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Review

THE IMPACT OF ANTIEPILEPTIC DRUG THERAPY ON ORAL HEALTH IN CHILDREN WITH EPILEPSY: CURRENT EVIDENCE, MECHANISMS, AND MANAGEMENT STRATEGIES

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ABSTRACT

Epilepsy represents one of the most common chronic neurological disorders worldwide, with approximately half of all cases diagnosed during childhood or adolescence. Although the condition remains incurable, effective seizure control can be achieved in up to 70% of patients through appropriately selected antiepileptic drugs (AEDs), administered as monotherapy or in combination. Despite their therapeutic efficacy, AEDs are associated with a range of adverse effects, including those affecting oral health, which may substantially impair patients' quality of life. This review summarizes current evidence regarding the impact of AED therapy on oral health in children with epilepsy and discusses potential pathophysiological mechanisms underlying these adverse effects. A comprehensive literature search was performed in the PubMed and Google Scholar databases using the free-text terms and Medical Subject Headings (MeSH), such as "Epilepsy/drug therapy" and "Anticonvulsants/adverse effects" and the following keywords: "antiepileptic drugs & side effects," "antiepileptic drugs & oral health status in children," "oral side effects," "antiepileptic drugs," as well as relevant synonyms such as "antiseizure medications," "AEDs," and "anticonvulsants." The review includes data from systematic reviews, meta-analyses, and original research conducted in Europe and globally. Reported oral manifestations associated with AED use include gingival overgrowth, gingivitis, xerostomia, and glossitis, particularly linked to first-generation agents such as phenytoin and valproic acid. Pediatric patients undergoing long-term AED therapy demonstrate increased susceptibility to dental caries, periodontal disease, tooth loss, and maxillofacial bone demineralization, which may elevate the risk of fractures following trauma. Further studies are warranted to elucidate the oral health implications of newer-generation AEDs and to clarify the molecular mechanisms responsible for these complications. Given the chronic nature of epilepsy and the cumulative impact of long-term pharmacotherapy, children receiving AEDs require individualized preventive strategies, emphasizing meticulous oral hygiene and regular dental monitoring to reduce the risk of treatment-related oral pathology.

KEYWORDS: AEDs, antiepileptic drugs, anticonvulsants adverse effects, oral health, gingival overgrowth.

1. Introduction

Epilepsy ranks among the most prevalent chronic neurological disorders globally, and a substantial proportion of cases manifest during childhood or adolescence. According to epidemiological studies, the incidence of epilepsy in children is approximately 5—7 per 10,000 children per year, and by age 20, nearly 1 % of the population will have been diagnosed with epilepsy [1]. Pediatric epilepsy is a heterogeneous group of conditions, encompassing syndromes that are unique to early life (e.g. epileptic spasms of infancy, self-limited epilepsy with centrotemporal spikes, childhood absence epilepsy and Lennox-Gastaut syndrome) alongside more broadly shared epileptic phenotypes (Table 1) [2—5]. The International League Against Epilepsy (ILAE) classifies etiologies into genetic, structural, metabolic, infectious, immune, and unknown categories, and defines epilepsy by criteria such as recurrent unprovoked seizures, a high risk

of recurrence, or a recognized epilepsy syndrome [2,3,6,7]. Differential diagnosis is essential, as various conditions such as syncope, migraines, or psychogenic non-epileptic seizures may mimic epileptic events [8].

In children, achieving seizure control is imperative not only for reducing neurologic morbidity but also for optimizing cognitive development, behavior, and quality of life. Antiepileptic drug (AED) therapy remains the mainstay of treatment in pediatric epilepsy, often implemented as monotherapy or in combination regimens depending on seizure type, syndrome, patient age, and drug tolerability. With appropriately chosen regimens, about two thirds to 70% of children with epilepsy may achieve remission at some stage [9]. Nevertheless, approximately 30% of patients are considered drug resistant and require alternative or adjunctive interventions [10]. In pediatric populations, drug selection is more complex due to developmental pharmacokinetics, drug–drug interactions, and heightened sensitivity to adverse effects [11].

Commonly used AEDs in children span both "older" and "newer" generations. Traditional agents such as phenytoin, phenobarbital, carbamazepine, and valproic acid have long histories of use, but are also associated with substantial side effect burdens, including hepatic toxicity, hematologic effects, cognitive impairment, and teratogenic risk [12,13]. Newer antiseizure medications (e.g. levetiracetam, lamotrigine, oxcarbazepine, topiramate) are frequently preferred today because of improved tolerability, fewer interactions, and more favorable side effect profiles [14,15]. Nonetheless, even newer AEDs are not free from adverse effects, and in pediatric cohorts they may still affect cognition, behavior, and systemic physiology (e.g. levetiracetam has been implicated in behavioral side effects) [16].

AED therapy is generally long-term, often lifelong, which places the oral cavity and surrounding tissues at sustained exposure to systemic drug influences. The mechanism of action and duration of treatment are thus relevant to the risk of adverse manifestations, including those in the mouth. For example, phenytoin's propensity to cause gingival overgrowth arises from its effects on fibroblast proliferation, collagen metabolism, and folate metabolism in gingival tissues, an effect that is modulated by inflammatory stimuli (e.g. dental plaque) and the duration and dose of exposure [17—19]. Importantly, many adverse effects are dose-dependent or cumulative over time.

