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ANTICONVULSANTS IN FEBRILE SEIZURE MANAGEMENT: A COMPREHENSIVE REVIEW OF PHARMACOLOGY, CHEMICAL STRUCTURES AND CLINICAL STRATEGIES

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ABSTRACT

Background: Febrile seizures are the most common neurological disorder in children aged 6 months to 6 years. Although generally benign, complex febrile seizures are associated with increased risk of epilepsy. **Objective:** This review analyzes anticonvulsant drugs used in febrile seizure management, emphasizing the correlation between chemical structure, pharmacokinetics, and clinical efficacy, while assessing the potential of emerging agents. **Method:** A narrative review was conducted using literature published between 2010 and 2025, retrieved from PubMed, ScienceDirect, and Google Scholar, with keywords related to anticonvulsants and febrile seizures. **Result**: Benzodiazepines demonstrate rapid onset and effectiveness in acute management due to their lipophilic structure. Prophylactic agents such as phenobarbital and valproate are effective but linked to long-term adverse effects. Newer agents like levetiracetam and lacosamide offer favorable pharmacokinetics, low toxicity, and selective non-GABAergic mechanisms. **Conclusions:** Anticonvulsant selection should be guided by chemical structure and pharmacokinetic profile. Benzodiazepines remain first-line treatment, while levetiracetam and lacosamide are promising options for complex cases. Further research is needed to strengthen clinical evidence in pediatric populations.

ABSTRAK

Latar Belakang: Kejang demam merupakan kondisi neurologis paling umum pada anak usia 6 bulan hingga 6 tahun. Sebagian besar bersifat jinak, namun kejang demam kompleks berisiko berkembang menjadi epilepsi. **Tujuan:** Artikel ini mengulas berbagai obat antikejang yang digunakan dalam penatalaksanaan kejang demam dengan menekankan hubungan antara struktur kimia, farmakokinetik, dan efektivitas klinis, serta mengevaluasi potensi agen baru. **Metode:** Tinjauan ini menggunakan pendekatan naratif berdasarkan literatur dari tahun 2010–2025 yang diperoleh melalui basis data PubMed, ScienceDirect, dan Google Scholar dengan kata kunci terkait obat antikejang dan kejang demam. **Hasil:** Benzodiazepin efektif pada fase akut karena struktur lipofilik dan onset cepat. Obat profilaksis seperti fenobarbital dan valproat terbukti efektif, namun memiliki efek samping jangka panjang. Levetiracetam dan lacosamide sebagai agen baru menawarkan profil farmakokinetik yang stabil, toksisitas rendah, serta mekanisme kerja selektif non-GABA. **Kesimpulan:** Pemilihan obat antikejang perlu mempertimbangkan struktur kimia dan profil farmakokinetik. Benzodiazepin tetap menjadi lini pertama,

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sedangkan levetiracetam dan lacosamide menjanjikan untuk kasus kompleks. Penelitian lebih lanjut diperlukan untuk memperkuat bukti klinis pada populasi anak.

INTRODUCTION

Febrile seizures (FS) are convulsive episodes that occur in association with fever, without evidence of central nervous system infection or underlying metabolic disorders (Corsello et al., 2024; J.Stpehen & Najib, 2023). They represent the most common neurological disorder in children aged 6 months to 6 years, particularly during the second year of life (Ferretti et al., 2024; Handryastuti, 2021). The global prevalence of FS ranges from 2% to 12% of the pediatric population, influenced by both genetic and environmental factors (Corsello et al., 2024; Handryastuti, 2021). While most episodes are brief and self-limiting, the complex type carries a higher risk of subsequent epilepsy (Handryastuti, 2021).

Intervention is often driven by parental anxiety as well as medical concerns (Laino et al., 2018; Waruiru & Appleton, 2004). Timely and appropriate management is essential to reduce recurrence and prevent further neurological complications (Hashimoto et al., 2021; Hustad et al., 2024). For seizures lasting longer than five minutes, benzodiazepines such as rectal diazepam, intranasal or intramuscular/buccal midazolam, and intravenous lorazepam are recommended in accordance with pediatric acute seizure management protocols (Mckenzie et al., 2021; Okazaki et al., 2024). In children at high risk of recurrence or with a history of complex FS, intermittent prophylaxis using oral diazepam during febrile episodes may be considered (Gavgani et al., 2023; Özdemir et al., 2023). However, long-term use of antiepileptic drugs should generally be avoided because of their significant adverse effect profile (Corsello et al., 2024; Ferretti et al., 2024; Xixis et al., 2024).

