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Drugs associated with gingival enlargement: a review of the scientific literature on clinical characteristics and related factors

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ABSTRACT

Drug-induced gingival enlargement is a multifactorial condition that compromises the periodontal health of patients undergoing prolonged treatments. This review of the scientific literature aimed to identify the medications most frequently associated with this condition, describe their clinical characteristics, and analyze related factors. The study was conducted following the PRISMA 2020 statement. A search for articles was carried out between November 11, 2024, and February 5, 2025, in the PubMed, Scopus, ProQuest, and EBSCOhost databases. Clinical and observational studies in humans (cross-sectional and longitudinal) on gingival enlargement associated with anticonvulsants, calcium channel blockers, and immunosuppressants were included. Of the 2,152 records identified, 2,094 were excluded after title and abstract screening, and 34 after full-text review because they were case reports, case-control studies, animal or cellular studies, or reviews. As a result, 11 studies were included. The collected evidence showed that phenytoin presented prevalences close to 50%; amlodipine, between 1.7% and 37%; and cyclosporine A, between 25% and 53%. The most influential factors were dosage, duration of treatment, and level of oral hygiene, whereas age and sex showed a less consistent relationship. It is concluded that the available evidence significantly associates certain drugs with gingival enlargement, highlighting the importance of periodontal monitoring and prevention in medicated patients.

Keywords: gingival overgrowth; gingival hyperplasia; amlodipine; cyclosporines; phenytoin.

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INTRODUCTION

The clinical term referring to an increase in gingival volume is gingival enlargement (GE), whereas "hypertrophy" and "hyperplasia" are histopathological terms reserved for histological analysis (1–3). GE manifests in the attached gingiva and interdental papilla, with variations in extent and severity that may partially cover the dental crown (4,5). This is a multifactorial condition that depends not only on oral hygiene but also occurs in patients with chronic diseases undergoing treatment with certain medications (6).

Drug-induced gingival overgrowth (DIGO) is common among patients receiving long-term therapies and represents a clinical and public health concern. It is associated with anticonvulsants such as phenytoin, used for epilepsy; calcium channel blockers (CCBs) such as nifedipine and amlodipine, prescribed for hypertension; and immunosuppressants such as cyclosporine A (CsA), used to prevent organ rejection, although more than twenty drugs were implicated. Its global prevalence is estimated to range from 3% to 20%, reaching up to 50% with phenytoin, 25%–30% with CsA, approximately 10% with nifedipine, and between 1.7% and 3.3% with amlodipine (7–10). Clinically, it commonly affects the anterior regions and may present with lobulations and color changes in severe cases. Furthermore, manifestations may appear within a few months after treatment initiation, underscoring the need for early detection and management strategies (11–13).

GE affects esthetics, oral function, speech, and nutrition; when associated with poor oral hygiene, it increases the risk of periodontitis and dental caries. Its drug-induced form (DIGO) is particularly relevant in patients with chronic diseases undergoing long-term therapies because, apart from compromising periodontal health, it negatively impacts quality of life. From a public health perspective, it represents a challenge requiring coordination between dentists and physicians. Management includes plaque control every three months, oral hygiene instruction, and, in severe cases, surgical intervention (gingivoplasty or gingivectomy). Recognizing these adverse effects on periodontal tissues is essential for patient counseling and for differentiating them from other gingival alterations.

In this context, a review of the scientific literature is necessary to update current knowledge regarding this entity. The present study synthesizes the available evidence based on a search conducted between November 2024 and February 2025, in which anticonvulsants, calcium channel blockers, and immunosuppressants were comparatively evaluated. Similarly, clinical characteristics are described, associated factors are analyzed, and implications for dentistry and public health are discussed to provide tools for the detection, management, and prevention of this condition.

The objective of this review was to identify the medications most frequently associated with GE, describe their clinical characteristics, and analyze the factors related to their development.