General adverse effects of AEDs in children include neurological (dizziness, sedation, cognitive slowing), hematologic, hepatic, endocrine, metabolic, and dermatologic reactions, among others [20]. In the oral realm, AED therapy has been associated with gingival enlargement, increased susceptibility to gingivitis and periodontitis, mucosal changes, soft tissue injury (lip/cheek biting), and dental trauma (e.g. fractures during seizures) [21]. The link between systemic drug therapy and oral health is complex, as it is mediated via direct effects of the drug, the influence of oral hygiene status, local inflammation, dietary habits, and cooperation in oral care.

Given this context, this review aims to synthesize the current state of knowledge regarding how antiepileptic drugs influence oral hygiene and oral health in children, exploring mechanisms, epidemiology of oral effects, and preventive strategies to mitigate harm.

2. Materials and Methods

A comprehensive literature search was conducted using the PubMed and Google Scholar databases to identify relevant studies on the impact of antiepileptic therapy on the oral health status of children with epilepsy. The search strategy included both free-text terms and Medical Subject Headings (MeSH), such as "Epilepsy/drug therapy" and "Anticonvulsants/adverse effects". To ensure a broad and inclusive search, the following keywords and Boolean combinations were used: "antiepileptic drugs & side effects," "antiepileptic drugs & oral health status in children," "oral side effects," "antiepileptic drugs," as well as relevant synonyms such as "antiseizure medications," "AEDs," and "anticonvulsants".

The review includes systematic reviews, meta-analyses, and narrative reviews, as well as original research articles published in English from European and international sources.

Articles were selected based on relevance to the topic, with priority given to studies focusing on pediatric populations, oral manifestations of AEDs, and preventive dental strategies. Titles and abstracts were screened, and full-text articles were reviewed when necessary to confirm eligibility and scientific quality.

Studies were included if they reported data on children and adolescents (aged 0—18 years) receiving AED therapy and provided information on oral health outcomes. While the aim was to cover the entire pediatric age range, most studies did not provide age-stratified data, limiting the possibility of separate analyses for infants, toddlers, school-aged children, and adolescents.

Both studies investigating monotherapy and polytherapy were considered. When available, data on monotherapy and polytherapy were analyzed separately; however, most studies either focused on monotherapy or did not distinguish between treatment regimens. Studies reporting non-epileptic conditions, or outcomes unrelated to oral health were excluded.

Titles and abstracts were screened by two independent reviewers, and full texts were examined to confirm eligibility and ensure scientific quality. Discrepancies were resolved through discussion or consultation with a third reviewer.

Table 1. Children's Epilepsy Syndromes according to ILAE (2022) [3], with seizure type classification update (ILAE 2025) [2].

Syndrome name	Age category	Seizure types	EEG / Clinical features
Benign familial neonatal seizures (BFNS)	Neonate/Infant	Focal seizures (preserved consciousness, observable motor)	Sharp waves over central regions; familial occurrence (KCNQ2/3 mutations).
Early infantile epileptic encephalopathy (Ohtahara syndrome)	Neonate/Infant	Generalized tonic seizures, spasms	EEG: suppression–burst pattern; onset <3 months.
Early myoclonic encephalopathy (EME)	Neonate/Infant	Generalized myoclonic, atonic, focal seizures	EEG: suppression–burst; metabolic etiology.
Infantile spasms (West syndrome)	Infant	Generalized epileptic spasms	EEG: hypsarrhythmia; clustered spasms.
Epilepsy of infancy with migrating focal seizures (EIMFS)	Infant	Focal seizures with impaired consciousness	EEG: migrating focal discharges; severe course.
Dravet syndrome (Severe myoclonic epilepsy of infancy)	Infant	Generalized tonic–clonic, myoclonic, focal impaired	Febrile seizures; SCN1A mutations.
Self-limited epilepsy with centrotemporal spikes (SeLECTS / Rolandic)	Childhood	Focal motor seizures (preserved consciousness)	EEG: centrotemporal spikes; nocturnal seizures.
Self-limited epilepsy with autonomic seizures (Panayiotopoulos)	Childhood	Focal autonomic seizures (preserved consciousness)	EEG: occipital spikes; autonomic symptoms.
Childhood absence epilepsy (CAE)	Childhood	Generalized nonmotor (absence, impaired consciousness)	EEG: 3 Hz spike–wave pattern; brief absences.
Epilepsy with myoclonic-atonic seizures (Doose syndrome)	Childhood	Generalized myoclonic-atonic seizures	EEG: 2–5 Hz polyspike–wave; idiopathic syndrome.
Lennox–Gastaut syndrome (LGS)	Childhood	Mixed generalized (tonic, atonic, atypical absence)	EEG: slow <2.5 Hz spike–wave; developmental epileptic encephalopathy.
Epileptic encephalopathy with spike-and-wave activation in sleep (DEE-SWAS / CSWS)	Childhood	Focal to bilateral tonic–clonic, atypical absence	EEG: continuous spike–wave activity during NREM sleep.
Jeavons syndrome (Epilepsy with eyelid myoclonia)	Childhood	Generalized myoclonic (eyelid), absence	EEG: photomyogenic response 3–6 Hz.
Febrile infection-related epilepsy syndrome (FIRES)	Childhood	Variable; often focal to bilateral tonic–clonic	EEG: diffuse discharges; post-infectious refractory status epilepticus.
Epilepsy with myoclonic absences (EMA)	Childhood	Generalized myoclonic-absence	EEG: 3 Hz spike–wave; myoclonia with impaired awareness.
Juvenile absence epilepsy (JAE)	Variable age	Generalized absence, generalized tonic–clonic	EEG: 3–4 Hz spike–wave; adolescent onset.
Juvenile myoclonic epilepsy (JME)	Variable age	Generalized myoclonic, tonic–clonic	EEG: 4–6 Hz polyspike–wave; morning seizures.
Progressive myoclonic epilepsies (PME)	Variable age	Generalized myoclonic ± tonic–clonic	Progressive encephalopathy; motor and cognitive decline.

