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Medication Adherence and Seizure Control in Children with Epilepsy: A Systematic Review

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ABSTRACT

Medication adherence is crucial for achieving seizure control in pediatric epilepsy, yet non-adherence remains a persistent challenge in clinical practice. This review evaluated the association between medication adherence and seizure control in children with epilepsy. A systematic review was conducted on online databases at Scopus, ScienceDirect, and PubMed for original articles published between 2015 to 2025. Keywords included "medication adherence", "compliance", "epilepsy", "seizure", "anticonvulsant", "anti-seizure", "seizure-free", "seizure control", and "treatment outcome". A total of eight studies were included, comprising five cross-sectional and three retrospective cohort studies. Medication adherence rates ranged from 48.5% to 91.64% across different measurement methods. All studies demonstrated statistically significant associations ($p<0.05$) between adherence and seizure outcomes. Six studies showed adherence was associated with seizure control, while two examined seizure control as a factor associated with adherence, suggesting a possible bidirectional relationship. Good medication adherence was associated with 2 – 5-fold higher odds of favorable seizure outcomes (AOR: 2.19-4.91). Available evidence consistently indicates an association between medication adherence and seizure control in children with epilepsy, though causal conclusions are limited given the predominantly cross-sectional study designs included. Notably, seven of eight studies were conducted in Ethiopia, which may limit generalizability to other geographic and healthcare settings. Systematic adherence assessment and targeted interventions should be prioritized as integral components of comprehensive epilepsy care to improve seizure outcomes in children.

Keywords:

Anti-seizure medications ; Children; MMAS-8; MPR; Pediatric epilepsy; Treatment adherence

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1. Introduction

Epilepsy represents a significant global neurological health burden that occurs in children with a global prevalence of 6.3 per 1,000 population [1],[2]. Based on data from 2021, more than eight million children and adolescents worldwide were living with epilepsy, including 4.37 million adolescents aged 10–19 years [3],[4]. Despite the lack of specific data on pediatric epilepsy in Indonesia, an estimated 474,000 children to have epilepsy on the country's projected 79 million children in 2022 [5]. Achieving optimal seizure control is the main goal of managing epilepsy in children to avoid major

outcomes like physical injury, cognitive impairment, social and educational limitations, and reduced quality of life [4], [6]. Antiepileptic drugs (AEDs) are the first-line treatment for most pediatric epilepsy cases and can achieve adequate seizure control in 60 –70% of patients when used appropriately [1],[7].

Despite the availability of effective AEDs, suboptimal medication adherence remains a persistent challenge in pediatric epilepsy management. Adherence rates vary widely across studies, ranging from 22.1% to 96.5%, with a pooled rate of 63.96% reported from a meta-analysis of 13,747 children [8]. Poor adherence is associated with increased seizure frequency, higher rates of emergency department visits and hospitalizations, reduced quality of life, and higher healthcare costs [9]. Multiple factors related to patient, medication, caregiver, healthcare system, and socioeconomic conditions influence medication adherence [10].

The relationship between medication adherence and seizure control in pediatric epilepsy remains inconsistently reported in the literature. While some studies have found no statistically significant correlation, others have shown a clear association between increased adherence and seizure control [11],[12]. This inconsistency is partly driven by methodological heterogeneity, including the use of diverse adherence measurement tools ranging from self-report instruments such as MMAS-8 to objective measures such as pharmacy refill records and medication possession ratio, as well as varying definitions of seizure control across studies. Methodological heterogeneity makes it difficult to directly compare findings and synthesize evidence across studies.

This systematic review aims to synthesize available evidence on the association between antiepileptic medication adherence and seizure control in pediatric epilepsy. To address the methodological heterogeneity identified in the existing literature, this review applies structured quality appraisal using validated tools and a narrative synthesis approach to ensure a rigorous and transparent evidence synthesis. This review will contribute valuable insights to guide clinical practice, inform the development of targeted adherence interventions, and support efforts to improve seizure control and outcomes for children with epilepsy [10].