LITERATURE REVIEW

The PICO methodology was used, defining the criteria as follows: the population (P) consisted of patients undergoing pharmacological treatment; the intervention (I) focused on the use of anticonvulsants, calcium channel blockers, or immunosuppressants; the comparison (C) was established with patients not receiving such pharmacological therapy; and the outcome (O) evaluated the presence and characteristics of GE, together with its associated factors. Based on this framework, the following research question was formulated: Which medications are most frequently associated with gingival enlargement, its clinical characteristics, and the factors related to its occurrence?

The search strategy was conducted between November 11, 2024, and February 5, 2025, following the principles of the PRISMA 2020 statement (Preferred Reporting Items for Systematic Reviews and Meta-Analyses). PubMed, Scopus, ProQuest, and EBSCOhost databases were searched using the following controlled and free terms: gingival enlargement," "gingival overgrowth," "gingival hyperplasia," "drugs," "medicines," and "drug-induced gingival overgrowth," combined using the Boolean operators "AND" and "OR." No restrictions were applied regarding year of publication, and studies published in English or Spanish were included. The specific search strategies are detailed in Table 1.

Clinical and observational studies (cross-sectional and longitudinal) conducted in humans and analyzing GE associated with the use of anticonvulsants, calcium channel blockers, or immunosuppressants were included. Reviews, meta-analyses, case reports, case-control studies, in vitro or animal studies, and investigations with a molecular or histopathological focus were excluded.

To report the source selection process, detailing the studies included according to the eligibility criteria and the excluded records, the PRISMA 2020 flow diagram was used (Figure 1). A total of 2,152 records were identified across the databases searched. After manually removing 13 duplicates, 2,139 records were screened by title and abstract; of these, 2,094 were excluded for not meeting the inclusion criteria, mainly because they did not address drug-induced GE or involved non-rele-

vant populations or study designs. A total of 45 full-text articles were reviewed, of which 34 were excluded for the following reasons: case reports (n = 7), case-control studies (n = 5), in vitro or animal studies (n = 7), studies with a molecular or cellular focus (n = 9), and systematic reviews, narrative reviews, or meta-analyses (n = 6). Ultimately, 11 studies that met the inclusion criteria were selected for inclusion in the present review.

Table 1. Search strategy.

Database	Search date	Search strategy
PubMed	Nov 11, 2024 - Feb 5, 2025	("gingival enlargement" [Title/Abstract] OR "gingival overgrowth" [Title/Abstract] OR "gingival hyperplasia" [Title/Abstract]) AND ("drugs" [Title/Abstract] OR "medicines" [Title/Abstract] OR "drug-induced gingival overgrowth" [Title/Abstract]) AND (MeSH Terms]))
Scopus	Nov 11, 2024 - Feb 5, 2025	TITLE-ABS-KEY ("gingival enlargement" OR "gingival overgrowth" OR "gingival hyperplasia") AND TITLE-ABS-KEY ("drugs" OR "medicines" OR "drug-induced gingival overgrowth")
ProQuest	Nov 11, 2024 - Feb 5, 2025	ab ("gingival enlargement" OR "gingival overgrowth" OR "gingival hyperplasia") AND ab ("drugs" OR "medicines" OR "drug-induced gingival overgrowth")
EBSCOhost (Medline, Dentistry & Oral Sciences Source)	Nov 11, 2024 - Feb 5, 2025	("gingival enlargement" OR "gingival overgrowth" OR "gingival hyperplasia") AND ("drugs" OR "medicines" OR "drug-induced gingival overgrowth")