3. Results

3.1. Pathophysiological and Clinical Aspects of AED-Induced Oral Changes

In children receiving antiepileptic drugs, a variety of oral alterations have been reported, including gingival enlargement, changes in bone metabolism, xerostomia, shifts in salivary pH and microbiota (Figure 1), all of which can negatively impact oral hygiene status and increase the risk of dental caries and periodontal disease. The severity and extent of these changes may vary depending on the type of AED administered. The following subsections summarize the current evidence on these AED-induced oral alterations, highlighting both their underlying biological mechanisms and clinical manifestations.

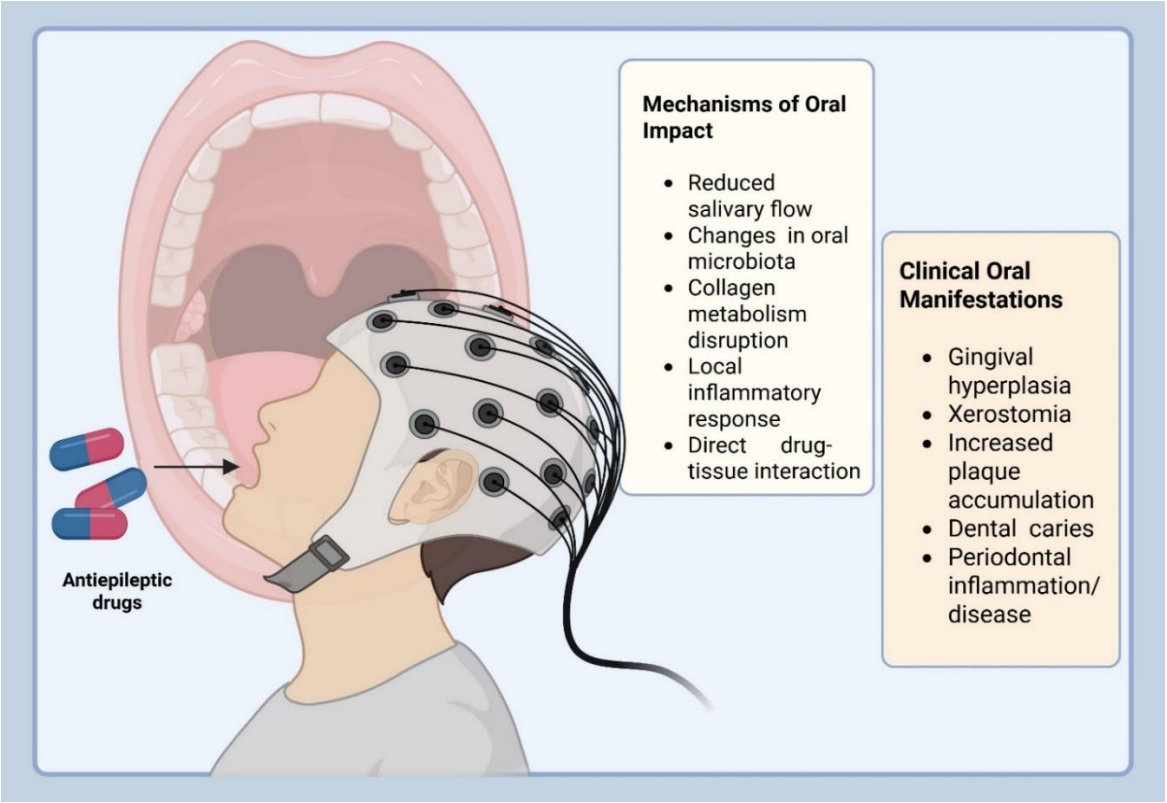

Fig. 1. Pathways linking antiepileptic drug use to oral health alterations in children (created with https://www.biorender.com) .

3.1.1. Gingival Enlargement Associated with AED Therapy

Gingival overgrowth can be caused by a local inflammatory process related to plaque accumulation, a systemic disease, or prescribed medications [22]. Drugs associated with this condition can be broadly divided into three categories: calcium-channel blockers, immunosuppressants, and anticonvulsants [23—25].

Among antiepileptic drugs, phenytoin remains the most established cause of drug-induced gingival enlargement, while phenobarbital, carbamazepine, valproate, gabapentin, lamotrigine, levetiracetam, and oxcarbazepine have been infrequently implicated in isolated case reports or small clinical series, suggesting a much lower and inconsistent risk of gingival enlargement [26].