2. Method

Eligibility Criteria

Studies were selected based on the PICO framework. The population (P) included children aged 0-17 years with a confirmed diagnosis of epilepsy receiving antiepileptic drug treatment. The intervention or exposure (I) was defined as medication adherence to antiepileptic drugs, assessed using any validated measurement method, including self-report questionnaires, electronic monitoring devices, pharmacy refill records, pill counts, or validated adherence scales. The comparator (C) included various levels of medication adherence or, in studies examining the reverse relationship, various levels of seizure control. The outcomes (O) encompassed measures of association between medication adherence and seizure control, including studies examining adherence as a predictor of seizure control or studies examining seizure control as a predictor of adherence. Studies were included if they were observational in design (cross-sectional, cohort, or case-control studies), published between 2015 to 2025, and excluded if they did not examine this relationship.

Information Sources and Search Strategy

A systematic literature search was conducted across PubMed, Scopus, and ScienceDirect following the Preferred Reporting Items for Systematic Reviews and Meta-

Analyses (PRISMA) 2020 guidelines. The search covered publications from 1 January 2015 to 31 December 2025, with the last search conducted on 31 December 2025. The search strategy was developed using a combination of MeSH terms and free-text keywords tailored to each database as follows:

PubMed: ("medication adherence" OR "compliance") AND ("epilepsy" OR "seizure") AND ("anticonvulsant" OR "anti-Seizure") AND ("seizure free" OR "seizure control" OR "treatment outcome") Filter: 2015-2025, Full text.

ScienceDirect: TITLE-ABS-KEY ("medication adherence" OR "compliance") AND ("epilepsy" OR "seizure") AND ("anticonvulsant" OR "anti-seizure") AND ("seizure free" OR "seizure control" OR "treatment outcome") Filter: 2015-2025, research article, medicine and dentistry, english.

Scopus: TITLE-ABS-KEY ("medication adherence" OR "compliance") AND ("epilepsy" OR "seizure") AND ("anticonvulsant" OR "anti-seizure") AND ("seizure free" OR "seizure control" OR "treatment outcome") Filter: 2015-2025, medicine, article, english, human.

Backward citation searching was performed on all included studies and relevant review articles to identify additional records not captured by the database searches.

Data Extraction

Data were extracted by the primary reviewer using a standardized form. Extracted information included study characteristics (author, publication year, country, design), population demographics (sample size, age, and epilepsy type), adherence measurement tools, seizure control metrics, statistical measures of association, and primary findings. The extracted data were subsequently reviewed and verified by a second reviewer to ensure accuracy and completeness. Any discrepancies during data extraction were resolved through discussion and consensus between the reviewers.

Quality Appraisal

The methodological quality of the included studies was assessed using the Newcastle-Ottawa Scale for cohort studies and the Joanna Briggs Institute Critical Appraisal Checklist for cross-sectional studies.

Data Synthesis

Findings from the included studies were synthesized narratively. Meta-analysis was not possible due to substantial variability in study characteristics, outcome definitions, and measurement approaches.

3. Result and Discussion

Study Selection

The literature search was conducted across three electronic databases, including PubMed (n=54), ScienceDirect (n=1789), and Scopus (n=361), yielding a total of 2,213 records. In addition, 29 records were found through other sources by manual screening of reference lists from included studies and relevant review articles. Prior to screening, 1,700 records were removed, including 31 duplicate records, 1,171 records published outside the 2015-2025 period, 420 non-research articles, 5 non-English language articles, and 73 records considered out of scope. This resulted in 542 records eligible for title and abstract screening.

During screening, 431 records were excluded based on titles and abstracts. The remaining 111 reports were sought for retrieval; 10 could not be obtained. A total of 101 full-text articles were assessed for eligibility, of which 93 were excluded due to wrong

population (n=28), wrong setting (n=15), wrong intervention (n=26), or wrong outcomes (n=24). Eight studies met the eligibility criteria and were included in this systematic review (**Figure 1**).