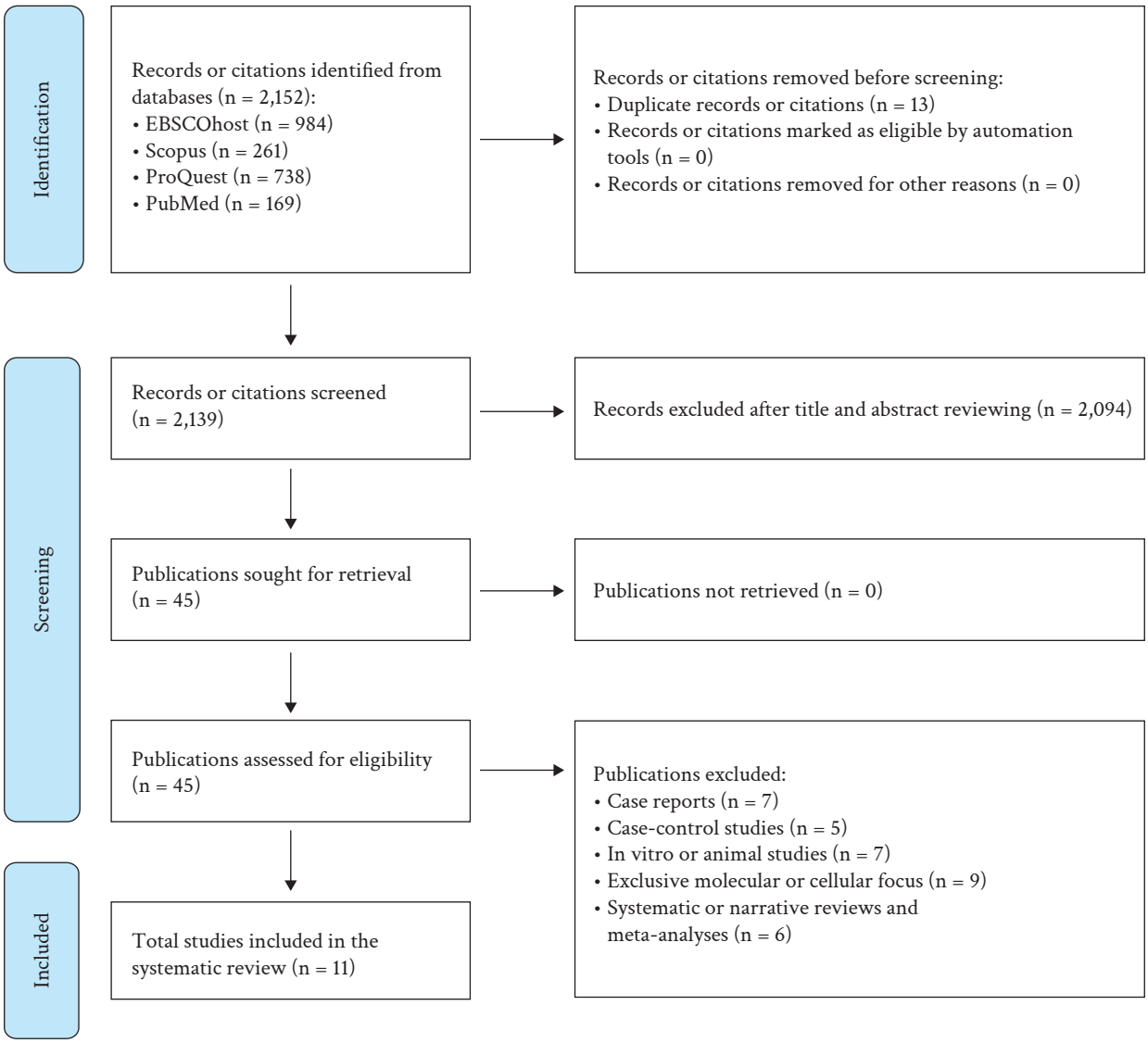

Figure 1. PRISMA 2020 flow diagram for study selection.

Study selection and data extraction were performed independently by two reviewers. Discrepancies were resolved by consensus with a third investigator. Data were recorded in a spreadsheet using Microsoft Excel and included the following variables: age, sex, sample size, type of drug administered, dosage, treatment duration, clinical characteristics of GE (location, extent, and severity), prevalence, and associated factors (oral hygiene, comorbidities, concomitant medication use, and genetic predisposition).

The evidence synthesis is presented narratively, detailing the reported frequencies and prevalence rates. Studies were grouped according to the pharmacological category involved: anticonvulsants, calcium channel blockers, and immunosuppressants.