Gingival hyperplasia related to phenytoin treatment was first reported by Kimball in 1939 [27], and since then many papers on this subject have appeared. It is currently estimated that approximately 50% (3—93%) of patients treated with phenytoin will develop clinically significant gingival hyperplasia [28]. Factors contributing to this complication include the presence of bacterial plaque (due to poor oral hygiene), higher serum phenytoin concentration, and younger patient age (which means that the pediatric population is at particular risk) [29,30].

In longitudinal pediatric cohorts, phenytoin monotherapy has been associated with gingival overgrowth in over 50% of children within three to six months of initiation (e.g. 53.6% in one study at three months) [18] and 57% in another six-month evaluation cohort [31]). Importantly, withdrawal of phenytoin has been shown to prompt regression of gingival enlargement: in one small pediatric series, a significant reduction in buccolingual gingival width was observed within one month after discontinuing the drug [32].

Although older antiepileptic drugs, such as phenytoin, remain well-known contributors to drug-induced gingival overgrowth, recent reviews continue to clarify the underlying pathophysiological mechanisms. Phenytoin appears to reduce fibroblast folic acid uptake, impair collagenase activation, and alter integrin expression, all of which contribute to excessive accumulation of extracellular matrix in gingival tissues. Local inflammation and dental plaque act as amplifying cofactors in this process [33]. Among anticonvulsant drugs associated with gingival overgrowth — phenobarbital, primidone, carbamazepine, valproic acid, lamotrigine, and oxcarbazepine [28,34] — levetiracetam has been increasingly preferred in pediatric populations due to its favorable safety profile and lower potential for drug interactions, although it may also be occasionally implicated in this complication [35].

A recent original study addressing newer- generation AEDs — specifically levetiracetam (LEV) and topiramate (TPM) monotherapy in children aged 6—12 years — demonstrated significantly higher plaque indices and gingival inflammation in treated children compared to healthy controls; in particular, 43.3% of children on TPM showed grade 2 gingival enlargement, and dental hygiene lapses were frequent (76.7% of AED-treated children) [36]. This underscores that even newer and ostensibly "safer" agents may still pose risks to oral health, especially when preventive care is suboptimal.

The development of gingival overgrowth in children treated with AEDs is closely linked to alterations at the cellular and molecular level.

3.1.1.1. Disruption of Collagen Metabolism and Extracellular Matrix Imbalance in AED-Induced Gingival Overgrowth

AED-induced gingival overgrowth is primarily driven by an imbalance between collagen synthesis and degradation within the gingival connective tissue. Antiepileptic drugs exert their effects through direct modulation of gingival fibroblast metabolism and extracellular matrix (ECM) homeostasis. One of the earliest described mechanisms involves a reduction in cellular folate uptake by gingival fibroblasts, particularly following phenytoin exposure, which leads to decreased activation of collagen-degrading enzymes such as matrix metalloproteinases (MMP-1 and MMP-2). This reduction in MMP activity, together with a simultaneous increase in tissue inhibitor of metalloproteinase-1 (TIMP-1), shifts the TIMP/MMP balance, markedly reducing ECM turnover and promoting the accumulation of type I and type III collagen fibers within the gingival connective tissue, thereby contributing to the fibrotic phenotype observed in drug-induced overgrowth [33,37—39].

Another crucial mechanism involves suppression of integrin α2β1 expression on the surface of gingival fibroblasts, a receptor that mediates collagen binding and endocytosis. Reduced integrin α2β1 availability limits fibroblast-mediated collagen internalization and degradation, thereby promoting persistent ECM accumulation [37].

Importantly, not all fibroblasts exhibit the same susceptibility to AEDs such as phenytoin. It has been shown that only specific fibroblast subpopulations display a "responsive phenotype," characterized by elevated TIMP-1 expression and suppressed collagenase activity following phenytoin exposure. This fibroblast heterogeneity likely explains interindividual differences in the clinical manifestation and severity of gingival overgrowth, despite comparable drug dosage or serum levels [39, 40]. Phenytoin exposure can also modify fibronectin–collagen interactions, further enhancing fibroblast adhesion and matrix production [39].

Secondary modulators, including inflammatory cytokines such as interleukin-1β (IL-1β) and transforming growth factor-β1 (TGF-β1), as well as alterations in fibronectin-collagen interactions, further exacerbate extracellular matrix dysregulation by enhancing fibroblast proliferation and collagen synthesis. These secondary modulators amplify fibroblast proliferation and collagen synthesis, particularly in the presence of bacterial plaque or mechanical irritation.

The cumulative effect of these molecular and cellular alterations leads to excessive extracellular matrix deposition and reduced matrix degradation, resulting in the clinically observed gingival enlargement associated with chronic AED therapy [23, 26].