Several reviews have evaluated the clinical effectiveness of anticonvulsant agents, but few have explored the relationship between their chemical properties (e.g., lipophilicity, blood–brain barrier penetration, metabolic pathways) and pharmacological characteristics (e.g., onset of action, duration, toxicity risk) (Sánchez et al., 2024; Singh et al., 2025). This article therefore aims to provide a comprehensive review of anticonvulsant drugs used in the management of FS, with emphasis on their pharmacological profiles and chemical attributes. Such an approach may support rational, effective, and safe therapeutic decisions in pediatric practice.

METHOD

This article is a narrative review that synthesizes scientific literature and journal articles published between 2010 and 2025. The literature search was conducted using PubMed, ScienceDirect, and Google Scholar databases with the following keywords: *"febrile seizure," "pediatric epilepsy," "pharmacology of antiepileptics," "chemical properties of antiepileptic drugs," "diazepam," "phenobarbital," "midazolam," "valproate,"* and *"anticonvulsants."*

RESULT

Clinical Approach

Acute Phase: Seizure Termination Strategy

Febrile seizures lasting longer than five minutes are classified as early status epilepticus and require urgent medical intervention (Wylie et al., 2023; Xixis et al., 2024). At this stage, pharmacological management plays a pivotal role in preventing the progression to status epilepticus and reducing the risk of neurological complications (Giorgi et al., 2024). Benzodiazepines remain the first-line treatment, as they act as positive allosteric modulators of GABA-A receptors, thereby enhancing neuronal inhibition and suppressing seizure activity (Rudolph & Möhler, 2006). Commonly recommended options include:

- **Intravenous lorazepam (0.1 mg/kg body weight):** frequently administered in emergency care settings, offering a longer duration of action compared to diazepam, though the IV route is more invasive (Handryastuti, 2021; Xixis *et al.*, 2024).
- **Intranasal or buccal midazolam (0.2–0.5 mg/kg body weight):** an effective alternative when IV access is unavailable, rapidly absorbed via the mucosa and producing a potent anticonvulsant effect (Corsello *et al.*, 2024).
- **Rectal diazepam (0.2–0.5 mg/kg body weight):** still recommended when other administration routes are not feasible, particularly for parental use at home due to its practicality (Ferretti *et al.*, 2024).

Prophylactic Phase: Strategies for Recurrence Prevention

Intermittent Prophylaxis

This approach involves administering oral or rectal diazepam during febrile episodes in children, with the aim of reducing the likelihood of recurrent febrile seizures. Evidence from Cochrane reviews indicates that intermittent diazepam significantly decreases recurrence rates (RR 0.64–0.73), with relatively mild adverse effects such as transient sedation and ataxia (Offringa *et al.*, 2021).

Continuous Therapy

This strategy includes the regular use of phenobarbital or valproic acid to prevent seizure recurrence, primarily through mechanisms associated with GABA modulation and ion channel regulation (Christian Machado Ximenes *et al.*, 2012; Hakami, 2021; Valproic Acid, 2024). Although continuous treatment can effectively reduce the frequency of recurrence, its adverse effects—including behavioral disturbances, chronic sedation, hyperactivity, cognitive impairment, and hepatotoxicity—often outweigh the therapeutic benefits (Livertox, 2020; Romoli *et al.*, 2018). Details regarding mechanisms of action and their relation to chemical structure are presented in Table 1.