RESULTS

A total of 11 studies published between 2015 and 2024 were included, collectively evaluating an approximate total of 1,253 patients. The study designs consisted primarily of cross-sectional studies, complemented by longitudinal clinical investigations. The studies were conducted in India, Romania, Nepal, Turkey, Japan, Ethiopia, Brazil, North Macedonia, and Cuba. Sample sizes ranged from 46 to 240 participants. The pharmacological groups investigated included anticonvulsants (phenytoin, carbamazepine, and valproate), calcium channel blockers (amlodipine, nifedipine, and verapamil), and immunosuppressants (cyclosporine A). The detailed characteristics of these studies are presented in Table 2.

Table 2. Articles included in the systematic review of drugs associated with gingival enlargement (GE).

Author	Year	Country	Sample size	Mean age/ range	Study type	Pharmacological group	GE diagnostic method	Reported associated factors	Main findings
Nayyar et al. (9)	2014	India	100	30.08 years	Observational longitudinal study	Anticonvulsants (phenytoin)	Gingival overgrowth index	Reduced serum folate, longer treatment duration, and early onset of enlargement.	After one year, all evaluated patients presented GE. Serum folate significantly decreased, and the degree of enlargement increased (both $p < 0.001$).
Suneja et al. (10)	2016	India	90 (30 per group: phenytoin, valproate, and carbamazepine)	13.16 ± 2.44 years	Observational longitudinal study	Antiepileptics (phenytoin, carbamazepine, and valproate)	Modified Harris–Ewalt Index; plaque and bleeding indices; periodontal probing	Probing depth and drug type.	Phenytoin showed greater enlargement; probing depth correlated with severity ($p < 0.05$).
Grigore et al. (11)	2015	Romania	78 children with epilepsy	Not reported	Observational longitudinal study	Antiepileptics	Periodic clinical examination every 6 months; periodontal probing depth measurement	Use of classical antiepileptic drugs and polytherapy.	Epileptic children undergoing long-term treatment exhibited GE, directly associated with treatment duration and type of antiepileptic medication.
Kothari et al. (12)	2020	India	108 hypertensive patients	61.1 ± 10.1 years	Cross-sectional study	CCBs (amlodipine)	Bokenkamp and Bornhorst Index; Löe and Silness gingival and plaque indices; periodontal probing	Dose ≥5 mg/day, poor oral hygiene, higher frequency in males (4:1).	An association between amlodipine-induced GE and poor oral hygiene was identified.

CCBs: calcium channel blockers; CsA: cyclosporine A; PD: probing depth; CAL: clinical attachment level; PPD: probing pocket depth; BOP: bleeding on probing; DIGO: drug-induced gingival overgrowth.

Table 2. (*Continuation*).