3.1.1.2. Local Inflammatory Mechanisms in AED-Induced Gingival Overgrowth

In addition to alterations in collagen metabolism and extracellular matrix homeostasis, AED-induced gingival overgrowth is strongly influenced by local inflammatory mechanisms. Immune cell activation, release of pro-inflammatory cytokines, and accumulation of dental plaque contribute to the initiation and progression of tissue hyperplasia. Dental plaque acts as a critical co-factor in drug-induced gingival enlargement [33]. Its accumulation triggers a local inflammatory response within gingival tissues, characterized by infiltration of immune cells and the release of cytokines such as interleukin-1β (IL-1β), interleukin-6 (IL-6), interleukin-8 (IL-8), transforming growth factor-β (TGF-β), connective tissue growth factor (CTGF), and fibroblast growth factor (FGF). These mediators promote fibroblast proliferation, increase synthesis and deposition of ECM components (notably collagen and fibronectin), and inhibit collagen degradation. The resulting imbalance between collagen production and breakdown contributes to excessive gingival tissue accumulation. Moreover, inflammation amplifies the fibrogenic effects of AEDs such as phenytoin by further upregulating profibrotic cytokines (particularly TGF-β and CTGF) and modulating fibroblast responsiveness to these signals [41]. Consequently, drug exposure and plaque-induced inflammation act synergistically to exacerbate gingival overgrowth and sustain chronic tissue remodeling [26, 33].

3.1.1.3. Microbial Changes Contributing to AED-Induced Gingival Enlargement

Disruptions in oral hygiene, minor tissue injuries (e.g., bites), and reduced salivary volume may contribute to alterations in the oral microbiota, including an increase in periodontal pathogens and bacteria associated with inflammation. Although direct studies investigating microbiome changes in children treated with AEDs are limited, reports indicate elevated plaque and gingival indices, particularly in children receiving valproate [42]. Furthermore, in children treated with valproate and other AEDs, significantly greater gingival enlargement, higher gingival index scores, increased plaque accumulation, and deeper periodontal pockets were observed compared to healthy controls [28].

Studies on the microbiota of children with cerebral palsy and epilepsy (CPE) indicate that the bacterial composition in the oral cavity significantly differs from that of healthy peers. In the study by Huang et al. (2022), reduced levels of Firmicutes and Bacteroides were observed, alongside an increased abundance of Actinomycetes, and dominance of Prevotella, Fusobacterium, and Neisseria [43]. These changes may promote an enhanced inflammatory response in gingival tissues, which, combined with AEDs exposure, predisposes to gingival overgrowth. Gingival enlargement in the context of AEDs use is also associated with oral dysbiosis, which can translocate to the gut, leading to systemic dysbiosis and chronic inflammation. This suggests that the mechanism of gingival overgrowth is not limited to the local effects of the drug but is part of a complex interaction between the medication, the microbiota, and the child's immune system.

3.1.2. AED-Induced Xerostomia and Reduced Salivary Flow

AEDs are known to alter salivary secretion, leading to xerostomia and decreased salivary flow, particularly in pediatric populations where dosing requirements are highly variable. Reduced salivary volume diminishes the oral cavity's natural cleansing ability, promotes bacterial accumulation, and weakens buffering capacity, thereby increasing the risk of dental caries, inflammation, and fungal infections [44].

Xerostomia is defined as a subjective complaint of oral dryness and is associated with a burning tongue sensation and difficulty in swallowing. Reduced salivary flow, which underlies this condition, frequently impairs quality of life,

contributing to feeding difficulties, mood disorders, and compromised oral hygiene; although xerostomia may have multiple etiologies, it is a relatively common adverse effect of antiepileptic drug therapy [21,45,46]. Reduced salivary flow and xerostomia contribute to higher risks of dental caries, mucosal lesions, and periodontal disease. Both older-generation drugs (e.g., phenytoin, carbamazepine, phenobarbital) and some newer agents (e.g., levetiracetam, lacosamide, lamotrigine) have been associated with these effects, though the underlying mechanisms differ depending on the drug's pharmacokinetic and pharmacodynamic properties [47]. Clinical manifestations of xerostomia may include carious lesions or decalcification on the labial surfaces of the maxillary incisors, resulting from plaque accumulation at the cervical region, reduced oral pH, and diminished salivary film mobility [48].

In a study by Zorlu et al. (2017), the effects of sodium valproate therapy on dental and periodontal health in children with epilepsy were investigated [42]. However, the study did not demonstrate a direct impact of valproate on salivary flow rate or buffering capacity. Nevertheless, when compared with healthy controls, children receiving valproate exhibited significantly higher plaque index (PI) and gingival index (GI) scores, suggesting a potential detrimental effect of the drug on oral hygiene and periodontal status, even in the absence of measurable salivary gland dysfunction.

AEDs and their metabolites reach the oral cavity, potentially contributing to oral alterations, while salivary levels provide a non-invasive means for therapeutic drug monitoring (TDM). This approach enables dose optimization, minimizes toxicity, and indirectly assesses the risk of salivary dysfunction, particularly in pediatric patients, as most AEDs distribute into saliva in accordance with their non-protein-bound plasma concentrations. For instance, phenytoin shows mean saliva-to-blood ratios of 0.09-0.13 for total phenytoin and 0.99-1.06 for free phenytoin, with strong correlation coefficients (r^2 = 0.92–0.99) between salivary and plasma levels. Carbamazepine and its active metabolite carbamazepine-10,11-epoxide exhibit saliva/plasma correlation coefficients ranging from r^2 = 0.84 to 0.99, while lamotrigine shows r^2 values between 0.677 and 0.9841 in both stimulated and unstimulated saliva samples. Levetiracetam has near 1:1 saliva-to-serum ratios (r^2 = 0.8428—0.93), and lacosamide demonstrates similar correlation coefficients (r^2 = 0.828–0.842) [49,50]. Despite their pharmacokinetic predictability in saliva, AEDs can adversely affect salivary gland function.

