awareness and poor documentation.
- Population-based studies are scarce, especially in developing countries where self-medication and over-the-counter drug use are prevalent.
- Long-term follow-up data on the progression or resolution of oral manifestations is lacking.

Future research should focus on establishing standardized classification systems, conducting prospective cohort studies, and integrating genetic and pharmacogenomic data to identify patients at risk for specific drug reactions.

Conclusion

In conclusion, this review emphasizes that orofacial manifestations can be critical early indicators of systemic drug reactions. Recognizing these signs, understanding their pharmacologic origins, and intervening early can significantly reduce morbidity and improve treatment outcomes. Dental practitioners play a pivotal role in pharmacovigilance, interdisciplinary care, and patient safety, particularly in an era of rapidly evolving drug therapies.

Summary and Clinical Implications

This systematic review identified a wide array of drugs implicated in orofacial adverse reactions, with cyclosporine A, phenytoin, methimazole, methotrexate, propranolol, and newer agents like BNT162b2 and pembrolizumab being the most frequently reported. The most common manifestations included gingival hyperplasia, painful ulcerations, mucosal erythema, crusting of the lips, and submucosal bleeding. In some pediatric cases, in utero exposure to medications like warfarin led to delayed tooth eruption and structural anomalies.

Management strategies predominantly involved:
- Withdrawal or substitution of the offending drug
- Use of corticosteroids, antihistamines, and analgesics to control inflammation and discomfort
- Supportive oral care including hygiene reinforcement, antifungal or antiseptic rinses, and in some cases, surgical intervention (e.g., gingivectomy)

Importantly, this review provides a comprehensive clinical resource for dental practitioners, enhancing their ability to recognize and manage drug-induced orofacial manifestations promptly and effectively. This knowledge is crucial in settings like India, where polypharmacy, over-the-counter drug use, and irrational prescription practices remain widespread.

Understanding the orofacial side effects of medications allows for early diagnosis, reduction in unnecessary investigations, and collaboration with physicians to adjust therapy—ultimately improving patient outcomes and reducing oral morbidity. Moreover, the findings highlight the need for individualized treatment approaches, especially in immunocompromised or medically complex patients. The role of genetic predisposition in drug reactions also warrants further investigation, as pharmacogenomic profiling could eventually inform more precise and safer prescribing practices.

Limitations and Future Directions

This review is limited by the inclusion of only English-language studies and the reliance on published case reports, many of which lacked consistent reporting of dosage, duration, and long-term follow-up. Additionally, while systemic manifestations were frequently noted, the review selectively focused on orofacial signs, potentially omitting relevant systemic-drug interactions.

Future research should explore:
- Population-based data on drug-induced oral effects
- Pharmacogenetic studies to understand individual susceptibility
- Development of standard diagnostic and reporting guidelines for oral adverse drug reactions

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