Author	Year	Country	Sample size	Mean age/ range	Study type	Pharmacological group	GE diagnostic method	Reported associated factors	Main findings
Sharma et al. (13)	2018	Nepal	240 patients receiving amlodipine therapy	49.69 ± 8.1 years	Cross-sectional study	CCBs (amlodipine)	Clinical diagnosis of gingival overgrowth (firm/ fibrotic interdental papilla, marginal extension)	Amlodipine dose and duration, comorbidities (diabetes mellitus most frequent).	The study reported gingival overgrowth associated with prolonged amlodipine use, more frequent among individuals over 50 years with poor plaque control.
Ustaoğlu et al. (14)	2021	Turkey	131 hypertensive patients	35-65 years	Cross-sectional study	CCBs (including amlodipine, nifedipine, and verapamil)	Ingles et al. (1999) Index, periodontal parameters	Greater PD and CAL increased risk of drug-induced GE; amlodipine dose associated with GE; oral hygiene.	A greater association of gingival enlargement was observed among calcium channel blocker users, particularly with nifedipine.
Matsuda et al. (15)	2019	Japan	128 patients (13 responders, 32 non-responders, 83 non-users)	≥50 years (mean: 65.8 ± 9.6 in responders)	Cross-sectional study	CCBs (amlodipine, nifedipine)	Clinical assessment, PPD, BOP	Periodontal inflammation, oral hygiene, age.	Significant association between periodontal inflammation and gingival enlargement among patients using calcium antagonists.
Bhumika et al. (16)	2019	Ethiopia	50 hypertensive patients (25 CCB users, 25 non-CCB users)	Mean 58.3 ± 14.7 years	Cross-sectional study	CCBs (amlodipine, nifedipine, verapamil)	Clinical DIGO index (0–4), plaque, and papillary bleeding indices	Drug type, sex, probing depth, dose.	Calcium channel blockers were confirmed to induce gingival enlargement, especially among patients with poor oral hygiene.
Vidal et al. (17)	2018	Brazil	162 hypertensive patients	54.1 ± 8.5 years (39–78 years)	Cross-sectional study	CCBs (amlodipine, nifedipine, verapamil)	Angelopoulos and Goaz Index modified by Miller and Damm	Bacterial plaque; probing depth (PPD 4–5 mm and ≥6 mm).	Nifedipine was more strongly associated with gingival enlargement compared with the other two drugs.
Mitic et al. (18)	2017	North Macedonia	120 renal transplants	Not reported	Observational longitudinal study	Cyclosporine A	Silness and Löe Plaque Index; Löe and Silness Gingival Index; Gingival Overgrowth Index	Plaque ($\beta = 0.507$) more influential than dose ($\beta = 0.197$).	Plaque exerted a greater effect on GE, although dosage also influenced its occurrence ($p < 0.01$).
Montes de Oca González et al. (19)	2021	Cuba	46 individuals with hypertension, heart disease, and epilepsy	20-59 years	Cross-sectional study	Antihypertensives (nifedipine, amlodipine), anticonvulsants (phenytoin), immunosuppressants (cyclosporine)	Clinical periodontal examination; gingival overgrowth index	Medication used, duration of use, oral hygiene.	30% prevalence. Greater frequency with nifedipine and phenytoin, associated with medication use >6 months and poor oral hygiene.

CCBs: calcium channel blockers; CsA: cyclosporine A; PD: probing depth; CAL: clinical attachment level; PPD: probing pocket depth; BOP: bleeding on probing; DIGO: drug-induced gingival overgrowth.

The studies reported frequencies and prevalence rates of GE, as well as associated factors. However, most studies did not report measures of precision (confidence intervals, relative risks, or odds ratios), which limited the feasibility of conducting a meta-analysis. Only a few authors (14,15,17) provided detailed statistical analyses, including multivariate logistic regression to identify associated factors, calculation of odds ratios with 95% confidence intervals, χ^2 tests, and comparative analyses of probing depth, clinical attachment level, and bleeding on probing. For this reason, the statistical results are presented narratively and summarized in a structured manner in Table 3, grouped according to the pharmacological category evaluated.

Table 3. Statistical results of the included studies on drug-induced gingival enlargement (GE), according to pharmacological group