A rare adverse effect observed in the oral cavity is sialadenosis, a non-inflammatory salivary gland disorder characterized by recurrent, bilateral enlargement of the parotid and submandibular glands, which has been reported in patients receiving valproic acid; histopathological examination reveals granular changes in the secretory cells without evidence of degeneration or neuropathy [51].

Despite saliva's essential role in maintaining oral homeostasis — through its buffering capacity, lubricating properties, formation of a protective pellicle, and contribution to enamel remineralization — the impact of anticonvulsant therapy on salivary flow and composition remains poorly understood [52,53]. Moreover, there is still a lack of studies comparing the incidence of xerostomia in patients treated with older-generation versus newer antiepileptic drugs, with most existing data focusing on classic agents such as valproate and carbamazepine.

3.1.3. Impact of AEDs on Bone Health and Mineral Density

Childhood, and especially adolescence, is a period of rapid skeletal growth and bone remodeling. A significant portion of peak adult bone mineral density (BMD) is deposited during adolescence and the five years corresponding to peak height velocity [54]. BMD is influenced by genetic factors as well as environmental factors, including medication exposure during periods of rapid growth. Reduced bone accumulation in children and adolescents increases susceptibility to fractures.

Several studies have demonstrated that in pediatric populations , treatment with AEDs can lead to reduced bone mineral density (BMD), osteopenia, osteoporosis, and an increased risk of fractures, primarily through accelerated vitamin D metabolism, hormonal disturbances, direct effects on bone cells, and reduced physical activity [55—57]. The systemic effects of AED-induced BMD reduction are also reflected in oral health.

Lower bone mineral density increases not only the risk of fractures but also the risk of dental caries [58]. In adult populations, fractal analysis of the mandible has shown that patients on AEDs with lower BMD have an increased risk of fractures in the dentoalveolar region, especially during epileptic seizures or trauma [59]. Since teeth are anchored in the alveolar bone, compromised bone health may weaken tooth support, exacerbate periodontal disease, and increase susceptibility to dental complications, highlighting the importance of integrated management of systemic and oral health in pediatric patients receiving long-term AED therapy.

The mechanisms by which AEDs affect bone structure are multifactorial. Enzyme-inducing AEDs, such as carbamazepine, phenytoin, and phenobarbital, accelerate vitamin D inactivation through cytochrome P450 induction, resulting in hypocalcemia, increased parathyroid hormone production, osteoclast activation, and enhanced bone resorption [60—62]. Additionally, these drugs can directly affect bone cells: in vitro studies on human osteoblast-like cells have shown that carbamazepine and phenytoin inhibit cell growth at concentrations corresponding to therapeutic doses [63].

Long-term therapy with valproic acid, which inhibits cytochrome P450, has also been associated with low BMD in both pediatric and adult populations, according to a meta-analysis of 19 studies published in 2019 [64]. Reduced levels of osteonectin and type I collagen have been proposed as potential mechanisms underlying these changes [64]. Moreover, a Danish study reported that prenatal exposure to valproate, either as monotherapy or polytherapy, is associated with dental agenesis [65].

The effects of newer-generation antiepileptic drugs on bone metabolism remain less extensively studied; however, a 2022 meta-analysis suggests that these agents may also exert deleterious effects on bone mineral density [66]. The authors emphasize the need for further research to determine the impact of drug type, dose, duration of therapy, and underlying mechanisms.

Recent evidence suggests that both incident epilepsy and the use of antiepileptic drugs, including enzyme-inducing and non-enzyme-inducing agents, are independently associated with an increased risk of osteoporosis. In a cohort of 6,275 adults with incident epilepsy followed between 1998 and 2019, epilepsy was associated with a 41% faster onset of osteoporosis compared to controls, after adjustment for confounders including age, sex, body mass index, corticosteroid use, comorbidities, smoking, and fracture history [67]. Enzyme-inducing AEDs accelerated osteoporosis onset by 9%, whereas non-enzyme-inducing AEDs accelerated it by 23%, independent of epilepsy. Finally, studies assessing oral health in children with epilepsy have shown that patients not receiving AEDs had significantly lower values of the decay-missing-filled teeth (DMF) index, highlighting the oral consequences of compromised bone and gingival support in medicated patients [36,44,68]. These findings underscore the importance of holistic oral health management in pediatric patients receiving long-term AED therapy, including regular dental check-ups, meticulous oral hygiene, and monitoring of bone health to mitigate both systemic and oral complications.

3.1.4. Effects of AEDs on Tooth Eruption

Available evidence suggests that AEDs, especially those of the older generation, may influence physiological tooth eruption processes. For example, there is a case report of a 4-year-old child on long-term phenytoin therapy who exhibited delayed eruption of the primary dentition, likely secondary to gingival overgrowth impeding the emergence of teeth [69]. Moreover, the teratogenic effects of AEDs have been linked not only to enamel defects but also to disturbances in dental development — prenatal exposure to valproate has been associated with a higher risk of dental agenesis in later childhood [65]. While most research focuses on gingival hyperplasia, disruptions in the timing of tooth eruption or arrest of root development (as seen in some AED-treated patients) are underexplored and could have significant long-term implications for occlusion and oral health [70]. Hence, investigating whether AED treatment is associated with delayed or abnormal eruption of permanent teeth — especially in children treated early or long-term — would enrich our understanding of the broader, potentially cumulative, oral health impacts of these medications.