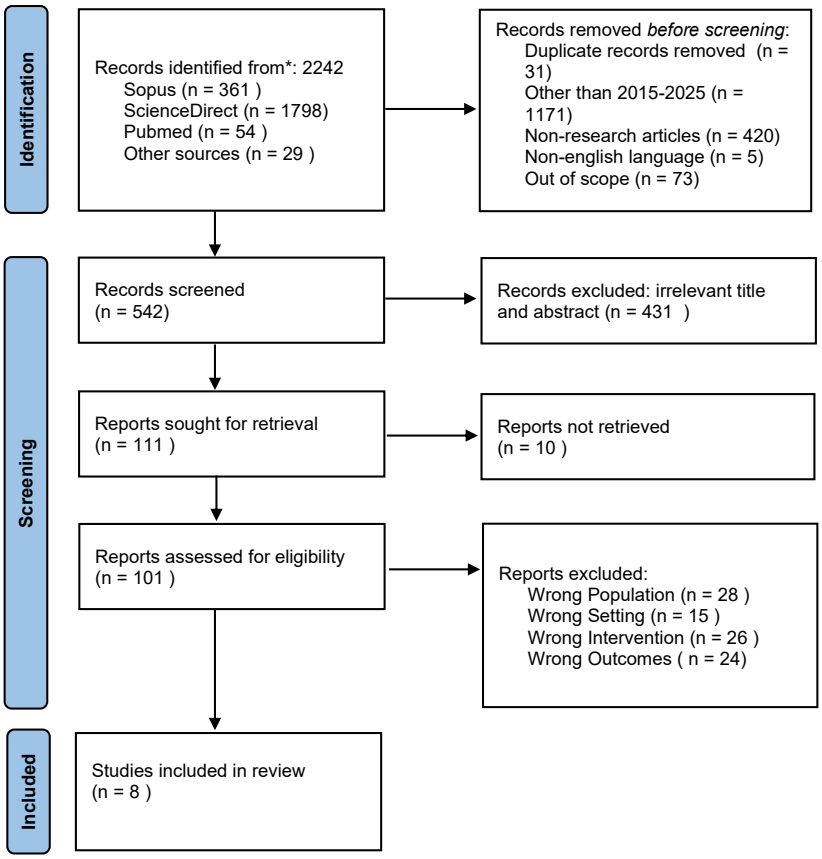

Figure 1. PRISMA flow diagram

Quality Appraisal

The methodological quality of included studies was assessed using the Joanna Briggs Institute (JBI) Critical Appraisal Checklist for the five cross-sectional studies and the Newcastle-Ottawa Scale (NOS) for the three retrospective cohort studies. Among cross-sectional studies, three were rated as good quality [13], [14], [15] and two as moderate quality [16], [17]. Among cohort studies, one was rated as high quality [18], one as good quality ,[19] and one as moderate quality [20]. Overall, 62.5% of included studies were rated good to high quality, with no study rated as low quality, indicating a low-to-moderate risk of bias across the body of evidence. The most frequently identified limitations were reliance on self-reported adherence measures, which are susceptible to recall and social desirability bias, and the cross-sectional design employed in five studies, which precludes causal inference.

Seizure Control Definition and Outcomes

Definitions of seizure control varied across the eight included studies and were grouped into three categories: seizure-free duration (complete absence of seizures over 6 to 12 months) as applied in three studies [13], [17], [19]; seizure frequency thresholds (good outcomes defined as ≤3 episodes within a 3-month window) as applied in four studies [14], [15], [16], [20]; and healthcare utilization as a surrogate indicator of poor seizure control (emergency department visits or hospitalizations due to seizure-related

reasons over a 2-year follow-up) applied in one retrospective cohort study [18]. This heterogeneity reflects the absence of a universally accepted operational definition of seizure control in pediatric epilepsy research, complicating direct cross-study comparisons and partially explaining differences in effect size estimates. Despite this variability, the consistent direction of association across all three definitional approaches suggests that adherence-seizure outcome relationship is robust, and greater standardization of outcome definitions would facilitate future meta-analyses in this field.