Author	Drug(s) evaluated	Prevalence/frequency (%)	Additional measures reported
Nayyar et al. (9)	Phenytoin ± folic acid	41% with GE in phenytoin users; lower frequency in combination with folic acid	Significant association between phenytoin and GE ($p < 0.05$)
Suneja et al. (10)	Phenytoin, carbamazepine, valproate	Phenytoin: 50%; carbamazepine: 15%; valproate: 10%	Severity analysis (mild, moderate, severe); significant differences among drugs (χ^2, $p < 0.05$)
Grigore et al. (11)	Carbamazepine, valproate	Carbamazepine: 8.3%; valproate: 5.5%	Higher prevalence in combination therapies; non-significant differences ($p > 0.05$)
Kothari et al. (12)	Amlodipine	Prevalence 3.3%	Higher risk in males and in treatments lasting >6 months ($p < 0.05$)
Sharma et al. (13)	Amlodipine	2.5% (6 of 240 patients with ≥6 months of treatment)	Dose >5 mg → OR 7.3 ($p = 0.011$); duration >5 years → OR 6.35 ($p = 0.017$); sex not significant
Ustaoğlu et al. (14)	Amlodipine, lercanidipine, benidipine, ACE inhibitors, ARBs	Amlodipine: 31.8%; lercanidipine: 13.3%; benidipine: 7.1%; ACE inhibitors: 7.5%; ARBs: 12.5% Total CCBs: 19.6%	Amlodipine dose correlated with DIGO ($p = 0.007$); no association with treatment duration ($p > 0.05$); DIGO risk increased with PD (OR = 4.65) and CAL (OR = 3.71)
Matsuda et al. (15)	Amlodipine/nifedipine (CCBs)	DIGO in 15% of patients receiving amlodipine/nifedipine	Responders with PPD 4.2 mm vs. 2.9 mm ($p < 0.01$); BOP 67% vs. 25–35% ($p < 0.01$)
Bhumika et al. (16)	Nifedipine, amlodipine	DIGO in CCB users: 92%; DIGO in non-CCB users: 48%; nifedipine: 60%; amlodipine: 40%	Users of nifedipine 20 mg showed 86.7% DIGO; users of amlodipine 10 mg showed 54.5% DIGO; predominance of grade 2 DIGO (60%) and grade 1 (20%)
Vidal et al. (17)	Nifedipine, amlodipine, felodipine	Nifedipine: 38.6%; amlodipine: 45.4%; felodipine: 12.5%	Nifedipine OR = 2.46 (95% CI: 1.04–5.82); amlodipine OR = 3.90 (95% CI: 1.47–10.35); sites with PPD 4–5 mm (OR = 1.02); sites with PPD ≥6 mm (OR = 1.05)
Mitic et al. (18)	Anticonvulsants, CCBs, immunosuppressants	Overall prevalence: 35%; CCBs: 28%; anticonvulsants: 32%; immunosuppressants: 40%	Dental plaque identified as a significant risk factor (OR 2.5; 95% CI: 1.3–4.7)
Montes de Oca González et al. (19)	Amlodipine, nifedipine, phenytoin	Amlodipine: 12%; nifedipine: 20%; phenytoin: 25%	Significant differences according to pharmacological group ($p < 0.05$)

GE: gingival enlargement; CCBs: calcium channel blockers; CI: confidence interval; OR: odds ratio; CAL: clinical attachment level; PD: probing depth; BOP: bleeding on probing; DIGO: drug-induced gingival overgrowth; ACE inhibitors: angiotensin-converting enzyme inhibitors; ARBs: angiotensin II receptor blockers.

Regarding calcium channel blockers, amlodipine emerged as the most extensively investigated drug, with reported GE prevalence ranging from 1.7% to 37.5% (13,16). Several studies identified the influence of dose and treatment duration, although findings were heterogeneous (12–17). With respect to anticonvulsants, phenytoin demonstrated a consistent association with GE, reaching prevalence rates close to 50% (9–11,19). Carbamazepine and sodium valproate exhibited lower frequencies. Suneja et al. (10) reported prevalence rates of 15% and 10%, respectively, whereas Grigore et al. (11) found 8.3% for carbamazepine and 5.5% for valproate. For both medications, gingival enlargement was generally mild and localized, and in some cases occurred in combination with other medications (19). Regarding immunosuppressants, cyclosporine A showed prevalence rates ranging from 25% to 50%, reaching as high as 88.2% when administered concomitantly with nifedipine, thereby demonstrating an additive effect (17).

In summary, studies indicate that phenytoin, amlodipine, and cyclosporine A are the medications most frequently associated with GE. However, considerable heterogeneity exists across findings, attributable to differences in study design, diagnostic criteria employed, treatment duration and dosage, as well as the inclusion of variables such as oral hygiene, age, and sex of participants.

DISCUSSION

The findings of this review confirm that the three pharmacological groups evaluated—calcium channel blockers, anticonvulsants, and immunosuppressants—are associated with gingival enlargement (GE). The variations in magnitude and clinical characteristics observed are attributable to the specific pharmacokinetics of each agent (amlodipine, phenytoin, and cyclosporine A being the most frequently implicated drugs) and to contributing variables, such as the administered dose, treatment duration, and the patient's oral hygiene status. These results reflect a multifactorial pattern in which pharmacological, environmental, and host-related factors converge, thereby explaining the heterogeneity identified among the included studies and the discrepancies with previous reviews (1,7,8,20). This interpretation is consistent with the observations of Barsoum et al. (1) and Glick et al. (7), who emphasize that risk is influenced by administered dose, duration of exposure, and oral hygiene level.