3.1. The Role of Early Intervention and Preventive Strategies in Managing AED-Induced Oral Changes

Children receiving AED therapy are at elevated risk of oral complications, particularly gingival enlargement and periodontal disturbances, and thus require proactive preventive measures and close interdisciplinary care. Because plaque accumulation and gingival inflammation appear to modulate the severity of these changes, rigorous daily oral hygiene is an essential preventive pillar [18].

Effective management requires early dental evaluation, strict daily oral hygiene practices, and regular professional follow-up every 3 to 6 months to detect early gingival changes, perform prophylaxis and scaling, remove calculus, and reinforce home care. From a clinical perspective, low-dose folic acid supplementation (e.g., 0.5 mg/day) in children receiving phenytoin is supported by robust evidence: in a randomized controlled trial, the incidence of gingival overgrowth decreased from 88 % in the placebo group to 21 % in the folic acid group, corresponding to an approximate 67 % absolute risk reduction [71]. Earlier studies using higher folic acid doses (5 mg/day) also showed delayed onset and reduced severity of overgrowth when combined with oral hygiene measures [72]. When clinically feasible, substitution or dose adjustment of AEDs with lower oral toxicity should be explored, in dialogue with neurology; such measures have been suggested in the literature as part of managing progressive gingival enlargement [73].

The reversibility of gingival changes after drug withdrawal further supports this strategy in selected cases [32]. In a classic study, noninstitutionalized epileptic children receiving intensive plaque control regimens from the outset of phenytoin therapy showed none developing pseudopockets over two years, whereas in those with delayed or moderate preventive care, roughly 40—46% developed pseudopockets [74]. Rigorous daily oral hygiene remains the cornerstone: use of a soft-bristle toothbrush (manual or, if feasible and tolerated, electric), supervised brushing twice daily with fluoride toothpaste, and interdental cleaning when possible. In situations where mechanical methods are constrained, adjunctive antiseptic rinses (e.g. alcohol-free chlorhexidine) may be considered under supervision, recognizing limitations in long-term use. In cases of significant gingival overgrowth that does not respond to non-pharmacological treatment, consideration of a gingivectomy is recommended, especially when the excess tissue affects functions such as chewing, speech, or hygiene, and the tissue becomes fibrous, making further conservative treatment difficult [75].

Children with epilepsy are also more likely to have a cariogenic diet, either due to parental overcompensation, limited food preferences, or the use of sugar-containing liquid medications [76]. Combined with inadequate plaque control — whether due to behavioral limitations or gingival overgrowth — this further elevates the risk of early childhood caries and periodontal issues [77].

Based on the study by Dogan and Yıldız (2024), different antiepileptic drugs can affect the color stability of pediatric restorative materials, with some medications causing greater discoloration than others [78]. Moreover, regular tooth brushing significantly mitigates these changes, highlighting the critical role of oral hygiene in maintaining the esthetic integrity of restorations in children receiving antiepileptic therapy.

Because successful prevention and management of AED-related oral complications depend heavily on daily behaviors and early intervention, education of patients and their caregivers is foundational. Caregivers must be educated on oral hygiene techniques and the potential oral side effects of AEDs, especially when using sugar-containing liquid formulations. According to some researchers, folic acid supplementation may reduce gingival hyperplasia in children treated with phenytoin and can be considered as part of a preventive regimen [71,79]. Importantly, interdisciplinary collaboration between pediatric dentists, neurologists, and caregivers is essential to ensure comprehensive care and to minimize the oral side effects of long-term antiepileptic therapy.

4. Discussion

Children undergoing antiepileptic drugs therapy require special consideration regarding oral health due to their unique

anatomical and physiological characteristics, compounded by pharmacological influences. Pediatric oral structures — including thinner oral mucosa, an immature immune response, and ongoing dental development — render children inherently more susceptible to oral diseases [80]. This vulnerability is further amplified in children with epilepsy, as both the disease itself and its treatment can negatively affect oral health.

Maintenance of proper oral hygiene in this population is particularly challenging. Children with epilepsy may exhibit impaired motor coordination, behavioral difficulties, or cognitive limitations that interfere with routine oral care [81]. Additionally, AED-related side effects — such as hyposalivation, and gingival overgrowth — further increase the risk of caries and periodontal disease [82].

Oral side effects of antiepileptic drugs (AEDs) vary by generation, with older AEDs generally causing more complications, as summarized in Table 2. One of the most clinically significant oral complications associated with long-term AED therapy is drug-induced gingival overgrowth [27]. This adverse effect is well-documented with phenytoin and, to a lesser extent, with valproate and phenobarbital [34]. Gingival overgrowth impairs effective oral hygiene by covering tooth surfaces and creating niches for plaque accumulation, leading to chronic inflammation. These anatomical changes often occur alongside salivary alterations, such as reduced flow, pH changes, or protein composition shifts, which disrupt the balance of the oral microbiome and diminish its natural cleansing and buffering capacity [34]. In pediatric populations, phenytoin can induce gingival enlargement in 16—94% of patients during long-term therapy [68]. Observational data also implicate lamotrigine, oxcarbazepine, and phenobarbital in gingival overgrowth (61%, 71%, and 53%, respectively), whereas phenytoin, valproic acid, and carbamazepine showed lower rates (50%, 44%, and 32%, respectively) [34].