Study Characteristics and Geographic Distribution

The characteristics of the included studies are summarized in **Table 1**. The studies were published between 2016 to 2025 and were conducted in Ethiopia (n=7), with one study from South Korea. Most studies employed a cross-sectional design (n=5), while the rest used retrospective cohort designs (n=3). All studies involved children (≤18 years) with epilepsy, with total sample sizes ranging from 140 to 976 participants.

The concentration of studies in Ethiopia likely reflects regional research priorities and the critical treatment gap characteristic of low- and middle-income country healthcare settings, where adherence is deeply shaped by systemic barriers including limited household income [16], restricted healthcare access [15], [17], and substantial caregiver burden related to health literacy and family structure [15], [16], [19]. The single study from South Korea [18], which reported the highest adherence rate (>87% across 3 years), suggests that healthcare system characteristics and socioeconomic contexts influence adherence behavior.

Medication Adherence Measurement and Rates

The included studies employed diverse tools and methods to assess medication adherence such as MMAS-8 for self-reports measure (n=3), objective adherence measured with medication refill records (n=3), the Medication Possession Ratio (MPR) (n=1), and pill count (n = 1). The reported medication adherence rates across the eight included studies proved substantial variation, ranging from 48.5% to 91.64%. The highest adherence was reported in a retrospective cohort study using MPR over a 3-year period (91.64%-87.29%), while the lowest rates were observed in studies using medication refill records (48.5%–70.5%). Studies using MMAS-8 reported adherence rates between 53.6% and 65%, while pill count reported adherence rates of 77.8%, as summarized in **Table 1**.

The wide range of adherence estimates reflects differences in measurement methods, thresholds for defining adherence, study populations, and healthcare contexts rather than true variation in adherence behavior alone. Subjective measures are subject to recall bias and may either underestimate or overestimate adherence depending on patient characteristics and social desirability factors, while pharmacy-based measure may overestimate adherence since it cannot confirm actual medication intake and may miss doses that were obtained but not consumed [21], [22]. Effect measures also varied in accordance with study design, seven studies reported AOR, while one retrospective cohort study reported an adjusted HR, reflecting its time-to-event analytical approach. Despite this methodological difference, all effect estimates consistently indicated a significant association between adherence and favorable seizure-related outcomes.

Table 1. Characteristics of Included Studies and Summary of Findings on Medication Adherence and Seizure Control

No	Author	Region	Study Design	Sample (n)	Adherence Tool	Adherence Rate (%)	Seizure Control Definition	Seizure Control Outcome	Measure of association	p-value	Main Finding
1	Mohammed et al., 2022 [15]	Ethiopia	Cross-sectional	170	MMAS-8	54.1% were adherent; 45.9% were non-adherent	• Controlled: No seizure in the last 3 months • Uncontrolled : ≥1 episode in the last 3 months	54.1% (controlled); 45.9% (uncontrolled)	AOR = 3.64 (95% CI 1.51-8.78)	0.004	Controlled seizures are associated with 3.64 times higher medication adherence
2	Lee et al., 2016 [18]	South Korea	Cohort Retrospective	976	MPR	91.64% (year 1), 88.99% (year 2), 87.29% (year 3); (≥80%)	Surrogate measure used – ED visits or hospitalizations due to seizure-related reasons	8.71% ED visits or hospitalization due to seizure-related reasons over 2 subsequent years	Adjusted HR: 2.10 (95% CI: 1.25-3.55)	<0.05*	Non-adherence doubled the risk of emergency visits for seizure-related reasons
3	Dima et al., 2022 [16]	Ethiopia	Cross-sectional	192	MMAS-8	65% were adherent; 35% were non-adherent	Seizure attack in the past 3 months YES/NO	44.3% No seizure attack in the past 3 months	AOR = 0.23 (95% CI: 0.1 – 0.55)	<0.05	Recent seizures (past 3 months) linked to 77% lower adherence
4	Adal et al., 2021 [17]	Ethiopia	Cross-sectional	261	Pill Count	77.8% were adherent; 22.2% were non-adherent	• Controlled: 12 months seizure-free • Uncontrolled : ≥1 seizure attacks in the	49% (controlled); 51% (uncontrolled)	AOR = 3.92 (95% CI: 1.84-8.36)	<0.001	Adherent patients had 3,92 times higher odds of achieving seizure control