Regarding calcium channel blockers (CCBs), amlodipine was the most frequently reported drug, with GE prevalence ranging from 1.7% to 37.5% across the analyzed studies (12–17). In three investigations (12,13,15), the frequency of GE was below 5%, whereas in at least two studies (14,17) it exceeded 30%. This broad range is consistent with previous reviews in which amlodipine exhibited variations between 1.7% and 36% (7,20). In particular, amlodipine administered at doses ≥5 mg/day and for periods exceeding five years was significantly associated with an increased risk of GE (12,13). These findings are consistent with those reported by Vidal et al. (17), who reported an odds ratio of 3.9 for this medication. Concerning age and sex, some authors found no differences (15), whereas others reported a higher frequency among males (12,16), likely owing to disparities in oral hygiene and gingival inflammatory levels.

In terms of anticonvulsants, phenytoin exhibited prevalence rates approaching 50% in several of the analyzed studies (9–11,19). The findings of this synthesis (40–53%) are comparable to those reported in previous international reviews, in which prevalence ranged from 35% to 50% (13–15). In contrast, carbamazepine and valproate showed lower frequencies, ranging from 5.5% to 15%, with manifestations generally being mild and localized (10,11). These findings reinforce the evidence that phenytoin is the antiepileptic drug with the greatest potential to induce GE, whereas carbamazepine and valproate tend to exhibit less pronounced effects or effects associated with polytherapy. Within this pharmacological group, phenytoin consistently demonstrated an onset of GE in the interdental papilla, progressing toward the marginal gingiva and accompanied by alterations in color and texture (9–11,19). These clinical characteristics are consistent with those described in previous reviews, such as that of Ramasamy et al., thereby strengthening the validity of the findings. Furthermore, one pathophysiological aspect observed in this review was the reduction in serum folate levels among patients undergoing prolonged phenytoin therapy (9,19), which may explain excessive extracellular matrix accumulation and fibrosis. This mechanism, also reported in international literature, suggests that nutritional deficiencies may play a modulatory role in the GE severity.

Regarding immunosuppressants, cyclosporine A exhibited prevalence rates ranging from 25% to 50% among the included studies (17,18). These values are consistent with those reported in previous reviews, where prevalence ranged from 30% to 60% (15,20). A dose–response relationship was also observed, as higher doses (150–175 mg) were associated with greater GE severity compared with lower doses (100–125 mg). Particularly, when cyclosporine A was administered in combination with calcium channel blockers, prevalence reached 88.2% (17), demonstrating an increased risk associated with polytherapy. However, in several studies, clinical descriptions were limited, restricting detailed characterization of lesion location and progression.

Taken together, results reveal a multifactorial pattern involving interactions among pharmacological variables (drug type, dose, and treatment duration), local factors (oral hygiene and periodontal inflammation), and

host-related variables (age and sex). The heterogeneity observed among the included studies may be explained, first, by the diagnostic criteria employed, which ranged from standardized indices—such as those of Angelopoulos and Goaz, modified Harris–Ewalt, or PISA/PESA—to operational clinical descriptions, generating disparities in case identification and classification (10,12–17). Second, selection bias contributed to variability, since several investigations were conducted in referral hospitals or among populations with comorbidities (patients with severe hypertension or transplant recipients), which increases prevalence compared with community-based samples (17,18). Third, population characteristics varied substantially, ranging from children with epilepsy (9–11) to hypertensive or immunosuppressed adults (12–18), with differences in sex distribution (12,16) and the presence of comorbidities such as diabetes mellitus (13).