Limited recent evidence from smaller cohorts suggests that polytherapy may increase prevalence modestly (e.g., 45% in polytherapy vs 37% in monotherapy), highlighting the need for further studies controlling for drug combinations, oral hygiene, and individual susceptibility [34]. Longitudinal pediatric evaluations further demonstrate that 53.6% of children on phenytoin monotherapy develop gingival enlargement within three months, whereas carbamazepine-treated children show no such changes in the same period [18].

Beyond gingival overgrowth, other less recognized AED-related oral side effects include xerostomia and impaired bone mineral density, which can predispose children to fractures [83]. The precise mechanisms by which specific AEDs affect the oral cavity, as well as the influence of treatment duration, remain poorly understood, particularly for newer-generation drugs.

Children with epilepsy exhibit higher rates of periodontal disease, dental caries, and tooth loss compared to healthy peers [36,44,68,84]. Studies indicate that oral health tends to be poorer regardless of whether children are on monotherapy or polytherapy, emphasizing the necessity for preventive strategies, caregiver education, and regular dental monitoring [84,85].

Optimal oral care in this population demands strong interprofessional collaboration. Pediatric dentists should be involved early to establish baseline assessments and preventive programs, neurologists should consider oral side effect profiles when selecting or modifying AED regimens, and caregivers must be trained in consistent oral hygiene practices. Frequent dental check-ups — potentially more often than for the general pediatric population — are recommended to maintain oral health and quality of life [86]. Success in mitigating AED-related oral morbidity relies on the triad of education, early intervention, and sustained communication among healthcare providers and caregivers.

Emerging evidence suggests that even newer antiepileptic drugs may contribute to gingival overgrowth through molecular mechanisms. For instance, gabapentin has been shown in in vitro studies on human gingival fibroblasts to upregulate genes involved in extracellular matrix synthesis (e.g., COL4A1, ITGA7, LAMB3) while downregulating matrix-degrading metalloproteinases (such as MMP11, MMP15, MMP16, MMP24), which may favor accumulation of connective tissue and hyperplasia [87].

Additionally, there are clinical case reports of gingival enlargement with lamotrigine [88] and levetiracetam [89], though the precise cellular pathways remain poorly defined.

Table 2. Commonly used antiepileptic drugs (AEDs) by generation and their reported oral adverse effects.

Generation	AED	Oral adverse effects (with References)
First	Phenytoin	Gingival overgrowth / hyperplasia [18]
	Phenobarbital	Gingival overgrowth [34]
Second	Sodium Valproate (Valproic Acid)	Minimal gingival overgrowth [18]
	Carbamazepine	Gingival hyperplasia reported in some patients [92]
	Ethosuximide	Gingival hyperplasia reported in some patients, data limited [93]
Third	Levetiracetam	Gingival hyperplasia / gingival enlargement [35]
	Oxcarbazepine	Gingival overgrowth [34]
	Gabapentin	Gingival overgrowth (in vitro data) [87]
	Topiramate	Dry mouth, taste changes, occasional ulceration [92]
	Lacosamide	No solid clinical reports of oral adverse effects; data limited
	Perampanel	No solid clinical reports of oral adverse effects; data limited
	Brivaracetam	No solid clinical reports of oral adverse effects; data limited
	Rufinamide	No solid clinical reports of oral adverse effects; data limited

More generally, the pathogenesis of drug-induced gingival overgrowth may involve disrupted calcium signaling, altered integrin expression, reduced collagenase activity, and individual patient susceptibility (e.g., genetic polymorphisms), as described in detailed mechanistic reviews [90].

These findings highlight the need for further mechanistic studies on how modern AEDs affect gingival tissue and patient-specific risk factors, as well as research on newer-generation AEDs to guide evidence-based preventive dental care in children with epilepsy [91].

5. Conclusions

Antiepileptic drugs can significantly influence oral health in children with epilepsy, contributing to a higher prevalence of gingival overgrowth, xerostomia, dental caries, and periodontal problems. The extent and nature of these oral adverse effects depend on the specific type, dosage, and duration of AED therapy, as well as on the child's individual susceptibility and oral hygiene practices. Regular dental monitoring and cooperation between pediatricians, neurologists, and dentists are crucial to minimize the negative impact of AEDs on oral health and to ensure comprehensive care for this vulnerable group. Further research into the adverse effects of antiepileptic drugs (especially newer-generation ones) would undoubtedly help to provide optimal dental care for this group of patients. Simultaneously, our findings underscore the need for future prospective studies that perform age-stratified analyses (e.g., infants, preschool children, and adolescents) and directly compare monotherapy and polytherapy, in order to clarify potential age-dependent effects of antiepileptic drugs on oral health outcomes.

Expanding current knowledge will enable the development of individualized preventive programs and early interventions aimed at improving both oral and overall health outcomes in pediatric epileptic patients.

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