No	Author	Region	Study Design	Sample (n)	Adherence Tool	Adherence Rate (%)	Seizure Control Definition	Seizure Control Outcome	Measure of association	p-value	Main Finding
							last one-year follow-up period				
5	Nasir et al., 2023 [19]	Ethiopia	Cohort Retrospective	385	Medication Refill	57.1% had excellent adherent; 15.1% had poor adherent	Controlled: Seizure-free for at least 12 consecutive months following anti-epileptic therapy	64.2% (controlled); 35.8% (uncontrolled)	AOR = 2.49 (95% CI: 1.23-5.03	0.011	Excellent adherence is associated with 2.49 times higher odds of controlled seizure
6	Alene et al., 2024 [14]	Ethiopia	Cross-sectional	200	Medication Refill	48.5% had excellent adherent; 27.5% had poor adherent	• Good outcome: ≤3 seizure episodes in 3 months after treatment start • Poor outcome: ≥4 seizure episodes within 3 months after treatment start	65.5% (good treatment outcome); 34.5% (poor treatment outcome)	AOR = 3.21 (95% CI: 1.42-7.25)	<0.05	Poor adherence resulted in a 3.21 times higher likelihood of poor treatment outcomes
7	Beyene et al., 2020 [20]	Ethiopia	Cohort Retrospective	210	Medication Refill	70.5% had excellent adherence; 7.6% had	• Successful outcome: ≤3 seizure episodes in	77.1% (successful treatment outcome);	AOR = 4.51 (95% CI: 1.53-13.42)	0.006	Excellent adherence is linked to 4.51 times higher

No	Author	Region	Study Design	Sample (n)	Adherence Tool	Adherence Rate (%)	Seizure Control Definition	Seizure Control Outcome	Measure of association	p-value	Main Finding
						poor adherence	the last 3 months after start of treatment • Not a successful outcome: ≥4 seizure episodes in the last 3 months after the start of treatment	22.9% (not successful treatment outcome)			odds of a successful treatment outcome
8	Saleye et al., 2025 [13]	Ethiopia	Cross-sectional	140	MMAS-8	• 46.4% poor adherent; • 53.6% were good adherent	• Good outcome: Seizure-free for at least 6 months • Poor outcome: >50% reduction in seizure frequency and ≥ 1 seizure per month over 6 months	59.3% (poor treatment outcome); 40.7% (good treatment outcome)	AOR = 4.917 (95% CI: 2.45-9.86)	<0.001	Poor adherence increased the risk of poor seizure control by 5-fold

Note: *AOR = Adjusted Odds Ratio; HR = Hazard Ratio; 95% CI = 95% Confidence Interval; MMAS-8 = Morisky Medication Adherence Scale-8; MPR = Medication Possession Ratio; ED = Emergency Department. *statistical significance at p<0.05.*

Association Between Medication Adherence and Seizure Control

All eight included studies reported a statistically significant association between medication adherence and seizure-related outcomes (p-values <0.05), with good adherence consistently associated with 2 to 5-fold higher odds of favorable seizure outcomes compared to non-adherent patients (AOR: 2.49–4.91). Six studies evaluated adherence as the independent predictor of seizure control, demonstrating that good adherence significantly increased the odds of achieving seizure-free status or reduced seizure frequency [13], [14], [15], [17], [19], [20]. The remaining two studies examined the reverse analytical direction, with seizure control status as a determinant of adherence behavior, poor seizure control has been associated with decreased adherence, primarily linked to treatment failure, recurrent seizures leading to emergency department visits or hospitalizations, and increased regimen complexity in refractory epilepsy requiring polytherapy [16], [18]. Despite differing analytical directions, all studies showed a consistent pattern of association between adherence behavior and seizure outcomes in pediatric patients with epilepsy.