Table 1. Clinical Management and Its Correlation with Chemical Structure

Medication & Administration Route	Dosage	Mechanism of Action & Pharmacokinetics	Onset of Action & Duration	References
Acute Phase				
Lorazepam (IV)	0,1 mg/kg (Max 4 mg)	Positive modulation of GABA-A receptors; moderate lipophilicity allows rapid blood–brain barrier penetration	Onset 1-3 min ; Duartion 6-12 h	(Eilbert & Chan, 2022; Ghiasi *et al.*, 2022; Giacois *et al.*, 2013; Griffin *et al.*, 2013).
Midazolam (IN/Buccal)	Buccal 0,3-0,5 mg/kg; IN: 0,2 mg/kg (Max 10 mg)	High affinity for GABA-A receptors; lipophilic properties enable rapid absorption at physiological pH	Onset : <2 min (IN/IM/IV); Duration 1-6 h	(Eilbert & Chan, 2022; Peter *et al.*, 2024; Ülgey *et al.*, 2012)
Diazepam (Rectal)	0,5 mg/kg (Max 20 mg)	GABA-A receptor agonist; highly lipophilic, leading to fast absorption	Onset :10-45 min ; Long duration of action	(Kienitz *et al.*, 2022; Mckenzie *et al.*, 2021)
Intermittent Prophylaxis Phase				
Diazepam (Oral) (During Fever)	0,3-0,5 mg/kg (every 8 h)	GABA-A receptor agonist; high lipophilicity supports rapid absorption	Onset :15-60 min; Long Duration (30-56 h)	(Kienitz *et al.*, 2022; Mckenzie *et al.*, 2021)
Continuous Prophylaxis Phase				
Phenobarbital	20 mg/kg/day (divided into 1-2 doses; max 1 gr)	GABA-A receptor agonist; prolongs chloride channel opening; moderate lipophilicity leading to slower blood–brain barrier penetration	Onset : 8-12 h ; Duration 2-7 days	(Li *et al.*, 2024; Richardson *et al.*, 2024)
Valproat	20-40 mg/kg/day (2-3 doses)	Increases GABA availability; blocks voltage-gated sodium channels; high lipophilicity enabling rapid blood–brain barrier penetration	Onset : 0,5-4 h ; Duration 13-18 h	(Nugraha *et al.*, 2021; Richardson *et al.*, 2024; Valproic Acid, 2024)

Newer agents: Levetiracetam and Lacosamide

The use of conventional antiepileptic drugs such as benzodiazepines, phenobarbital, and valproate has long been the standard approach in the management of febrile seizures. However, prolonged administration of these agents is limited by adverse effects, including behavioral disturbances, sedation, cognitive impairment, and hepatic toxicity (Corsello *et al.*, 2024; Livertox, 2020; Romoli *et al.*, 2018). Advances in neuropharmacology have led to the development of newer-generation antiepileptic agents that act through non-GABAergic pathways, offering more stable pharmacokinetic profiles and reduced toxicity risk (Löscher, 2024; Zelleke *et al.*, 2020). Among these, levetiracetam and lacosamide have demonstrated significant potential in seizure control in children, particularly in cases of complex febrile seizures (CHEN *et al.*, 2016; Elberry *et al.*, 2012; Sanmartí-Vilaplana & Díaz-Gómez, 2018).

- **Levetiracetam,** exerts its effect by binding to Synaptic Vesicle Protein 2A (SV2A), a key regulator of neurotransmitter release. This interaction reduces glutamate release without affecting GABAergic transmission or ion channels (Zeytin Demiral *et al.*, 2024). Reported adverse effects include a low risk of psychosis, and compared with other antiepileptic agents, levetiracetam shows fewer drug–drug interactions due to its minimal plasma protein binding (Mckenzie *et al.*, 2021; Zelleke *et al.*, 2020).
- **Lacosamide,** stabilizes sodium channels through selective enhancement of slow inactivation, without interfering with normal physiological transitions (Hakami, 2021; Sanmartí-Vilaplana & Díaz-Gómez, 2018). Common adverse effects include ataxia, diplopia, and headache, but it is generally well tolerated in pediatric patients (Carona *et al.*, 2021; Hakami, 2021). The recommended initial dose is 1–2 mg/kg/day for 2–4 weeks, with gradual titration up to 6–12 mg/kg/day (BNSSG, 2012; Xiong *et al.*, 2024).

Table 2. Clinical Approaches and Their Relationship to Chemical Structure

Medication & Administration Route	Dosage	Mechanism of Action & Pharmacokinetics	Onset of Action & Duration	References
Levetiracetam (IV)	10-20 mg/kg/day (Max 60-80 mg/kg/day)	SV2A binding; Hydrophilic; Renal elimination, and absence of hepatotoxic effects.	Onset 5-15; $t_{1/2}$ 6–8 h	(Kumar *et al.*, 2023; Pokorná *et al.*, 2023; Zelleke *et al.*, 2020)
Lacosamide (IV)	1–12 mg/kg/day (2 doses)	Modulasi inaktivasi lambat kanal Na^+; Amphifilik → cukup mampu melewati BBB ; Ekskresi Ginjal	Onset 1–4 h; $t_{1/2}$ 13 h	(BNSSG, 2012; Carona *et al.*, 2021; Xiong *et al.*, 2024)