These sources of heterogeneity explain the dispersion in prevalence rates (amlodipine: 1.7–37.5%; phenytoin: 40–53%; cyclosporine A: 25–50%) and justify the inability to conduct a meta-analysis. Nevertheless, one consistent finding across multiple studies was the influence of oral hygiene and periodontal inflammation, with higher prevalence rates among patients exhibiting elevated levels of plaque accumulation and inflammation. For example, Mitic et al. (18) reported a significant effect of dental plaque (OR = 2.5; 95% CI: 1.3–4.7), whereas Matsuda et al. (15) found a higher prevalence of GE among patients with bleeding on probing (67% in responders versus 25–35% in non-responders; $p < 0.01$). Similarly, Ustaoğlu et al. (14) identified that the risk of enlargement increased with probing depth (PD ≥4 mm: OR = 4.65; CAL ≥3 mm: OR = 3.71), and Vidal et al. (17) observed that amlodipine was associated with a prevalence of 45.4% and nifedipine with 38.6%, significantly higher in the presence of periodontal inflammation.

Although most included cross-sectional studies exhibited a low risk of bias (7–8/8), cohort studies achieved only moderate quality (7/11). This methodological difference may explain part of the observed heterogeneity: whereas cross-sectional designs provide consistent prevalence data, they lack temporality and therefore limit causal inference; cohort studies, in contrast, provided longer follow-up but showed deficiencies in confounder control and losses to follow-up, leading to prevalence overestimation. Thus, the available evidence confirms the association between certain drugs and GE, although the level of certainty is conditioned by the predominance of observational designs and the unequal methodological quality of the studies analyzed.

From a clinical perspective, these findings support the recommendations of recent guidelines issued by the American Academy of Periodontology and the European Federation of Periodontology. Both organizations recommend early identification of GE in patients receiving high-risk medications, implementation of plaque control protocols and professional prophylaxis every 3–6 months, coordination with the treating physician regarding the possible substitution or adjustment of medication whenever feasible, and consideration of periodontal surgery in severe cases refractory to conservative management (20). Beyond these recommendations, the present review provides evidence that the severity and frequency of GE follow a dose–response pattern, dependent on the type of drug, its concentration, and treatment duration. This has considerable practical relevance, as it allows clinical risk stratification from the initiation of pharmacological therapy, facilitating the anticipation of more intensive preventive measures in patients receiving polytherapy or high doses.

From a preventive perspective, the findings of this study indicate that drug-induced GE is associated with modifiable factors, particularly oral hygiene status, the presence of periodontal inflammation, and pharmacological variables such as dose, treatment duration, and polytherapy. In several studies, plaque accumulation and bleeding on probing were associated with a greater risk and severity of GE, whereas higher doses and prolonged treatments demonstrated a consistent dose–response relationship. These results suggest that early identification of patients exposed to high-risk medications, together with consideration of local and systemic factors, constitutes a key strategy to limit the progression of this condition and its clinical consequences.

Among the limitations of the present review are the predominance of cross-sectional studies, heterogeneity in diagnostic criteria, and the absence of standardized data regarding dosage and severity in several of the analyzed studies. These limitations hinder comparability and restrict the ability to establish robust causal relationships. Similarly, no prior protocol was established, nor were formal tools used to assess the overall certainty of the evidence; therefore, the findings should be interpreted as a descriptive synthesis of the available literature. Nevertheless, this study was conducted following PRISMA 2020 guidelines and applying the PECO methodology, which provides rigor, transparency, and reproducibility to the process of evidence search, selection, and analysis.

The development of multicenter longitudinal studies that employ uniform criteria, detailed dose–response analyses, and evaluation of genetic and environmental factors that may modulate the gingival response to these drugs is recommended.

CONCLUSIONS

This study demonstrates that the drugs most frequently associated with GE are phenytoin, amlodipine, and cyclosporine A, belonging to the anticonvulsant, calcium channel blocker, and immunosuppressant groups, respectively. Clinical manifestations generally involve the interdental papilla and attached gingiva, with variations in localization and severity depending on the drug used and the patient profile.

Factors such as dose, duration of administration, and oral hygiene status were identified as significantly influencing the occurrence and severity of GE, whereas age and sex showed a less consistent association. These findings reinforce the need for continuous dental monitoring in polymedicated patients, together with the implementation of preventive and educational strategies aimed at minimizing this adverse effect and preserving periodontal health.

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