The variation in analytical direction across the included studies suggests a possible bidirectional relationship between adherence and seizure outcomes, though this interpretation requires careful qualification. The majority of included studies employed a cross-sectional design, which precludes the determination of directionality or causation. The observed bidirectional pattern therefore reflects statistical associations rather than confirmed causal pathways, and longitudinal studies with prospective designs are needed to firmly establish the directionality of this relationship.

Comparison with Previous Evidence

The findings of this review align with previous evidence proving a significant association between medication adherence and seizure control in patients with epilepsy. Multiple studies in adult populations have reported that non-adherence to AEDs is associated with increased risk of uncontrolled seizures and elevated emergency department use [23], [24], [25], [26]. Although literature specifically examining the adherence-seizure control relationship in pediatric populations is more limited, the magnitude of associations observed in this review (AOR ranging from 2.49 to 4.91) indicates that adherence plays a clinically meaningful role in seizure outcomes in children, consistent with patterns reported in adult epilepsy research. This review further extends prior evidence by demonstrating that the association holds across heterogeneous measurement approaches and diverse healthcare settings, from low-resource environments in sub-Saharan Africa to high-income healthcare systems in East Asia.

Clinical Significance and Developmental Considerations

Medication adherence is a clinically significant and modifiable factor in pediatric epilepsy management. Antiepileptic drugs remain the primary therapeutic modality for seizure suppression, [27], and inconsistent medication intake can cause fluctuations in drug plasma concentrations that increase susceptibility to breakthrough seizures, particularly for agents with a narrow therapeutic index [28], [29]. Beyond pharmacological mechanisms, the findings of this review highlight that adherence in pediatric epilepsy is further complicated by age-specific developmental factors. Toddlers demonstrated significantly lower adherence (OR=0.26) compared to adolescents due to complete caregiver dependence, while older children face inconsistent self-management challenges [18]. Medication palatability contributed to child refusal in 18.3% of cases [17], and forgetfulness remained the most consistently reported barrier, reported by 16-70% of caregivers across studies [15], [16], [17].

These findings highlight the need for a multicomponent adherence support approach in pediatric epilepsy clinics. Routine screening using MMAS-8 can identify at-risk patients early,

while structured caregiver education addressing forgetfulness and treatment understanding has shown moderately positive effects on adherence in epilepsy populations [30]. Regimen simplification, particularly reducing dosing frequency, can reduce caregiver fatigue in younger age groups [31], and reminder-based tools such as mobile alerts alongside improved medication access through community pharmacy programs are especially relevant in low-resource settings [30], [32]. Taken together, a multicomponent approach that combines screening, education, regimen optimization, and access support is most likely to produce meaningful and sustained improvements in adherence and seizure outcomes in pediatric epilepsy clinics.

Limitations

This review is limited by the concentration of research in Ethiopia, which restricts the generalizability of findings to other settings. Methodological heterogeneity in adherence measures and seizure control definitions precluded meta-analysis. The predominance of cross-sectional designs limits causal inference and inter-rater reliability was not formally quantified. Publication bias cannot be excluded, as all included studies reported statistically significant associations.

4. Conclusion

This systematic review found a consistent association between medication adherence and seizure control in children with epilepsy across eight observational studies. Patients with good adherence were associated with 2 to 5 times higher odds of achieving favorable seizure control. However, causal conclusions cannot be drawn given that the majority of included studies were cross-sectional in design, which inherently limits the ability to establish directionality. These findings nonetheless highlight medication adherence as a clinically significant and modifiable factor that warrants systematic attention in pediatric epilepsy management.

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Conflicts of Interest:

The author reported no conflict of interest in this study.

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