Clinical Implications and Potential Use

Levetiracetam and lacosamide are not currently recommended as first-line therapy for simple febrile seizures. Their therapeutic role appears more relevant in cases of complex febrile seizures, recurrent episodes, or in children with a history of epilepsy and underlying neurological disorders (Ben-Menachem *et al.*, 2021; Jin *et al.*, 2025; Yang *et al.*, 2021). Several prospective studies have investigated the effectiveness of these drugs in atypical febrile seizures and early-onset epilepsy in pediatric populations (Hsiao *et al.*, 2024; Yang *et al.*, 2023).

The pharmacokinetic advantages of levetiracetam and lacosamide include minimal drug–drug interactions and the absence of significant hepatotoxicity (Carona *et al.*, 2021; Mckenzie *et al.*, 2021; Zelleke *et al.*, 2020). Furthermore, their favorable long-term safety profile supports their use as second-line options or alternatives for patients with contraindications to phenobarbital and benzodiazepines (Wirrell *et al.*, 2017; Yang *et al.*, 2021).

DISCUSSION

From both pharmacological and chemical perspectives, the choice of antiepileptic therapy in febrile seizures is highly dependent on molecular characteristics and pharmacokinetic properties (Sánchez *et al.*, 2024; Singh *et al.*, 2025). Benzodiazepines such as diazepam and midazolam possess lipophilic structures that enable rapid penetration across the blood–brain barrier (BBB), making them highly effective in terminating acute seizures (Griffin *et al.*, 2013). However, adverse effects such as sedation and behavioral disturbances limit their long-term use (Corsello *et al.*, 2024; Ferretti *et al.*, 2024). Phenobarbital and valproate are also effective as prophylactic agents to reduce seizure recurrence, but their chronic use is associated with hepatotoxicity, respiratory depression, and negative impacts on cognitive development in children (Khajeh *et al.*, 2018; Livertox, 2020; Romoli *et al.*, 2018).

Newer antiepileptic drugs, particularly levetiracetam and lacosamide, have shown considerable promise in managing complex febrile seizures. Levetiracetam acts through binding to SV2A, independent of GABAergic pathways, offering selectivity and a lower risk of pharmacological interactions. Its hydrophilic nature results in predominant renal elimination, stable clearance, and avoidance of hepatic metabolism (Kumar *et al.*, 2023; Pokorná *et al.*, 2023).

Lacosamide stabilizes sodium channels via enhancement of slow inactivation, differing from classical sodium-channel blockers. Its amphiphilic property facilitates sufficient BBB penetration, and clinical data support its favorable tolerability in children (BNSSG, 2012; Carona *et al.*, 2021; Xiong *et al.*, 2024). Both agents demonstrate relatively rapid onset, moderate-to-prolonged duration of action, and acceptable side-effect profiles, making them rational candidates for cases unresponsive to conventional therapies or in patients with contraindications to benzodiazepines and phenobarbital (CHEN *et al.*, 2016; Chen *et al.*, 2011; Giráldez *et al.*, 2015).

Nevertheless, direct evidence assessing the efficacy of levetiracetam and lacosamide specifically in febrile seizures remains scarce. Most available data are derived from studies on

epilepsy or non-febrile status epilepticus, making their application in febrile seizures largely extrapolative. Large-scale clinical trials focusing exclusively on febrile seizures are still lacking (Angurana & Suthar, 2021; Glauser *et al.*, 2016). While their pharmacological profiles are promising, stronger clinical evidence is required before their role as first-line therapy can be established.

CONCLUSION

Rational selection of antiepileptic therapy for febrile seizures should integrate the relationship between chemical structure, pharmacokinetics, and clinical considerations of each agent. Benzodiazepines remain the mainstay for acute seizure termination due to their rapid onset and efficient BBB penetration. However, in recurrent, complex, or refractory cases, levetiracetam and lacosamide may be considered safer and more selective alternatives. Their use should be individualized, taking into account patient characteristics and long-term tolerability.

RECOMMENDATION

More large-scale prospective studies are needed to evaluate the specific efficacy and safety of this new agent in pediatric febrile seizures.

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